Providence
Medicare Advantage Plans

PROVIDENCE MEDICARE ADVANTAGE PLANS

2024 PRIOR AUTHORIZATION CRITERIA FOR PART B DRUGS

Effective 4/1/2024

For more recent information or other questions, please contact Providence Health Assurance Customer Service at 503-574-8000 or 1-800-603-2340 or, for TTY users, 711, seven days a week, between 8 a.m. and 8 p.m. (Pacific Time), or visit ProvidenceHealthAssurance.com.

H9047_2024RX_PHA262_C

Medicare Part B Drug Prior Authorization

Our job as your health plan is to make sure that you receive the right care at the right time and at the most affordable price. Providence Medicare Advantage Plans requires you (or your physician) to get approval for certain medical services, including administration of certain medications, before we will agree to cover the drug for you. This is called "prior authorization." Sometimes the requirement for getting approval in advance helps guide appropriate use of certain drugs including specialty drugs injected or infused by your provider. If you do not get this approval, your drug might not be covered by the plan.

This document contains the Prior Authorization requirements for certain Part B eligible drugs.

For more recent information or other questions, please contact Providence Health Assurance Customer Service at 503-574-8000 or 1-800-603-2340 (TTY users should call 711), seven days a week, between 8 a.m. and 8 p.m. (Pacific Time), or visit ProvidenceHealthAssurance.com.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM025.1223	**HEMATOLOGICAL AGENTS** **ACUTE HEREDITARY ANGIOEDEMA THERAPY** See Appendix 2 for medications covered by policy
Effective Date: 2/1/2024	**Review/Revised Date**: : 04/10, 06/11, 12/11, 10/12, 10/13, 10/14, 12/14, 04/15, 10/15, 09/16, 07/17, 09/18, 11/19, 10/20, 01/21, 07/21, 11/21, 11/22. 11/23 (DJW)
Original Effective Date: 06/10	**P&T Committee Meeting Date**: 04/10, 06/11, 12/11, 10/12, 10/13, 10/14, 12/14, 04/15, 10/15, 10/16, 10/17, 9/18, 10/18, 12/19, 12/20, 02/21, 08/21, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:

1. For initiation of therapy (new starts), all the following must be met:
    a. Diagnosis of Hereditary Angioedema (HAE) as confirmed by one of the following:
        i. For HAE Type I and Type II, documentation of the following (per laboratory standard):
            1) Serum C4 level below the lower limit of normal

            AND

            2) One of the following:
                a) C1-Inhibitor (C1-INH) protein level less than 50 percent of the lower limit of normal, or
                b) C1-INH protein function less than 50 percent of the lower limit of normal
        ii. For HAE with normal C1-INH or HAE Type III:
            1) Confirmed Factor 12 (FXII), ANGPT1, PLG, or KNG1 gene mutation, **OR**
            2) Positive family history for HAE and attacks that lack response with high dose antihistamines or corticosteroids

   b. For coverage of **Berinert®, Kalbitor®, or Ruconest®** for members 18 years and older: Documentation of trial and failure or contraindication to generic icatibant
2. For patients established on the requested therapy (within the previous year):
   a. Documentation must be provided showing benefit of therapy with reduction of length and severity of HAE attack episodes.

EXCLUSION CRITERIA: Concurrent use with other products indicated for the acute treatment of HAE attacks

AGE RESTRICTIONS:
Kalbitor® - 12 years and older
Ruconest® - 13 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an immunologist or an allergist.

COVERAGE DURATION:
Initial authorization will be approved for up to six months. Reauthorization will be approved for up to one year.

QUANTITY LIMIT: N/A

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Kalbitor® (ecallantide), Berinert® (human C1 inhibitor), and Ruconest® (recombinant C1 inhibitor) are injectable medications used to treat acute swelling attacks in patients with hereditary angioedema (HAE).

Kalbitor® is a kallikrein inhibitor which blocks the synthesis of bradykinin. Bradykinin is a vasodilator which is thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Ecallantide is given subcutaneously and must be administered by a healthcare provider.

Berinert® and Ruconest® are C1 inhibitors produced from different sources that replenishes C1 inhibitor level in HAE patients who have low levels of endogenous or functional C1 inhibitor. C1 inhibitor is a normal component of human blood that helps regulate the inflammatory and clotting response. Both Berinert® and Ruconest® are given intravenously and can be self-administered by patients upon recognition of an HAE attack after proper training.

FDA APPROVED INDICATIONS:

- Kalbitor® is indicated for the treatment of acute attacks of hereditary angioedema in patients 12 years of age and older.
- Berinert® is indicated for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and pediatric patients.
- Ruconest® is indicated for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE). Effectiveness was not established in HAE patients with laryngeal attacks.

POSITION STATEMENT:

- Hereditary angioedema (HAE) is a condition characterized by acute attacks of sudden edema formation in the skin or in the walls of the upper respiratory tract or gastrointestinal tract. Management of patients with C1 inhibitor deficiency should cover their long-term, short-term and acute needs.
    - Cases of laryngeal edema can rapidly become life threatening. The most frequent cause of death is airway obstruction secondary to laryngeal edema.
    - Cases of gastrointestinal attacks have been misdiagnosed and have led to unnecessary surgeries.
    - Typically swelling worsens over the first 24 hours and slowly subsides over the next 48-72 hours. Clinical course can vary from attacks lasting less than 24 hours to nine days.
    - Factors that precipitate attacks can be vague in nature. Observational studies suggest minor trauma (e.g. dental work) and stress to be triggers. Initiation of ACE-Inhibitor (leading to subsequent increase in bradykinin) and estrogen (unknown mechanism) can also lead to attacks. However, many attacks have no apparent cause.

  - The approach to treatment has two main goals: (1) prevent acute attacks of hereditary angioedema from developing and (2) rapidly treat acute angioedema attacks if they do occur.
- Diagnosis of HAE requires laboratory confirmation
  - Laboratory tests should be performed in an accredited laboratory registered with a suitable quality assurance scheme
  - Serum C4 level is a good screening test for C1 INH deficiency as serum C4 is invariably low in untreated HAE (C4 less than 30% of mean normal level). It has been shown that for untreated C1 INH deficiency low C4 has 100% sensitivity, 100% negative predictive value and is thus an effective screening test.
  - The diagnosis of type I HAE (85% of cases) is made by measuring low amounts of C1 inhibitor protein. If C1 inhibitor value appears normal or raised (and C4 is low), a test of C1 inhibitor function should be carried out as an absence of function suggests a type II defect.
  - Complement studies are not a reliable tool for diagnosis of HAE in infants less than 1 year of age due to high variability of levels.
  - Complement studies for diagnosis must be performed when the patient is not receiving C1INH concentrate, because it will alter results. If it has been initiated, it should be discontinued for one week before diagnostic complement studies are obtained. Patients receiving androgens will often still have low C4 and C1INH levels, but if complement results are normal, androgens should be withheld for a week and testing repeated.
  - There are no routine laboratory tests to confirm diagnosis of HAE-nC1, though genetic testing may be helpful in confirming this diagnosis. The most common mutation linked to HAE-nC1 involves the F12 gene which can be detected by commercially available PCR assay.
- Kalbitor® carries a black box warning for anaphylaxis. Because of the risk of anaphylaxis, Kalbitor® should be administered by a health care provider with appropriate medical support to manage anaphylaxis and hereditary angioedema, patients should be monitored closely.
- Berinert® is made from human plasma and may carry the risk of transmission of infectious agents (e.g. viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent). Serious arterial and venous thromboembolic have also been reported.
- Ruconest® is a recombinant C1 inhibitor purified from the milk of genetically modified rabbits. While it does not carry the theoretical risk of viral transmission as with plasma-derived products, there is still warning for hypersensitivity reaction and serious arterial and venous thromboembolic events.

REFERENCE / RESOURCES:

1. Kalbitor® package insert. Burlington, MA: Dyax Corp.; 2021 Nov.
2. Berinert® package insert. Kankakee, IL: CSL Behring LLC.; 2021 Sept.
3. Ruconest package insert. Raleigh, NC: Salix Pharmaceuticals, Inc.; 2019 Oct.
4. Schneider L, Lumry W, Vegh A et al. Critical role kallikrein in hereditary angioedema pathogenesis: A clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clin Immunol*. 2007;120:416-22.
5. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J *Allergy Clin Immunol*. 2009;124:801-8.
6. Zuraw BL, Bernstein JA, Lang DM et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013;131(6):1491.
7. Lang DM, Aberer W, Bernstein JA et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109(6):395.
8. Magerl M, Germenis AE, Mass C et al. Hereditary Angioedema with Normal C1 Inhibitor. *Immunol Allergy Clin N Am*. 2017;37(3)571-584.
9. Bowen T, Cicardi M, Farkas H, et al. 2010 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Allergy, Asthma, and Clinical Immunology.* 2010; 6:24.
10. Cicardi M, Banerji A, Bracha F, et al. Icatibant, a New Bradykinin-Receptor Antagonist, in Hereditary Angioedema. N Engl J Med. 2010; 363:532-41.
11. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy 2014; 69:602.
12. 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.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM025.1223	HEMATOLOGICAL AGENTS ACUTE HEREDITARY ANGIOEDEMA THERAPY See Appendix 2 for medications covered by policy

APPENDIX 1: Complement Studies

HAE Type	C4 (10-40mg/dL)*	C1INH Protein (21-39mg/dL)	C1 Function (greater or equal to 68%)**	C1q (5.0-8.6mg/dL)
Type I	Low	Low	Low	Normal
Type II	Low	Normal or Elevated	Low	Normal
HAE-nC1 (Type III	Normal	Normal		Normal

*The normal range for C4 is extremely wide and may be reported as a concentration, absolute level, or percentage of normal. If the C4 level is presented in mg without a percent, 25 mg would be considered a normal level (100 percent), and levels less than 10 mg are strongly suggestive of C1INH deficiency (pathologic), while levels between 10 and 15 mg are possibly pathologic, and levels greater than 15 mg are not pathologic.

** 41-67% = equivocal, less than or equal to 40% = abnormal

APPENDIX 2: Dosage and Administration

Drug	HCPCS Code	How supplied	Dose for acute attack	Formulation	Administration
Berinert® (human C1INH)	J0597	Vial – 500 IU lyophilized powder	20 IU/kg IV	IV	Self or Health Care Provider
Kalbitor® (Ecallantide)	J1290	Three 10 mg/mL single-use vials packaged in a carton.	30 mg SQ in three 10 mg injections. May repeat the recommended dose once within a 24 hour period, if the attack symptoms persist.	SQ	Health care provider ONLY
Ruconest® (rhC1INH)	J0596	Vial - 2,100 IU lyophilized powder	<84 kg: 50 IU/kg; No more than two doses should be administered within a 24 hour period. ≥84 kg: 4,200 IU; No more than two doses should be administered within a 24 hour period.	IV	Self or Health Care Provider

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM026.1223	**HEMATOLOGICAL AGENTS** **ADAKVEO®** (crizanlizumab-tmca vial)
Effective Date: 2/1/2024	**Review/Revised Date**: 04/20, 10/20, 07/21, 11/21, 10/22, 11/23 (JH)
Original Effective Date: 06/20	**P&T Committee Meeting Date**: 04/20, 04/20, 06/20, 12/20, 08/21, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), all the following criteria must be met:
    a. Confirmed medical history or diagnosis of sickle cell disease
    b. Patient has experienced at least two sickle cell-related pain crises in the prior year
    c. Documentation that patient meets one of the following:
        i. Patient will continue taking hydroxyurea with the requested therapy and patient has been on a maximally tolerated dose of hydroxyurea for at least six months
        ii. Patient has had a therapeutic failure of hydroxyurea despite use of a maximally tolerated dose for at least six months
        iii. Patient has had an intolerance or contraindication to hydroxyurea (For many patients, myelosuppression is dose-dependent and reversible. Intolerance due to myelosuppression will only be considered if patient continues to experience myelosuppression despite dose adjustments)
2. For patients established on the requested agent within the previous year: Documentation that the number or severity of sickle cell-related pain crises has decreased from baseline

EXCLUSION CRITERIA:
Used in combination with voxelotor (Oxbryta®)

AGE RESTRICTIONS:
May be approved for patients 16 years of age and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist or a provider experienced with the treatment of sickle cell disease

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Crizanlizumab (Adakveo®) is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1. By binding to P-selectin, crizanlizumab inhibits interactions between endothelial cells, platelets, red blood cells, and leukocytes, which may result in decreased platelet aggregation, maintenance of blood flow, and minimized sickle cell-related pain crises.

FDA APPROVED INDICATIONS:
To reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease.

POSITION STATEMENT:
Sickle cell disease (SCD) is a common genetic disease, affecting about 100,000 people in the United States, resulting in a shortened life span of about 50 years in

severe subtypes, impaired quality-of-life, and increased healthcare utilization. The disease is characterized by chronic hemolytic anemia, vaso-occlusion, and progressive vascular injury affecting multiple organ systems. In patients with SCD, polymerization of deoxygenated hemoglobin leads to a cascade of pathologic events: erythrocyte sickling, vaso-occlusion, tissue ischemia, reperfusion injury, hemolysis, abnormal activation of inflammatory and oxidative pathways, endothelial dysfunction, increased oxidative stress, and activation of coagulation pathways. These abnormalities have acute and chronic clinical consequences across multiple organ systems, including acute pain episodes, chronic pain syndromes, acute chest syndrome, anemia, stroke and silent cerebral infarcts, cognitive dysfunction, pulmonary hypertension, and other clinical consequences. Vaso-occlusion leads to recurrent painful episodes (sickle cell crisis).

Hydroxyurea is a mainstay in the overall management of individuals with SCD, decreasing incidence of acute painful episodes, decreasing hospitalization rates, and prolonging survival. Recommendations for hydroxyurea per the 2014 NHLBI guidelines:

- All patients should be counseled on therapy
- Should be offered for all children nine months and older regardless of clinical severity
- Should be initiated in adults who meet any of the following:
- Have three or more sickle cell–associated moderate to severe pain crises in 12 months
- Have a history of severe or recurrent acute chest syndrome (ACS)
- Have sickle cell– associated pain that interferes with daily activities and quality of life
- Have severe symptomatic chronic anemia that interferes with daily activities or quality of life
- Should be stopped in pregnant and breastfeeding women

Myelosuppression is the major dose-liming toxicity with hydroxyurea. However, for most individuals, myelosuppression is predictable, dose-dependent, and reversible. Myelosuppression is used to adjust hydroxyurea dosing and can be easily controlled as long as there is regular hematologic monitoring and dose reduction for severe neutropenia, anemia, or thrombocytopenia.

The FDA approval of crizanlizumab was based on the SUSTAIN trial, which was a 52 week, randomized, placebo-controlled, double-blind study in 198 patients with SCD. Patients were randomized crizanlizumab 5 mg/kg, crizanlizumab 2.5 mg/kg, or placebo. The primary endpoint was the annual rate of VOCs leading to a healthcare visit for pain medication. Acute chest syndrome, hepatic sequestration, splenic

sequestration, and priapism (requiring a visit to a medical facility) were also considered to be VOC crisis events. Patients who received crizanlizumab 5 mg/kg had a lower median annual rate of VOC vs. patients who received placebo (1.63 vs. 2.98; p = 0.010). Based on this trial crizanlizumab may provide a benefit to patients by reducing acute pain crises. However, the long-term benefits of this therapy are currently unknown. Crizanlizumab does represent a new treatment option for a disease with limited therapies. It may be a reasonable option for those that are still having pain crises despite hydroxyurea use or for those that are not able to tolerate hydroxyurea.

The safety and efficacy of voxelotor and crizanlizumab given in combination has not been established and the combination of these therapies will not be approved at this time.

REFERENCE/RESOURCES:

1. Adakveo package insert. Novartis Pharmaceuticals Corporation. East Hanover, NJ: 2022 Sept
2. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel: Management of Sickle Cell Disease. *JAMA.* 2014;312(10):1033-1048.
3. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *The New England Journal of Medicine.* 2017;376(5):429-439.
4. National Heart Lung and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. 2014; https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease. Accessed: November 2, 2023.
5. Liles D, Cancado R, Kanter J, et al. Established Prevention of Vaso-Occlusive Crises with Crizanlizumab is Further Improved in Patients who Follow the Standard Treatment Regimen: Post Hoc Analysis of the Phase II Sustain Study. *Blood.* 2018;132(Supplement 1):1082.
6. Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *The New England Journal of Medicine.* 2019;381(6):509-519.
7. Field JJ, Vichinsky EP. Overview of the Management and Prognosis of Sickle Cell Disease. Last updated on 10/18/2023. In: UpToDate, Tirnauer JS (Ed), UpToDate, Waltham, MA, 2023.
8. Yawn BP, John-Sowah J. Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. Am Fam Physician. 2015;92(12):1069-1076.

9. Crizanlizumab, voxelotor, and l-glutamine for sickle cell disease: effectiveness and value: Evidence Report. Institute for Clinical and Economic Review. February 9, 2021. https://icer.org/wp-content/uploads/2021/02/ICER_SCD_Evidence-Report_031220-FOR-PUBLICATION.pdf

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCRES006.0623	**RESPIRATORY AGENTS** **ALPHA-1 PROTEINASE INHIBITORS** **Aralast NP®, Glassia®** **Prolastin®-C, Zemaira®** (human alpha-1 proteinase inhibitor)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 02/11, 06/11, 02/12, 06/13, 06/14, 06/15, 04/16, 05/17, 04/18, 05/19, 04/20, 04/21, 05/22, 04/23 (CJD) P&T Committee Meeting Date: 02/11, 06/11, 02/12, 06/13, 06/14, 10/14, 06/15, 06/16 , 06/17, 06/18, 06/19, 06/20, 06/21, 06/22, 06/23 Original Effective Date: 04/11 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Documentation of:

1. One of the following:
    a. Serum alpha-1 antitrypsin (AAT) concentrations less than 11 micromol/L (approximately 50 mg/dL by nephelometry or 80mg/dL by immunodiffusion)
    b. Patient has one of the following high-risk phenotypes by protease inhibitor (PI) typing: PI*ZZ, PI*Z(null), PI*(null,null)

AND

2. Diagnosis of emphysema with one of the following:
    a. Forced expiratory volume per one second (FEV-1) of 35 to 65% of predicted volume
    b. Rapid lung function decline as evidence by reduction of FEV-1 of 100 mL/year or greater

AND

3. Documentation that the patient has never smoked or has abstained from smoking for at least the previous six months

Reauthorization requires documentation of positive clinical response to therapy (e.g., reduction in exacerbations, reduced progression of emphysema as assessed by computed tomography (CT) densitometry, slowing of FEV-1 decline)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for six months and reauthorization will be approved for one year.

QUANTITY LIMIT:
60 mg/kg infused every seven days, subject to audit.
Note: Dose may be rounded down to the nearest gram (500 mg for Aralast®) within 10% of calculated dose.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCRES006	RESPIRATORY AGENTS ALPHA-1 PROTEINASE INHIBITORS Aralast NP®, Glassia® Prolastin®-C, Zemaira® (human alpha-1 proteinase inhibitor)

Human alpha$_1$-proteinase inhibitors (Aralast NP®, Glassia®, Prolastin®-C, and Zemaira®) contain alpha$_1$-antitrypsin (AAT) protein purified from pooled human plasma. These products are given intravenously to replace the deficient protein in patients diagnosed of alpha$_1$-proteinase inhibitor (A_1-PI) deficiency, which is a rare genetic disease affecting primary the liver and lung. The recommended dose is 60mg/kg IV once weekly.

Drug availability: Aralast NP powder 500 mg or 1000 mg vial, Glassia solution 1000 mg/50 mL vial, Prolastin-C powder 1000 mg vial, Prolastin-C solution 1000 mg/20 mL, Zemaira powder 1000 mg vial

FDA APPROVED INDICATIONS:
For chronic augmentation and maintenance therapy in adult patients with emphysema due to congenital deficiency of alpha$_1$-PI.

POSITION STATEMENT:
- Alpha$_1$-proteinase inhibitor (A_1-PI) deficiency, also known as alpha$_1$-antitrypsin (AAT) deficiency, is an autosomal, codominant, hereditary disorder characterized by low serum and lung levels of A_1-PI. Severe forms of the deficiency are frequently associated with slowly progressive, moderate to severe panacinar emphysema that most often manifests in the third to fourth decades of life, resulting in a significantly lower life expectancy. The rate of decline in lung function occurs earlier in smokers. Evidence to support augmentation therapy in current smokers is lacking.
- The *SERPINA1* gene encodes AAT and located on the 14th chromosome. The normal allele is *M* (proteinase [PI] genotype MM is normal). Severe cases of AAT deficiency are most commonly associated with people who are homozygous for the *Z* allele. Heterozygotes of the M allele (e.g., MZ, MS) are expected to produce a enough AAT to prevent developlement of emphasyema. Individuals with the SZ phenotype may be at increased susceptibility for lung disease but evidence is inconclusive.
- Augmentation therapy is not currently recommended for individuals who are heterozygous with serum AAT levels greater than 11 micromol/L or individuals without emphysema. Benefits of augmentation therapy with severe and mild lung disease is not clear.
- In patients with alpha $_1$-antitrypsin deficiency, the cause of the development of emphysema is not well understood; however, it is believed to be due to a chronic biochemical imbalance between neutrophil elastase (an enzyme capable of degrading elastin tissues) and alpha $_1$-PI (the principal inhibitor of neutrophil

elastase) that is deficient in alpha $_1$-antitrypsin disease. This imbalance appears to result in alveolar structures being unprotected from chronic exposure to elastase, which results in the progressive degradation of elastin tissues. Replacement therapy with alpha $_1$-PI reverses the biochemical abnormalities and brings the antineutrophil elastase capacity of the serum into the normal range in direct proportion to the serum concentrations of alpha$_1$-PI.

- Population studies suggest a minimum plasma threshold of 11µM/L (57 mg/dL by nephelometry) below which there is insufficient AAT to protect the lung. Emphysema is most common with ATT levels less than 9 micromol/L. Most patients below this level will have PiZ phenotype. Initiation of augmentation therapy should be considered with levels below the protective threshold in the setting of documented emphysema (reduced forced expiratory volume in 1 second [FEV_1]). The effect of augmentation therapy with an Alpha$_1$-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha$_1$-PI deficiency has not been demonstrated in randomized, controlled clinical trials.
- The Global Initiative for Chronic Obstructive Pulmonary Disease guidelines (GOLD) suggests alpha-1 antitrypsin augmentation therapy in never or ex-smokers with FEV1 of 35 to 60% predicted, based on observational studies. Meanwhile, the guidelines by the COPD Foundation recommend augmentation therapy in patients with AAT deficiency and FEV1 less than or equal to 65%. For patients with lung disease related to AAT deficiency but has FEV1 greater than 65%, a discussion with patient is recommended regarding potential benefits of reducing lung function decline despite high cost and lack of evidence for benefit.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with Alpha$_1$-PI treatments is not available.
- Alpha1-PI treatments are not indicated as therapy for lung disease in patients in whom severe Alpha$_1$-PI deficiency has not been established.
- Use in patients with immuneglobulin A (IgA) defiency with anitbodies against IgA is contraindicated due to increased risk for hypersensitivity.
- There are no studies to demonstrate that one medication has superiority over other alpha$_1$-PI products for safety or efficacy.

REFERENCES/RESOURCES:

1. Aralast NP [package insert]. Lexington, MA: Baxalta US Inc; 2018, Dec
2. VA/DoD clinical practice guideline for management of outpatient chronic obstructive pulmonary disease. 1999 Aug (revised 2007). NGC:006639.

3. Glassia® [Alpha$_1$-proteinase inhibitor (human)] prescribing information. Westlake Village, CA: Kamada Ltd and Baxter Healthcare Corporation; 2022, Mar.
4. Aralast NP®, In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
5. Hubbard, RC, Crystal RG. Augmentation therapy of alpha1-antitrypsin deficiency. *Eur Respir J Suppl*. 1990 ;9:44s-52s
6. DeMeo DL, Silverman EK. Alpha1-antitrypsin deficiency 2: genetic aspects of alpha(1)-antitrypsin deficiency: phenotypes and genetic modifiers of emphysema risk. *Thorax*. 2004;59(3): 259-64.
7. Prolastin®-C [Alpha$_1$-proteinase inhibitor (human)] prescribing information. Research Triangle Park, NC: Grifols Therapeutics Inc; 2020, May
8. Prolastin C®, In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
9. Abboud RT, Ford GT, Chapman KR. Emphysema in alpha1-antitrypsin deficiency: Does replacement therapy affect outcome? *Treat Respir Med*. 2005;4(1):1-8.
10. Global initiative for Chronic Obstructive Lung Disease. Available at: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Accessed April 21, 2021.
11. Zemaira® [Alpha$_1$-proteinase inhibitor (human)] prescribing information. Kankakee, IL: CSL Behring LLC. 2019 Apr.
12. Zemaira® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
13. Strnad P, McElvaney NG, Lomas DA. Alpha1-Antitrypsin Deficiency. *N Engl J Med*. 2020; 382: 1443-1455. DOI: 10.1056/NEJMra1910234
14. Sandhaus RA, Turino GT, Brantly ML, et al. The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult. *Journal of the COPD Foundation.* 2016; 3(3): 668-682. doi: 10.15326/jcopdf.3.3.2015.0182.
15. Alpha-1 antitrypsin deficiency. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/alpha-1-antitrypsin-deficiency. Published April 15, 2020. Accessed April 23, 2020.
16. Miravitlles M, Dirksen A, Ferrarotti I, *et al*. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency. *Eur Respir J.* 2017;50.
17. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818.

18. 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.
19. Teschler H. Long-term experience in the treatment of alpha-1 antitrypsin deficiency: 25 years of augmentation therapy. *Eur Respir Rev*. 2015;24:46.
20. McElvaney GN, Sandhaus RA, Miravitlles M *et al*. Clinical considerations in individuals with α_1-antitrypsin PI*SZ genotype. *Eur Respir J*. 2020 Jun 18;55(6):1902410.

CODES:

J0257= Glassia, Alpha 1-proteinase inhibitor, human 10mg IV, liquid
J0256= Aralast NP, Prolastin-C, Zemaira, Alpha 1-proteinase inhibitor, human 10mg IV, powder

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM037.1023	**HEMATOLOGICAL AGENTS** **ALTUVIIIO®** (Antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl vial)
Effective Date: 1/1/2024	**Review/Revised Date**:
Original Effective Date: 01/24	**P&T Committee Meeting Date**: 10/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization:

1. Diagnosis of congenital FVIII deficiency (hemophilia A)
2. Use for one of the following indications:
    a. On-demand treatment and control of bleeding episodes
    b. Perioperative management of bleeding
    c. Routine prophylaxis to reduce the frequency of bleeding episodes
3. Documentation of patient weight
4. Appropriate dosing per FDA-approved or compendia-supported guidelines

Reauthorization requires documentation of positive clinical response to therapy such as reduction in the number/severity of bleeds when use for routine prophylaxis

EXCLUSION CRITERIA: Use for treatment of von Willebrand disease (VWD)

AGE RESTRICTIONS: N/A

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM037.1023	HEMATOLOGICAL AGENTS **ALTUVIIIO®** (Antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl vial)

PRESCRIBER RESTRICTIONS: Must be prescribed by or in consultation with a hematologist.

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION: Antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl (Altuviiio®) is a recombinant antihemophilic factor fusion protein extended-half-life factor VIII replacement therapy, for use in adults and children with hemophilia A (congenital factor VIII deficiency). It is designed to extend the half-life of the FVIII molecule and sustain high factor VIII (FVIII) levels for most of the dosing interval. It is the first FVIII replacement therapy with once weekly dosing.

FDA APPROVED INDICATIONS:
Adults and children with hemophilia A (congenital factor VIII deficiency) for:

- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

POSITION STATEMENT:
Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of functional coagulation factor VIII. Affecting predominately males, the estimated number of males living with hemophilia (A or B) in the United States is between 30,000-33,000[10] with approximately 76% of them having hemophilia A. About 60% of

these individuals have the severe form of the disorder[5], which is defined as less than 1% of baseline clotting factor activity. Individuals with hemophilia (particularly those with severe disease) are at risk for life-threatening bleeding, including intracranial bleeding. Individuals often have bleeding following an injury and may also have frequent spontaneous bleeding episodes, most commonly into the joints (hemarthrosis) or muscles. Joint and muscle bleeds occur most frequently and can lead to substantial disability.

Prophylaxis with plasma-derived or recombinant standard half-life factor, extended half-life factor, or non-factor replacement emicizumab (Hemlibra®) to prevent bleeding is the current standard of care of patients with severe hemophilia to prevent musculoskeletal complications from recurrent joint and muscle bleeds[6,7]. This is typically started early in life before the age of 3. Patients who develop inhibitors may eradicate inhibitors through immune tolerance induction (ITI) therapy. Patients who do not respond to enhanced factor dosages or ITI may use bypassing agents or emicizumab. All available prophylaxis products can effectively prevent bleeding; however, each can have different patient responses, safety profiles (inhibitor development risks), costs, and product characteristics (half-life, effects on monitoring). The choice of prophylaxis product is made as a team evaluating the patient's specifics circumstances and needs. The World Federation of Hemophilia does not recommend a certain FVIII product over another but recommends prophylaxis at a dose and dosing interval to prevent hemarthrosis and spontaneous bleeding[6]. The goal of prophylaxis is to prevent bleeding at all times.

FVIII clotting factor concentrates can also be used for on-demand treatment and control of bleeding episodes as well as for the perioperative management of bleeding.

Current FVIII products have half-lives ranging from 8 to 22 hours and are dosed daily to every 3-4 days depending on the product and individual. Altuviiio has an extended half-life of approximately 40 – 48 hours and is the only FVIII product with once weekly dosing.

Approval of Altuviiio® was based on evidence from two phase 3, open label, multicenter, prospective trials of 52 weeks duration. The studies included individuals with severe hemophilia who have previously been exposed to a FVIII product. The XTEND-1 study included individuals 12 years of age or older. Arm A (N=133) received weekly prophylaxis with Altuviiio® and Arm B (N=26) received Altuviiio® on-demand for 16 weeks followed by prophylaxis for 26 weeks[4].

- Altuviiio® prophylactic use once weekly resulted in a treated annualized bleed rate (ABR) of 0.7 (95% CI: 0.52 to 0.97).

    - Switching from pre-study prophylaxis to Altuviiio® decreased the mean ABR from 2.96 to 0.69 (ABR ratio, 0.23; 95% CI, 0.13-0.42; p<0.0001) – key secondary endpoint
- In the XTEND-Kids study, for those less than 12 years of age (N=62), Altuviiio® prophylactic use once weekly resulted in estimated mean ABR of 0.89 (95% CI, 0.56 to 1.42)
- No inhibitors were developed during study periods

Long-term efficacy, long-term potential for inhibitor formation, and direct performance comparison to emicizumab-kxwh (Hemlibra®) and other factor VIII products are not yet known.

Altuviiio® has the highest estimated prophylaxis cost of a factor VIII replacement therapies and higher cost than emicizumab-kxwh (Hemlibra®). Compared to other factor VIII therapies, Altuviiio® has less frequent (once weekly) administration, a significantly longer average half-life of up to 48.2 hours and higher mean factor activity levels.

REFERENCE/RESOURCES:

1. Altuviiio package insert. Bioverativ Therapeutics Inc. Pharma, Waltham, MA: March 2023.
2. Altuviiio In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September 3, 2023.
3. Altuviiio In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed September 3, 2023.
4. von Drygalski A, Chowdary P, Kulkarni R, *et al*. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318.
5. National Hemophilia Foundation. Hemophilia A. Available at https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a (Accessed September 3, 2023)
6. Srivastava, A, Santagostino, E, Dougall, A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158.
7. “MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors: NBDF.” MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors, National Bleeding Disorders Foundation, 27 Apr. 2022.
8. Thornburg CD, Adamski K, Cook K, et al. Health care costs and resource

utilization among commercially insured adult patients with hemophilia A managed with FVIII prophylaxis in the United States. Journal of Managed Care & Specialty Pharmacy 2022 28:4, 449-460.

9. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 125771 BLA Clinical Review Memorandum. Available at https://www.fda.gov/vaccines-blood-biologics/altuviiio (Accessed September 3, 2023)
10. Centers for Disease Control and Prevention (CDC). A new study of hemophilia occurrence finds many more cases in the United States. Accessed August 24, 2023. https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-US.html

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCPSY006.0224	**PSYCOTHERAPEUTIC AND NEUROLOGICAL AGENTS** **ANTI-AMYLOID MONOCLONAL ANTIBODIES** See Table 1 for Medications
Effective Date: 4/1/2024	**Review/Revised Date**:
Original Effective Date: 04/24	**P&T Committee Meeting Date**: 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 10	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Medicare Part B:
Requests for Aduhelm (aducanumab-avwa) and Leqembi (lecanemab-irmb), for the treatment of Alzheimer's disease, may be covered when the following criteria are met:

1. **Initial authorization:**
    a. Documentation confirming diagnosis of mild cognitive impairment or early dementia caused by Alzheimer's disease
    b. Documentation confirming the presence of amyloid beta pathology prior to initiating treatment
    c. Medication is prescribed by a qualified physician with an appropriate clinical team and follow up care
    d. Member and/or prescriber is enrolled in an eligible registry/clinical trial in accordance with the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3))

2. **Reauthorization:**
    a. Member has obtained an MRI prior to subsequent infusions as outlined in the applicable package label. If radiographically observed ARIA occurs, treatment is adjusted based on type, severity, and presence of symptoms
    b. Continued enrollment in an eligible registry/clinical trial in accordance with the Centers for Medicare & Medicaid Services (CMS) National Coverage Determination (Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3))

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist or provider that specializes in the treatment of Alzheimer's disease

COVERAGE DURATION:
Initial and reauthorization will be approved for six months

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Aducanumab (Aduhelm®) and lecanemab (Leqembi®) are monoclonal antibodies that target the buildup of amyloid plaque in the brain.

FDA APPROVED INDICATIONS:

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCPSY006	PSYCOTHERAPEUTIC AND NEUROLOGICAL AGENTS ANTI-AMYLOID MONOCLONAL ANTIBODIES See Table 1 for Medications

Table 1. Drugs applicable to this policy

Drug	FDA Indication
Aducanumab-avwa (Aduhelm®)	For the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).
Lecanemab-irmb (Leqembi®)	For the treatment of Alzheimer's disease. Treatment should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.

POSITION STATEMENT:
Based on all currently available information, there is insufficient evidence of a clinical benefit and significant safety concerns. For Medicare Part B, coverage of the requested drug will be provided in accordance with CMS' National Coverage Determination, Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3), when the policy criteria outlined above are met.[14]

On July 6, 2023, the FDA granted traditional approval to lecanemab. As a result, Medicare broadened its coverage to enrolled Medicare members who are diagnosed with mild cognitive impairment or mild Alzheimer's disease dementia with documented evidence of beta-amyloid plaque on the brain. In addition, the medication must be prescribed by a physician who participates in a qualifying registry with an appropriate clinical team and follow-up care.[15] The Centers for Medicare & Medicaid Services (CMS) covers Food and Drug Administration (FDA) approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD) when furnished under coverage with evidence development (CED). Refer to the CMS Coverage with Evidence Development webpage for approved CED studies: https://www.cms.gov/medicare/coverage-evidence-development/monoclonal-antibodies-directed-against-amyloid-treatment-alzheimers-disease-ad

Cognitive assessments are utilized to evaluate patients presenting with memory loss. Examples of validated cognitive assessments include the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Clinical Dementia Rating (CDR) scale. Please note, not all providers agree on cut-offs for each stage of dementia, so it is important to take into consideration other health exams.

- Mini-Mental Status Exam (MMSE)[16, 17]
    - 30-point scale with items that assess orientation, memory, attention/concentration, language, and visuospatial function. The score relates to the member's level of dementia and are generally grouped as follows:
        - 25 - 30 suggests normal cognition
        - 20 - 24 suggests mild dementia
        - 13 - 20 suggests moderate dementia
        - Less than 12 suggests severe dementia
- Montreal Cognitive Assessment (MoCA)[18]
    - 30-point scale with items that assess delayed word recall, visuospatial/executive function, language, attention/concentration, orientation. Average scores for the following ranges are:
        - Mild Cognitive Impairment: 19 - 25
        - Mild Dementia: 11 - 21
        - Normal: 26 and above
- Clinical Dementia Rating (CDR) Scale [19, 20]
    - 5-point scale that assess memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The score relates to the member's level of dementia:
        - 0 = Normal
        - 0.5 = Very Mild Dementia
        - 1 = Mild Dementia
        - 2 = Moderate Dementia
        - 3 = Severe Dementia

Aducanumab (Aduhelm®)

- In November 2020, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted that the results from EMERGE did not provide sufficient evidence to support the effectiveness of aducanumab as a treatment for Alzheimer's disease, and recommended against the approval [3]
- An evidence report released by the Institute for Clinical and Economic Review (ICER) found there is insufficient evidence to determine whether or not aducanumab slows the loss of cognition in patients with Alzheimer's, and there is

uncertainty if it will provide a benefit to patients that would outweigh the potential risks and harms of treatment [4]

- On June 7, 2021, the FDA approved aducanumab (Aduhelm®) for the treatment of Alzheimer's disease. This indication was approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with aducanumab. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials
- On July 8, 2021 the FDA updated the broad indication to specify that treatment should only be initiated in patients with mild forms of Alzheimer's disease as this was the population treated in clinical trials; no safety and effectiveness data is available on initiating treatment in earlier or later stages of the disease than were studied
- Efficacy for aducanumab was evaluated in two, 18-month, double-blind, randomized, placebo controlled, parallel group studies (EMERGE and ENGAGE) in patients with mild cognitive impairment or mild Alzheimer's disease. Both studies were terminated early based on interim analysis showing the trials would not meet their primary endpoints[1,2]
    - Upon subsequent data analysis, it was announced that EMEREGE met the primary endpoint for a subset of patients, while ENGAGE did not.
    - In EMERGE, high-dose aducanumab was associated with statistically significant change from baseline in Clinical Dementia Rating-Sum of Boxes (CDR-SB) compared to placebo at week 78 (treatment difference of -0.39 [-22%], p = 0.0120). Low-dose aducanumab was numerically better than placebo, but the difference was not statistically significant
    - In ENGAGE, no statistically significant difference was observed in the aducanumab treated and placebo-treated patients for the CDR-SB endpoint at week 78
    - A subgroup of patients from EMERGE and ENGAGE were evaluated for changes in key biomarkers using positron emission tomography (PET) and cerebrospinal fluid assays. Individuals receiving high-dose demonstrated significant reductions in beta amyloid plaques compared with placebo
    - The discordant results of these identically designed trials have provided insufficient evidence to support that the lowering of beta amyloid plaque yields a clinical benefit of improved cognition and delayed Alzheimer's disease progression
    - The length of these trials are also insufficient to determine how effective aducanumab is at treating Alzheimer's disease as cognitive decline associated with MCI and mild Alzheimer's disease dementia often spans years

- There are significant safety concerns with aducanumab. The most common adverse events (AEs) included amyloid related imaging abnormalities (ARIA), headache, fall, and diarrhea[1]
    - In the clinical trials ARIA, (brain hemorrhage or brain edema or both) was observed in 41% of patients treated with high dose (10 mg/kg) of aducanumab
    - Approximately one in 10 patients will need to stop treatment due to concerns related to ARIA
    - One patient in the aducanumab arm of an earlier phase trial died of an intracranial hemorrhage determined to be related to study treatment.
    - Per the package label, it is recommended to obtain a recent (within one year) brain magnetic resonance imaging (MRI) prior to initiating treatment followed by subsequent MRI's prior to the 5th, 7th, 9th and 12th infusions
        - ARIA-E
            - For patients with evidence of moderate or severe ARIA-E on MRI, it is recommended to suspend dosing. If there is evidence of mild ARIA-E on MRI but moderate or severe clinical symptoms are present, it is recommended to suspend dosing
        - ARIA-H
            - For patients with evidence of moderate or severe ARIA-H on MRI, dosing should be suspended. If patient is symptomatic, dosing should be suspended regardless of MRI severity

Lecanemab (Leqembi®)

- Low quality evidence based on one phase 2b and phase 3 trial that lecanemab may slow disease progression for patients with early Alzheimer's disease
    - Study 201[9]: Accelerated approval based on surrogate endpoint (beta amyloid burden)
        - Lecanemab had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint (change in Alzheimer's Disease Composite Score (ADCOMS)) relative to placebo at 12 months. The primary endpoint, requiring an 80% probability of ≥25% reduction in clinical decline compared to placebo, was not met
        - Key secondary endpoint analysis demonstrated that lecanemab reduced brain amyloid and sustained activity over the 18-month period for several clinical measures
    - CLARITY AD (phase 3)[10]:

        - The change from baseline at 18 months in the primary endpoint (change in Clinical Dementia Rating-Sum of Boxes (CDR-SB)) was less with lecanemab than with placebo, with a difference of 0.45 (95%CI -0.67 to -0.23; p<0.001)
            - Definition of clinically meaningful effects in the primary endpoint are not established. While the difference of 0.45 points between groups on the CDR-SB scale is statistically significant, this may or may not result in a clinically significant change[11, 12]
        - Key secondary endpoints demonstrated greater reduction in brain amyloid burden with lecanemab than with placebo
    - Phase 3 clinical trial demonstrated moderately less decline on cognition and function scales than placebo but was associated with adverse events. At this time it is unknown if these statistically significant results translate to clinically meaningful effects. Longer trials are necessary to determine the efficacy and safety of lecanemab in early Alzheimer's disease
- Institute for Clinical and Economical Review (ICER): Lecanemab for Early Alzheimer's Disease Final Policy Recommendations [13]
    - ICER's report rates treatment with lecanemab in patients with early Alzheimer's disease as "promising but inconclusive"
        - Moderate certainty of a small or substantial net health benefit, small likelihood of a negative net health benefit
        - The net health benefits of lecanemab in patients with early Alzheimer's disease may be small or even substantial, but there remains a possibility of net harm from ARIA
        - Uncertain that targeting amyloid burden is an appropriate surrogate outcome for clinical benefit
        - Cost-effective annual list price range of $8,900 to $21,500
- Safety[6]
    - Warnings and precautions: amyloid related imaging abnormalities (ARIA)
        - In Study 201, ARIA (symptomatic and asymptomatic events) occurred in 12% of patients treated with lecanemab and 5% treated with placebo. In CLARITY-AD, ARIA occurred in 21% of patients treated with lecanemab and 9% treated with placebo.
        - Apolipoprotein E4 (ApoE4) homozygous gene carriers have an increased risk of developing ARIA
        - ARIA can occur at any time, though in clinical trials most events occurred early in treatment (within the first seven doses). It is recommended to obtain a recent (within one year) brain magnetic

resonance imaging (MRI) prior to initiating treatment followed by subsequent MRI's prior to the 5th, 7th, and 14th infusions
    - ARIA-E
        - For patients with evidence of moderate or severe ARIA-E on MRI, it is recommended to suspend dosing. If there is evidence of mild ARIA-E on MRI but moderate or severe clinical symptoms are present, it is recommended to suspend dosing
    - ARIA-H
        - For patients with evidence of moderate or severe ARIA-H on MRI, dosing should be suspended. If patient is symptomatic, dosing should be suspended regardless of MRI severity
- Due to risks of intracerebral hemorrhage with therapy, caution is recommended when considering use of an antithrombotic or a thrombolytic agent (tissue plasminogen activator) in a patient being treated with lecanemab
- Most common adverse effects include infusion related reactions

REFERENCE/RESOURCES:

1. Aduhelm [package insert]. Cambridge, MA; Biogen Inc; July 2021
2. Knopman DS, Jones DT, and Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimer's Dement. 2020; 1-6
3. U.S. Food and Drug Administration. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee – Aducanumab. November 6, 2020. Accessed July 30, 2021. https://www.fda.gov/advisory-committees/advisory-committeecalendar/november-6-2020-meeting-peripheral-and-central-nervous-system-drugsadvisory-committee-meeting
4. Lin GA, Whittington MD, Synnott PG, McKenna A, Campbell J, Pearson SD, Rind DM. Aducanumab for Alzheimer's Disease: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, June 30, 2021. https://icer.org/assessment/alzheimers-disease-2021/.
5. Kuller LH, Lopez OL. ENGAGE and EMERGE: Truth and consequences? Alzheimer's Dement. 2021 Apr;17(4):692-695. doi: 10.1002/alz.12286. Epub 2021 Mar 3. PMID: 33656288.
6. Leqembi® package insert. Nutley, NJ: Eisai Inc.; 2023 July.
7. Leqembi® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed January 30, 2023.

8. Leqembi® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed July 18, 2023.
9. Swanson CJ, Zhang Y, Dhadda S, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. Alzheimers Res Ther. 2021 Apr 17;13(1):80. doi: 10.1186/s13195-021-00813-8. Erratum in: Alzheimers Res Ther. 2022 May 21;14(1):70.
10. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2022 November 29. DOI:10.1056/NEJMoa2212948
11. Lansdall CJ, McDougall F, Butler LM, et al. Establishing Clinically Meaningful Change on Outcome Assessments Frequently Used in Trials of Mild Cognitive Impairment Due to Alzheimer's Disease. J Prev Alzheimers Dis. 2023;10(1):9-18.
12. Andrews JS, Desai U, Kirson NY, et al. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimer's Dement (N Y). 2019 Aug 2;5:354-363.
13. Lin GA, Whittington MD, Wright A, Agboola F, Herron-Smith S, Pearson SD, Rind DM. Lecanemab for Early Alzheimer's Disease Final Evidence Report. Institute for Clinical and Economic Review, April 17, 2023.
14. Centers for Medicare & Medicaid Services Medicare Coverage Database. National Coverage Determination: Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (200.3). December 12, 2022. Available at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=375&ncdver=1&keyword=amyloid&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed July 18, 2023.
15. Centers for Medicare & Medicaid Services. Statement: Broader Medicare Coverage of Leqembi Available Following FDA Traditional Approval. Found on the internet at https://www.cms.gov/newsroom/press-releases/statement-broader-medicare-coverage-leqembi-available-following-fda-traditional-approval
16. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res.1975;12(3):189-98.
17. Tsoi KK, Chan JY, Hirai HW, Wong SY, Kwok TC. Cognitive Tests to Detect Dementia: A Systematic Review and Meta-analysis. JAMA Intern Med. 2015 Sep;175(9):1450-8. doi: 10.1001/jamainternmed.2015.2152. PMID: 26052687.

18. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x. Erratum in: J Am Geriatr Soc. 2019 Sep;67(9):1991. PMID: 15817019.
19. O'Bryant SE, Waring SC, Cullum CM, et al. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. Arch Neurol. 2008;65(8):1091-1095.
20. CDR Dementia Staging Instrument. Knight Alzheimer Disease Research Center. https://knightadrc.wustl.edu/cdr/cdr.htm. Accessed: August 18, 2023.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCBIO009.0623	**BIOLOGICAL** **BENLYSTA®** (belimumab intravenous powder for solution, belimumab subcutaneous solution)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/12, 04/13, 10/13, 12/14, 12/15, 10/16, 08/17, 11/17, 10/18, 11/19, 10/20, 01/21, 05/21, 08/21, 04/22, 04/23 (JH) P&T Committee Meeting Date: 08/11, 12/13, 12/14, 12/15, 12/16, 10/17, 12/17, 12/18, 12/19, 12/20, 02/21, 06/21, 10/21, 06/22, 06/23 Original Effective Date: 10/11 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 9

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”)

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For patients initiating therapy for Systemic Lupus Erythematous (SLE) and active lupus nephritis, all the following must be met:

1. Documented diagnosis of Systemic Lupus Erythematosus (SLE) or active lupus nephritis by a rheumatologist or nephrologist
   AND
2. Documentation of laboratory test results indicating that patient has presence of auto-antibodies, defined as one of the following:
   a. Positive Antinuclear antibody (ANA)
   b. Positive anti-double-stranded DNA (anti-dsDNA) on two or more occasions, OR if tested by ELISA, an antibody level above laboratory reference range
   c. Positive anti-Smith (Anti-Sm)
   d. Positive anti-Ro/SSA and anti-La/SSB antibodies

AND

3. Documented failure of an adequate trial (such as inadequate control with ongoing disease activity and/or frequent flares), contraindication, or intolerance to at least one of the following:
    a. For SLE without Active Lupus Nephritis:
        i. Oral corticosteroid(s)
        ii. Azathioprine
        iii. Methotrexate
        iv. Mycophenolate mofetil
        v. Hydroxychloroquine
        vi. Chloroquine
        vii. Cyclophosphamide
    b. For SLE with Active Lupus Nephritis:
        i. mycophenolate for induction followed by mycophenolate for maintenance, OR
        ii. cyclophosphamide for induction followed by azathioprine for maintenance.
4. Documentation that patient will continue to receive standard therapy (e.g., corticosteroids, hydroxychloroquine, mycophenolate, azathioprine, methotrexate)

For patients established on therapy, the following criteria must be met: :

1. Documentation of positive clinical response to belimumab (e.g. improvement in functional impairment, decrease of corticosteroid dose, decrease in pain medications, decrease in the number of exacerbations since prior to start of belimumab, reduction of renal related events)
2. Patient currently receiving standard therapy for SLE and active lupus nephritis

EXCLUSION CRITERIA:

Belimumab will not be approved if any of the following are present:

1. Severe active central nervous system lupus
2. Current use of other biologic immunomodulator
3. Documentation of previous use of dialysis in the past 12 months or currently using dialysis
4. Concurrent use of voclosporin (Lupkynis®) or anifrolumab (Saphnelo®**)**

AGE RESTRICTIONS:

Age five years and older for IV infusion
Age 18 years and older for subcutaneous injection

PRESCRIBER RESTRICTIONS:

Must be prescribed by or in consultation with a rheumatologist, nephrologist or a provider with experience treating SLE or lupus nephritis

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for 12 months

QUANTITY LIMIT:
- Belimumab 200 mg/mL single-dose prefilled auto injector and glass syringe for subcutaneous injection: 4 mL per 28 days
    - Adults with SLE without active lupus nephritis allowed loading dose: none
    - Adults with SLE with active lupus nephritis allowed loading dose: 400-mg dose (two 200-mg injections) once weekly for four doses, then 200 mg once weekly thereafter
- Belimumab powder for solution for IV use only (subject to audit): Initial dose of 10 mg/kg IV every two weeks for three doses and then continue every four weeks thereafter as maintenance
    - Applicable to adults with SLE or active lupus nephritis and pediatric patients with SLE
- Belimumab IV is available as:
    - 120 mg in a 5-mL single-dose vial
    - 400 mg in a 20-mL single-dose vial for injection
- Correct vial combination for each patient should be calculated to minimize waste (see Appendix 1)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Belimumab is a recombinant human monoclonal antibody that binds to and inhibits B-lymphocyte stimulator (BLyS), which is a potent B cell-activating factor that has been associated with systemic lupus erythematosus (SLE) and correlates with disease activity.

Belimumab is available as an intravenous infusion in patients aged five years and older or a self-administered subcutaneous injection for patients aged 18 years and older. It is FDA-approved for patients who are receiving standard therapy for SLE and active lupus nephritis Belimumab should not be used as monotherapy.

Belimumab has not been studied and is not recommended in severe active central nervous system lupus, or in combination with other biologics.

FDA APPROVED INDICATIONS:
- Treatment of patients aged five years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy
- Treatment of patients aged five years and older with active lupus nephritis who are receiving standard therapy

Limitations of Use: The efficacy of belimumab has not been evaluated in patients with severe active central nervous system lupus

POSITION STATEMENT:
The efficacy and safety of belimumab IV was established in two randomized, double-blind, multicenter, Phase III, pivotal studies. In both studies, patients were required to meet the American College of Rheumatology (ACR) Criteria for SLE and have autoantibody-positive (i.e. antinuclear antibody [ANA] titer ≥1:80 or anti- dsDNA antibody ≥ 30IU/ml) with active, but stable, SLE (defined as Safety of Estrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index [SELENA-SLEDAI] score of 6 or greater). All patients were also required to be receiving a stable regimen with fixed doses of standard regimen for SLE (i.e. corticosteroids, immunosuppressants, antimalarials, or nonsteroidal anti-inflammatory drugs [NSAIDs]) for at least 30 days. Addition of angiotensin-converting enzyme (ACE) inhibitors after Month 4 or statins after Month 6 were prohibited. Patients were randomized in a 1:1:1 ratio to receive belimumab 10 mg/kg, belimumab 1 mg/kg, or placebo. Major exclusion criteria were severe lupus kidney disease, treatment for CNS lupus in the past 60 days, past treatment with a B-cell targeted agent, pregnancy, or treatment with IV cyclophosphamide within the past 6 months. Patients were stratified by SELENA-SLEDAI score, proteinuria, and race. For the

primary efficacy evaluation, those patients requiring rescue medications were considered non-responders.

The primary endpoint for both studies was the SLE Responder Index (SRI) at Week 52. There are three individual components of the SRI including: 1) SELENA-SLEDAI score, a validated SLE disease activity index that captures the patient's condition over the ten days prior to the visit; 2) Physician's Global Assessment (PGA) of general health status rated on a visual analog scale; and 3) The British Isles Lupus Assessment Group (BILAG) Classic Index, assessed to measure organ-specific changes in disease activity over the past 28 days. The BILAG assigns each domain a score from A through E with an "A" score representing disease activity sufficient to require intensification of therapy with high-dose steroids or immunosuppressants; a "B" score representing moderate, reversible manifestations requiring antimalarials, NSAIDs, or low dose steroids; and scores C through E, representing stages of stable or no disease activity. To meet the primary endpoint, patients were required to have a reduction of ≥ 4 points (weighted from baseline) in the SELENA-SLEDAI score AND no worsening in general health status measured by the PGA AND no new BILAG A organ domain score and no more than one new BILAG B organ domain score compared with baseline at the time of assessment. Both studies reported a significant response in belimumab treated subjects as compared to placebo as measured by SRI at week 52. However, this response was no longer statistically significant at week 76. Further studies are needed to determine durability of response. The Phase III pivotal studies had small numbers of black patients (n = 148), but the results suggested that black patients did not respond to treatment with belimumab. In a Phase II study, black patients (n = 106) appeared to respond to belimumab. The reasons for the difference in response in the Phase II and III studies are unknown. Additional studies are therefore planned to evaluate the safety and efficacy of belimumab in black patients.

The safety and efficacy of belimumab subcutaneous injection for SLE was established in a phase III 52 week, large, multicenter, randomized, double blind, placebo-controlled trial. Patients were required to have a diagnosis of SLE according to the American College of Rheumatology criteria, with antinuclear antibodies and/or anti–double-stranded DNA (anti-dsDNA) antibodies and a score of ≥8 the SELENA version of the SLEDAI at screening. SLE Responder Index (SRI) response with belimumab versus placebo was 61.4% vs 48.4%, respectively (P = 0.0006). In the belimumab group more patients were able to reduce their corticosteroid dosage by 25% or greater (to ≤7.5 mg/day) during weeks 40-52 (18.2% vs 11.9%; P = 0.0732), compared with placebo. There currently are no studies comparing efficacy of the IV infusion to the subcutaneous injection.

According to the 2019 update of EULAR recommendations, belimumab may provide beneficial effects in patients with SLE who are unable to obtain adequate control with standard therapies or unable to taper systemic corticosteroids daily dose to acceptable levels (daily maximum prednisone-equivalent dose of 7.5 mg)

The FDA granted approval to belimumab IV infusion for treatment of SLE in pediatric patients in April 2019. Approval was based on a 52-week multicenter, randomized, double-blind, placebo-controlled trial with 93 pediatric patients (age 5 to 17 years) and the composite primary endpoint was SLE response index (SRI-4) at Week 52. The proportion of patients achieving SRI-4 index was higher in patients who received belimumab plus standard therapy, compared to those who received placebo (52.8% vs. 43.6%, OR 1.49, 95% CI 0.64-3.46). Severe flares were also less frequent in the belimumab group compared to placebo group (OR 0.38, 95% CI 0.18, 0.82). Safety profile was similar to those reported in trials with adult patients.

The FDA granted approval to belimumab IV infusions for treatment of active lupus nephritis in December 2020. Approval was based on a 104-week randomized, double-blind, placebo-controlled trial in 448 patients with active proliferative and/or membranous lupus nephritis. The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at Week 104, defined as a response at Week 100 confirmed by a repeat measurement at Week 104 of the following parameters: urine protein:creatinine ratio (uPCR) ≤0.7 g/g and estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 or no decrease in eGFR of >20% from pre-flare value. The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving belimumab plus standard therapy compared with placebo plus standard therapy. In the belimumab plus standard therapy group, 43% vs. 32% in the placebo group of patients were primary efficacy renal responders with an odds ratio of 1.6 (1.0, 2.3) p=0.031. Also, more patients in the belimumab group had a complete renal response compared to the placebo group (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P = 0.02 The risk of a renal-related event or death was lower among patients who received belimumab than among those who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P = 0.001). The safety profile of belimumab was consistent with that in previous trials.

Institute for Clinical and Economic Review (ICER):
ICER conducted a review of belimumab added to standard induction therapy (high-dose corticosteroids combined with either mycophenolate mofetil or cyclophosphamide) for the initial treatment of patients with lupus nephritis (LN). Belimumab has demonstrated an increase in complete renal response (CRR) and primary efficacy renal response (PERR) at two years compared to standard therapy alone, with benefits seen after the first year appearing stable at year two. There

were no significant increases in adverse events or discontinuations compared with standard induction therapy for LN. There was a greater proportion of patients receiving 5 mg or less of prednisone in the belimumab group (36.8% versus 27.8%). ICER does note uncertainty of how these short-term assessments of renal response equate to clinically significant long-term outcomes for patients. The review also points out the limited data on the efficacy among different racial and ethnic groups. The incremental cost-effectiveness ratio was estimated to be approximately $90,000 per quality adjusted life year (QALY), and $78,000 per equal value of life years gained (evLYG). ICER concludes that belimumab provides improved clinical outcomes for patients and may offer important benefits beyond those directly measured in clinical and cost-effectiveness analyses. The price of belimumab is judged to be reasonable for coverage of patients included in the FDA indication.

Outcome	One Year		Two Years	
	Placebo	Belimumab	Placebo	Belimumab
CRR	25.5%*	32.5%*	19.7%	30.0%
PERR	35.4%	46.6%	32.0%	43.0%

*One-year results are approximations read from Figure 1 in the NEJM publication

REFERENCES:

1. Benlysta® package insert. Rockville, MD: Human Genome Sciences, Inc.; 2023 Feb.
2. Data on file. Benlysta (benlimumab) infusion: BLA125370. Updated September 20, 2013. Accessed November 19, 2019. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125370Orig1s000SumR.pdf
3. Balluz L, Philen R, Ortega L, et al. Investigation of systemic lupus erythematosus in Nogales, Arizona. *Am J Epidemiol.* Dec 1 2001;154(11):1029-36.
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. doi: 10.1136/annrheumdis-2019-215089. Epub 2019 Mar 29
5. Gladman DD, Urowitz MG, Kagal A, Hallett D. Accurately describing changes in disease activity in Systemic Lupus Erythematosus. *J Rheumatol*. 2000 Feb;27(2):377-9.
6. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum.* Jan 2008; 58(1):15-25.

7. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: A critical review. *J Autoimmun*. 2014; 48-49: 10-3. doi: 10.1016/j.jaut.2014.01.004. Epub 2014 Jan 21
8. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. *Medicine (Baltimore).* May 2006;85(3):147-56.
9. Liang MH, Fortin P, Schneider M, Abrahamowicz M, et al. The American College of Rheumatology Response Criteria for Systemic Lupus Erythematosus Clinical Trials: Measures of Overall Disease Activity. *Arthritis Rheum.* 2004; 50(11):3418-26.
10. Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomized, placebo-controlled, phase 3 trial. *Lancet.* 2011 Feb 26: 377(9767):721-731.
11. Stohl W, Schwarting A, Okada M, Scheinberg M, et al. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study Arthritis Rheumatol. 2017 May; 69(5):1016-1027
12. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology Guidelines for Screening, Treatment, and Management of Lupus Nephritis. *Arthritis Care and Research.* 2012 June; 64(6):797-808
13. Ruperto N, Abud-Mendoza C, Viola DO, et al. FRI0181 The Pluto Study: Intravenous Belimumab in Children with Systemic Lupus Erythematosus (Poster Presentation). *Ann Rheum Disease*. 2019; 78(suppl 2). http://dx.doi.org/10.1136/annrheumdis-2019-eular.4884
14. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, Amoura Z, Yu X, Mok CC, Santiago MB, Saxena A, Green Y, Ji B, Kleoudis C, Burriss SW, Barnett C, Roth DA. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128. doi: 10.1056/NEJMoa2001180.
15. Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value. Institute for Clinical and Economic Review. Available at: https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Final-Evidence-Report_041621.pdf. (Accessed on April 27, 2022).
16. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. The New England journal of medicine. 2020;383(12):1117-1128.

Appendix 1: Vial Combination for IV Infusion

Patient Weight		Dose of BENLYSTA	Vial Combination
lb	kg	mg	
100	45.5	455	4
105	47.7	477	4
110	50.0	500	1 1
115	52.3	523	5
120	54.5	545	5
125	56.8	568	5
130	59.1	591	5
135	61.4	614	2 1
140	63.6	636	2 1
145	65.9	659	6
150	68.2	682	6
155	70.5	705	6
160	72.7	727	3 1
165	75.0	750	3 1
170	77.3	773	2
175	79.5	795	2
180	81.8	818	7
185	84.1	841	4 1
190	86.4	864	4 1
195	88.6	886	1 2
200	90.9	909	1 2
205	93.2	932	8
210	95.5	955	8
215	97.7	977	5 1
220	100.0	1000	5 1
225	102.3	1023	2 2
230	104.5	1045	9
235	106.8	1068	9
240	109.1	1091	6 1
245	111.4	1114	6 1
250	113.6	1136	3 2

120 mg (in 5-mL vial) 400 mg (in 20-mL vial)

Brand Name	Generic Name	HCPCS Code
Benlysta® Vial	belimumab	J0490

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU030.1223	**NEUROMUSCULAR DRUGS** **BOTULINUM TOXIN** See FDA Approved Indications for Covered Drugs
Effective Date: 2/1/2024	**Review/Revised Date**: 05/19, 08/19, 11/19, 03/20, 04/20, 01/21, 07/22, 07/23, 12/23 (BS)
Original Effective Date: 09/19	**P&T Committee Meeting Date**: 06/19, 08/19, 10/19, 12/19, 02/20, 04/21, 08/21, 08/22, 08/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
The following Centers for Medicare & Medicaid Service (CMS) guidelines should be utilized for medical necessity coverage determinations. Click the link provided in the table below to access applicable medical necessity criteria. All listed guidelines apply.

Service	Medicare Guidelines
Botulinum Toxin	Local Coverage Determination (LCD) criteria – LCD35172

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Botulinum toxin injections are used to treat various focal muscle spastic disorders and excessive muscle contractions such as dystonias, spasms, twitches, etc. These drugs produce a presynaptic neuromuscular blockade by preventing the release of acetylcholine from the nerve endings. The resulting chemical denervation of muscle produces local paresis or paralysis and allows individual muscles to be weakened selectively. Botulinum toxins have the advantage of being potent neuromuscular blocking agents with good selectivity and duration of action.

Botulinum toxins types A and B are neurotoxins produced by Clostridium Botulinum. Botulinum Toxin Type A and Botulinum Toxin Type B have many similarities and as experience has been gained, medical consensus has gradually developed that the two toxins have similar, but not identical, properties. Each botulinum toxin product is pharmacologically and clinically distinct, and therefore, not interchangeable with any other botulinum toxin product. As a result, approved indications for the two toxins differ.

The rationale for treatment is to create temporary paralysis of sufficient depth and duration that the injected muscles become slightly atrophied and stretched. The antagonist muscle shortens simultaneously taking up the slack created by agonist paralysis. After several weeks enervation to the injected muscle returns. The safety and efficacy of long term use of Botox, Myobloc, Dysport or Xeomin is unknown.

FDA APPROVED INDICATIONS:
Botox® (onabotulinumtoxinA)
- Bladder Dysfunction in adults
- Chronic Migraine in adults
    - Limitations of Use: Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies
- Spasticity in patients two years of age and older
    - Limitations of Use: has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture.
- Cervical dystonia in adults
- Primary axillary hyperhidrosis in adults that is inadequately managed with topical agents
    - Limitations of use:
        - Safety and effectiveness for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and

blepharoptosis may occur in patients who receive treatment for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease
    - Safety and effectiveness have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18
- Blepharospasm and strabismus associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older.
- Pediatric Detrusor Overactivity associated with a Neurologic Condition

Dysport® (abebotulinumtoxinA)
- Glabellar Lines
- Cervical dystonia in adults
- Spasticity in patients two years of age and older

Myobloc® (rimabotulinumtoxinB)
- Cervical dystonia in adults
- Chronic sialorrhea in adults

Xeomin® (incobotulinumtoxinA)
- Chronic Sialorrhea in patients two years of age and older
- Glabellar Lines
- Cervical dystonia in adult patients
- Upper limb spasticity in adult patients
- Upper limb spasticity in pediatric patients two to 17 years of age, excluding spasticity caused by cerebral palsy
- Blepharospasm in adult patients

Jeuveau® (prabotulinumtoxinA-xvfs)
- Glabellar Lines

Daxxify® (DaxibotulinumtoxinA-lanm)
- Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults
- Cervical dystonia in adults

POSITION STATEMENT:

Coverage Guidance from LCD: “Botulinum toxin injections are used to treat various focal muscle spastic disorders and excessive muscle contractions such as dystonias, spasms, twitches, etc. These drugs produce a presynaptic neuromuscular blockade by preventing the release of acetylcholine from the nerve endings. The resulting chemical denervation of muscle produces local paresis or paralysis and allows individual muscles to be weakened selectively. Botulinum toxins have the advantage of being potent neuromuscular blocking agents with good selectivity and duration of action.

Botulinum Toxin Type A (Botox-onabotulinumtoxinA, Xeomin -incobotulinumtoxinA, Dysport-abotulinumtoxinA, and daxibotulinumtoxinA-lanm) are derived from a culture of Hall strain Clostridium Botulinum. Botulinum Toxin Type B (Myobloc – rimabotulinumtoxinB) is derived from the Bean strain of Clostridium Botulinum. Type B has the same action on neuromuscular conduction (blockade) as Type A.

Botulinum Toxin Type A and Botulinum Toxin Type B have many similarities and as experience has been gained, medical consensus has gradually developed that the two toxins have similar, but not identical, properties. Each botulinum toxin product is pharmacologically and clinically distinct, and therefore, not interchangeable with any other botulinum toxin product. As a result, approved indications for the two toxins differ. This A/B MAC has determined that the separate accepted indications for the four toxins will be combined into a single list of covered indications in this Local Coverage Determination (LCD) policy. However, it is the responsibility of providers to use each drug in accordance with the FDA approved indications unless there are valid and documented reasons stating why the unapproved/off label form is used. “Providers should consult the package insert of each neurotoxin to identify the FDA approved indications for each product.”

BILLING GUIDELINES

See the associated local coverage article (LCA) for additional billing and coding guidance:

Billing and Coding: Botulinum Toxin Types A and B (A57186)

CPT/HCPCS CODES

Medicare Part B Only	
Prior Authorization Required	
31513	Laryngoscopy, indirect; with vocal cord injection
31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic
43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance

43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
46505	Chemodenervation of internal anal sphincter
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64640	Destruction by neurolytic agent; other peripheral nerve or branch
64642	Chemodenervation of one extremity; 1-4 muscle(s)
64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
64644	Chemodenervation of one extremity; 5 or more muscles
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscles (List separately in addition to code for primary procedure)
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenervation of trunk muscle(s); 6 or more muscles
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (eg, scalp, face, neck), per day
67345	Chemodenervation of extraocular muscle
95873	Electrical stimulation for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)
95874	Needle electromyography for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)
J0585	Injection, onabotulinumtoxina, 1 unit
J0586	Injection, abobotulinumtoxina, 5 units
J0587	Injection, rimabotulinumtoxinb, 100 units
J0588	Injection, incobotulinumtoxin a, 1 unit
Unlisted Codes All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**	
43499	Unlisted procedure, esophagus
64999	Unlisted procedure, nervous system

REFERENCE/RESOURCES:

1. Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD): Botulinum Toxin Types A and B (L35172). Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=35172&ver=68&keyword=botulinum%20toxin&keywordType=starts&areaId=all&docType=NCD,MCD,F,P&contractOption=all&sortBy=relevance&bc=1 (Accessed July 8, 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH020M.1023	**MISCELLANEOUS PRODUCTS** **CONTINUOUS GLUCOSE MONITORS FOR PERSONAL USE** Dexcom G6, G7 FreeStyle Libre 14-day, Libre 2™, and Libre 3
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 4/19, 8/19, 9/19, 09/20, 11/20, 02/21, 05/21, 09/21, 10/21, 09/22, 03/23, 09/23 (BS) P&T Committee Meeting Date: 05/18 (CV), 06/19 (CV), 08/19 (CV), 09/19 (CV), 10/19, 10/20, 12/20, 02/21 (CV), 04/21, 06/21, 10/21 (CV), 12/21, 10/22, 04/23, 10/23 Original Effective Date: 05/18 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

For coverage of professional continuous glucose monitoring systems, see Medical Policy 25: Advanced Diabetes Management Technology (Medicare)

POLICY CRITERIA:

COVERED USES:
Coverage criteria are based on the Noridian Local Coverage Determination (LCD) L33822

REQUIRED MEDICAL INFORMATION:

I. Continuous glucose monitors may be considered medically necessary and covered for the treatment of diabetes when all the following criteria are met:
   A. The requested device is FDA-approved and is being used in accordance with the approved indications of use, **and**
   B. One of the following:
      1. The patient is using insulin. This may automatically adjudicate with history of pharmacy claim for insulin within the previous 120 days.
      2. The patient has experienced hypoglycemia, defined as documentation of at least one of the following

a. Recurrent hypoglycemic events, [defined as glucose less than 54mg/dL (3.0mmol/L)] that persist despite multiple attempts to adjust medication(s) and/or modify the diabetes treatment plan
b. History of one hypoglycemic event [defined as glucose less than 54mg/dL (3.0mmol/L)] characterized by altered mental and/or physical state requiring third-party assistance for treatment of hypoglycemia

3. Within six months prior to ordering the CGM, the treating practitioner has an in-person or Medicare-approved telehealth visit with the beneficiary to evaluate their diabetes control and determined that criteria above are met.

Replacement of Continuous Glucose Monitors

II. Upgrade or replacement of continuous glucose monitor systems may be considered medically necessary and covered when there is documentation that one or more of the device components meet all of the following criteria (A.-C.):
    A. Are no longer functional, and
    B. Are not under warranty, and
    C. Cannot be repaired.
III. Upgrade or replacement of continuous glucose monitor systems is considered not medically necessary and not covered when criterion II above is not met.

Upon approval, concurrent use of test strips will be limited to:

- Dexcom G6/Freestyle Libre/Libre 2: 150 test strips per 30-day supply
    - Requests above this quantity are not considered medically necessary. Coverage may be allowed with discontinuation of continuous glucose monitoring system and is subject to test strip quantity criteria (See Diabetic DME policy).

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:

Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMIT:
Reader/receiver: one unit every five years, subject to upgrade/replacement criteria above
Sensors: one pack per 30 days
Transmitters: one per three months

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Therapeutic continuous glucose monitoring (CGM) devices for personal use are now available on the market for patients. The systems offer unique advantages over traditional test strips in that they typically reduce or eliminate the need for finger-sticks and monitor glucose levels throughout the day.

CGMs for personal use are intended for patients to self-monitor their glucose levels and make treatment decisions (e.g., insulin dose) in real-time. These products differ from professional CGMs in that the readings are not monitored by medical professionals in real-time (although the history can be downloaded for provider review).

"CGMs are designated by the Food and Drug Administration (FDA) as either adjunctive or non-adjunctive. A non-adjunctive CGM can be used to make treatment decisions without the need for a stand-alone home blood glucose monitor to confirm testing results"[1]

The receive/reader component of CGMs are classified as durable medical equipment (DME) for the purposes of coverage by the Centers for Medicare and Medicaid Services (CMS). DME is only covered by Medicare once every five years, unless the system has become unusable and is unable to be fixed.[2]

POSITION STATEMENT:
To improve access, the CGMs for personal use are available through the retail pharmacy distribution channel to insulin-dependent patients with a clinical need for continuous monitoring.

Per the American Diabetes Association (ADA) 2023 Standards of Care:

- CGMs should be considered for adults with diabetes on insulin regimens (such as multiple daily injections, basal insulin therapy, or insulin pump therapy)
- CGMs should be considered for children on intensive insulin regimens (such as multiple daily injections or insulin pump therapy)
- There is limited clinical benefit, and insufficient evidence to support the use of CGM in patients with diabetes who are not on insulin regimens (such as oral medications only)
- Blood Glucose Monitoring (BGM) has not been shown to provide a clinically significant reduction in A1C levels for patients on noninsulin therapy
- When used as an adjunct to pre- and postprandial self-monitoring of blood glucose, continuous glucose monitoring can help to achieve A1C targets in diabetes and pregnancy.
    - Dexcom G7 is the only personal use product cleared for use during pregnancy
- Patients having gone through bariatric surgery may experience post-bariatric hypoglycemia (PBH). This typically manifests longer than one year after surgery and clinicians should exclude other disorders that may be contributing to hypoglycemia (such as malnutrition, medications, dumping syndrome, and insulinoma).
    - Treatment is multi-factorial and should include education, medical nutrition therapy, and medication treatment, as needed
    - CGMs can be important tool for patients with severe hypoglycemia or hypoglycemia unawareness [3]

These systems are intended to replace finger-sticking with traditional test strips. However, patients should have access to BGM for the following reasons/situations:

- CGM accuracy concerns (inclusive of clinical settings where rapidly changing glucose levels (>2 mg/dL/min) may result in inaccurate CGM readings

- CGM calibration (when applicable)
- CGM warnings/alerts

REFERENCE/RESOURCES:

1. Centers for Medicare & Medicaid Services (CMS) Medicare Coverage Database. CGS Administrators, LLC Local Coverage Determination (LCD) L33822 “Glucose Monitors”. Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33822&ver=55 (Accessed March 17, 2023)
2. CMS. Medicare National Coverage Determinations Manual Chapter 1, Part 1 (Sections 10 – 80.12) Coverage Determinations. Available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part1.pdf (Accessed March 17, 2023)
3. CMS. Medicare Claims Processing Manual Chapter 20 - Durable Medical Equipment, Prosthetics, Orthotics, and Supplies (DMEPOS). Available at https://www.cms.gov/regulations-and-guidance/guidance/manuals/downloads/clm104c20.pdf (Accessed March 17, 2023)
4. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2023; 46:Issue Supplement 1. Available at https://diabetesjournals.org/care/issue/46/Supplement_1 (Accessed March 13, 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND053.0423	**ENDOCRINE & METABOLIC DRUGS** **CRYSVITA®** (burosumab-twza vial)
Effective Date: 6/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/18 , 02/19,12/19, 02/20, 08/20, 03/21, 02/22, 03/23 (JN) P&T Committee Meeting Date: 08/18, 04/19, 12/19, 04/20, 10/20, 04/21, 04/22, 04/23 Original Effective Date: 10/18 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Initial authorization for new starts all of the following criteria must be met:

1. One of the following diagnoses:
    a. Diagnosis of X-linked hypophosphatemia (XLH) supported by ONE or more of the following:
        i. Confirmed PHEX mutation in the patient or a directly related family member with appropriate X-linked inheritance
        ii. Elevated Serum fibroblast growth factor 23 (FGF23) level greater than 30 pg/mL
    b. Clinical diagnosis of tumor-induced osteomalacia (TIO) and all of the following:
        i. Associated with tumors that cannot be identified or curatively resected
        ii. FGF23 level of at least 100 pg/mL, and

2. Documentation that serum phosphorus level is below the normal range for age, (use laboratory-specific reference ranges if available, otherwise, see appendix for ranges), and
3. One of the following:
    a. Patient's epiphyseal plate has NOT fused, or
    b. Patient meets all of the following:
        i. Patient's epiphyseal plate has fused, and
        ii. Patient is experiencing clinical signs and symptoms of disease (e.g., limited mobility, musculoskeletal pain, bone fractures), and
4. Failure of calcitriol with an oral phosphate agent, unless contraindicated or clinically significant adverse effects are experienced, and
5. Documentation of patient's current weight and that dosing is in accordance with the United States Food and Drug Administration approved labeling

For patients established on therapy with burosumab for X-linked hypophosphatemia all of the following criteria must be met:

1. Documentation of recent serum phosphorus level and levels have normalized while on therapy, and
2. Documentation of at least one of the following responses to therapy:
    a. Improvement in skeletal deformities
    b. Healing of fracture or pseudofractures
    c. Reduction in number of fractures/pseudofractures
    d. Increase in growth velocity, and
3. Documentation of patient's current weight and that dosing continues to be in accordance with the United States Food and Drug Administration approved labeling

For patients established on therapy with burosumab for hypophosphatemia in tumor induced osteomalacia (TIO) all of the following criteria must be met:

1. Documentation that tumor continues to be unidentifiable or unresectable
2. Documentation of recent serum phosphorus level and levels have normalized while on therapy, and
3. Documentation of at least one of the following responses to therapy:
    a. Improvement in skeletal deformities
    b. Healing of fracture or pseudofractures
    c. Reduction in number of fractures/pseudofractures
    d. Increase in growth velocity, and
4. Documentation of patient's current weight and that dosing continues to be in accordance with the United States Food and Drug Administration approved labeling

EXCLUSION CRITERIA:

Pediatric patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m2 or adult patients with creatinine clearance (CLcr) less than 30 mL/min.

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, an endocrinologist or specialist experienced in the treatment of metabolic bone disorders.

COVERAGE DURATION:
Initial authorization will be approved for six months and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Burosumab-TWZA (Crysvita®) is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH), also known as vitamin D-resistant rickets. XLH is caused by a loss of function mutation in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene which leads to an overproduction of FGF23 which is the primary regulator of phosphate homeostasis. This overproduction causes impairment in renal phosphate reabsorption and the renal production of 1,25 dihydroxy vitamin D, which leads to defective mineralization and delayed ossification of bone. Burosumab binds to and inhibits the biological activity of FGF23 restoring renal phosphate reabsorption and increasing the serum concentration of 1,25 dihydroxy vitamin D.

The severity of XLH can vary widely. Mildly affected individuals may have hypophosphatemia without other signs and symptoms. In children, the main clinical consequences of the disease are rickets, lower extremity skeletal deformities, gait abnormalities and loss of growth potential. In adulthood, the disease is associated with osteomalacia, musculoskeletal pain/stiffness and dental abscesses.

Burosumab-TWZA (Crysvita®) is also approved to treat FGF23-related hypophosphatemia in tumor induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors. This is a rare syndrome that closely resembles XLH with increased FGF23 levels that disrupts phosphate homeostasis, but the clinical presentation is often more severe with lower levels of serum phosphate and calcitriol. The tumors are typically benign, small, and slow growing. Resection of the tumor is curative, but they are generally difficult to localize and resect. Most affected patients will have biochemical and bone abnormalities including rickets in children, and bone histomorphometry shows severe osteomalacia in all affected subjects.

FDA APPROVED INDICATIONS:
Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients six months of age and older.

Treatment of FGF23-related hypophosphatemia in tumor induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumors that cannot be curatively resected or localized in adult and pediatric patients two years of age and older.

POSITION STATEMENT:

- FDA approval of burosumab for X-linked hypophosphatemia was based on four clinical trials, two in pediatric patients and two in adult patients.
    - Study one was a randomized, open-label, phase two study in 52 XLH pediatric patients (age five to 12) that compared burosumab administered every two weeks versus every four weeks. Radiographic evidence of rickets was observed in 94% of patients at baseline and 96% of patients had received treatment with oral phosphate supplements and vitamin D analogs. Mean Thacher rickets severity total score decreased from 1.9 at baseline to 0.8 at week 40 with every-2-week dosing and from 1.7 at baseline to 1.1 at week 40 with every-4-week dosing ($P<0.001$ for both comparisons); improvements persisted at week 64. Improvements from baseline were also seen in height velocity, six minute walk test and sport and physical functioning scores.
    - Study two was a 64 week open-label, single arm, phase 2 study in 13 children one to four years old with XLH. All patients in the study

received burosumab every two weeks. All patients had radiographic evidence of disease and had previously taken oral phosphate supplements and vitamin D analogs. The RSS score in patients decreased from 2.9 at baseline to 1.2 at week 40.

- Study 3 was a randomized, double-blind, placebo-controlled study (in 134 adult XLH patients. Patient received burosumab at a dose of 1 mg/kg every four weeks or placebo. At baseline, all patients had skeletal pain associated with XLH or osteomalacia and 90.3% of patients had previously received conventional therapy. At week 24, 94% of the burosumab a serum phosphorous above the lower limit of normal compared to 8% of the placebo group. Patients in the burosumab group experienced bone healing in 43% of total bone total bone fractures compared to 8% of total fractures in the placebo group. Reductions in WOMAC physical function subscale and Brief Pain Inventory worst pain did not achieve statistical significance.
- Study 4 was a 48-week, open-label, single-arm study in 14 adults with XLH. After 48 weeks of treatment, healing of osteomalacia was observed in 10 patients as demonstrated by decreases in Osteoid volume/Bone volume from a mean (SD) score of 26% (12.4) at baseline to 11% (6.5), a change of -57%.

- Based on these clinical trials burosumab may promote healing of rickets and growth and improve physical function in XLH pediatrics patients with severe disease that have not responded to oral phosphate and calcitriol. There is currently no data on long term benefits of therapy in pediatric patients. Burosumab may be beneficial in the healing of psudeofractures and fractures in adult patients with XLH, but these trials did not demonstrate any improvement in pain or physical function. There is currently no data on long term benefits of therapy in adult patients.
- In the pediatric and adult trials, the majority of patients had previously tried conventional therapy with oral phosphate supplements and vitamin D analogs.[10,11] Therefore, it is reasonable to require a trial of conventional therapy prior to approval of burosumab.
- Burosumab is an expensive therapy with an estimated drug cost of around $160,000/child/year and $200,000/adult/year per manufacture statements. However, dosing of burosumab is based on weight and phosphorus levels and therefore an individual patient's cost could potential be significantly higher. For patient's needing the maximum dose (90 mg every two weeks for children or 90 mg every four weeks for adults) the estimated drug cost would be ~$889,000/child/year and ~$444,500/adult/year.
- The European Medicines Agency (EMA) approved indication for burosumab is treatment of X-linked hypophosphatemia with radiographic evidence of

bone disease in children one year of age and older and adolescents with growing skeletons.
    - An indication for the adult population was not pursued by the applicant.
    - The EMA assessment report notes that the pediatric studies include subjects aged one (1) to 12 years and some children reached the age of 14 by the end of the studies but that there is not currently data in adolescents with mature skeletons. They not that "the reasoned extrapolation to adolescents with growing skeletons without a strict upper age limit is based on shared mechanism of action and aim of therapy and improved x-ray appearance of affected growing bones after longer term exposure to burosumab.
    - The labeling also indicates that patients must have radiographic evidence based on the inclusion criteria for the studied population. "The current pediatric studies have included only children with radiographic evidence of bone disease but very mildly affected individuals with XLH may have hypophosphatemia without other signs and symptoms throughout the life."
- The National Institute for Health and Care Excellence published their draft guidance of burosumab in June 2018. Their review is based on the EMA labeled indication only. In their draft guidance they recommended against the use of burosumab.
    - "Evidence from clinical trials suggests that burosumab provides short-term clinical benefits in children aged between one and 12 years, but the evidence is limited and uncertain, and there is no evidence in young people between 13 and 17 years."
    - "The cost-effectiveness estimates for burosumab are all much higher than the range NICE normally considers acceptable for highly specialized technologies. Therefore, burosumab does not appear to provide value for money within the context of a highly specialized service, and is not recommended for use in the NHS."
- FDA approval of burosumab for tumor-induced osteomalacia was based on two single-arm, open-label studies.
    - Study six (NCT 02304367): Patients received CRYSVITA every four weeks at a weight based starting dose of 0.3 mg/kg that was titrated to achieve a fasting serum phosphorus level of 2.5 to 4.0 mg/dL. The mean dose was 0.83 mg/kg at Week 20, 0.87 mg/kg at Week 48, 0.77 mg/kg at Week 96 and 0.71 mg/kg at Week 144.
        - Serum phosphate mean increased from 1.60 (0.47) mg/dL at baseline to 2.64 (0.76) mg/dL averaged across the midpoint of dose intervals through Week 24
    - Study 7 (NCT 02722798): Patients received CRYSVITA every four weeks at a weight based starting dose of 0.3 mg/kg that was titrated to

achieve a fasting serum phosphorus level of 2.5 to 4.0 mg/dL. The mean (SD) dose was 0.91 (0.59) mg/kg at Week 48, and 0.96 (0.70) mg/kg at Week 88.
    - Serum phosphate mean increased from 1.62 (0.49) mg/dL at baseline to 2.63 (0.87) mg/dL averaged across the midpoint of dose intervals through Week 24
- Use of Crysvita is contraindicated in patients with severe renal impairment as outlined by the FDA in the package insert as an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73m2 for pediatric patients or a creatinine clearance (CLcr) less than 30 mL/min for adults

APPENDIX:

Reference Serum Phosphorus Levels Based on Gender and Age

Females	Males
1-7 years: 4.3-5.4 mg/dL	1-4 years: 4.3-5.4 mg/dL
8-13 years: 4.0-5.2 mg/dL	5-13 years: 3.7-5.4 mg/dL
14-15 years: 3.5-4.9 mg/dL	14-15 years: 3.5-5.3 mg/dL
16-17 years: 3.1-4.7 mg/dL	16-17 years: 3.1-4.7 mg/dL
≥ 18 years: 2.5-4.5 mg/dL	≥ 18 years: 2.5-4.5 mg/dL

REFERENCE/RESOURCES:

1. [Crysvita] package insert. Ultragenyx Pharmaceutical Inc; Novato, CA. December 2022.
2. [Crysvita] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed [03/14/2023].
3. Scheinman SJ, Drezner MK. Hereditary hypophosphatemic rickets and tumor-induced osteomalacia In: UpToDate, Hoppin AG (Ed), UpToDate, Waltham, MA, 2017.
4. Carpenter TO, Whyte MP, Imel EA et al. Burosumab Therapy in Children with X-Linked Hypophosphatemia. N Engl J Med. 2018 May 24;378(21):1987-1998.
5. Ruppe MD. X-Linked Hypophosphatemia. In: GeneReviews® [Internet]. Updated April 13 2017. https://www.ncbi.nlm.nih.gov/books/NBK83985/.Acessed [07/02/2017].
6. National Institute For Health And Care Excellence Evaluation Consultation Document: Burosumab for treating X-linked hypophosphatemia in children and young people. National Institute for Health and Care Excellence. June 15

2018. https://www.nice.org.uk/guidance/gid-hst10016/documents/evaluation-consultation-document-2. Accessed [07/16/2018].
7. Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to x-linked hypophosphatemia. J Bone Miner Res. 2011 Jul; 26(7): 1381–1388.
8. Clinicaltrials.gov. Searched: NCT 02304367 and NCT 02722798. Search preformed July 30, 2020.
9. Florenzano P, Gafni RI, Collins MT. Tumor-induced osteomalacia. *Bone Rep*. 2017;7:90-97. Published 2017 Sep 20.
10. Imel E, Glorieux F, Whyte M. Burosumab versus conventional therapy in children with x-linked hypophosphataemia: a randomized, active-controlled, open-label, phase 3 trial. *The Lancet.* Published 2019 June 15.
11. Padidela R, Whyte M, Glorieux F. Patient-reported outcomes from a randomized, active-controlled, open-label, phase 3 trial of burosumab versus conventional therapy in children with x-linked hypophosphatemia. *Calcified Tissue International.* Published 2021 January 23.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH017.1023	**MISCELLANEOUS PRODUCTS** **DIABETIC DURABLE MEDICAL EQUIPMENT (DME)** Non-preferred diabetic DME products/supplies and quantity limit exceptions
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 01/17, 05/18, 09/18, 11/18, 02/19, 09/19, 09/20, 09/21, 09/22, 08/23, 09/23 (BS) P&T Committee Meeting Date: 02/17, 06/18, 09/18 (cv), 12/18, 04/19, 10/19, 10/20, 10/21, 10/22, 08/23, 10/23 Original Effective Date: 04/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

Medicare Part B: Coverage criteria are based on the Noridian Local Coverage Determination (LCD) L33822

REQUIRED MEDICAL INFORMATION:
Non-preferred test strips and/or blood glucose meter:
1. Patient is using an insulin pump that requires a meter that synchronizes with their pump.
   OR
2. Patient has physical or mental limitations that makes utilizing BOTH of the preferred products (manufactured by Roche and LifeScan) unsafe, inaccurate, or otherwise not feasible.

Test strip quantity exceptions:

1. For patients using a **continuous glucose monitoring systems for personal use:** Patients that have been approved for use of a continuous glucose monitor for personal use will be restricted to the following:
    a. Dexcom or Freestyle Libre: 150 test strips per 30-day supply.
    b. Requests above this quantity are not considered medically necessary. Coverage may be allowed with discontinuation of continuous glucose monitoring system and is subject to test strip quantity criteria below

2. For patients using **traditional "finger-stick" glucose monitors**, quantities up to 10 strips per day may be covered if the patient meets one of the following criteria:
    a. Patient has a diagnosis of Type 1 diabetes mellitus (T1DM)
    b. Patient is currently using an insulin pump
    c. Patient has an intensive insulin regimen (more than three insulin injections per day)
    d. Patient is pregnant
    e. Patient is less than 18 years of age
    f. Prescriber provides clinical rationale to support the need for additional testing

3. For patients using **traditional "finger-stick" glucose monitors**, quantities exceeding 10 strips per day are not considered medically necessary and will not be covered

For **reauthorization of quantity exceptions**, all of the following are required:
1. Documentation that the patient continues to need the requested quantity
2. Documentation that there is a clinical benefit associated with the increased quantity.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for 12 months. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes

QUANTITY LIMIT:

Test strips will be covered up to five test strips per day without authorization required, unless patient is on a continuous glucose monitor as outlined above.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Monitoring of blood glucose levels is a critical component of a comprehensive diabetes treatment plan. Providence Health Plan provides coverage of supplies for blood glucose testing, subject to products and limits described in benefit summaries.

There are two primary methods for monitoring glucose response to the recommended treatment plan, for a patient with diabetes: Blood Glucose Monitoring (BGM) and periodic assessment of the hemoglobin A1C. The recommended frequency of BGM depends on several factors, including age, duration of diabetes, current medication therapy, patient experience, and ability of the patient to adhere to the prescribed regimen. Performing BGM alone does not lower blood glucose levels; this information must be integrated into a clinical and self-management plan. The ongoing need for and frequency of BGM should be periodically monitored to avoid overuse.

POSITION STATEMENT:

Blood Glucose Monitoring (BGM) for diabetic patients is an important element of their treatment plan. It allows a means to assess efficacy and safety of a patient's current treatment regimen and facilitates medication dose adjustments. The value of BGM is widely accepted in Type 1 diabetes mellitus (T1DM). The value of BGM in Type 2 diabetes mellitus (T2DM) is still considered controversial in patients not

receiving insulin therapy. Newer studies suggest some benefit for newly diagnosed T2DM patients that are not receiving insulin therapies in terms of providing education to the patient regarding glucose levels around meal-time and at bedtime.

Major clinical practice guidelines support frequent BGM in patients with T1DM. Increased frequency of testing in these patients has been associated with lower A1C and lower risk of complications.

BGM in T2DM patients can provide benefit in some patients. It provides immediate feedback regarding glycemic control and assists in patient education. The use of BGM in this population should be individualized to each patient. For BGM to be of value, the patient must be taught how and when to test. The test results also need to be communicated with the healthcare team. The recommended frequency of tests for these patients varies depending on patient characteristics and treatment regimen.

The 2023 American Diabetes Association Standards of Care recommendations for BGM.

Treatment Regimen	Recommendations
Patients using insulin regimens	• Check when appropriate for insulin regimen • May include checking prior to meals and snacks, at bedtime, postprandially, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving.
Patients on noninsulin therapy	• Routine glucose monitoring may be of limited additional clinical benefit • It may be helpful when making lifestyle changes in combination with adjustments to treatment

The following blood glucose test strip brands are preferred formulary products for Providence Health Plan:

- Johnson & Johnson (OneTouch®)
- Roche (AccuChek®)

All other test strips will require a clinical reason why the preferred test strips cannot be used. Providence Health Plan acknowledges that in certain situations, the use of non-preferred products will be advantageous to the patient. The technology associated with insulin pumps and meters has advanced to the point that these

devices can sync with each other. Additionally, some patients may have visual or dexterity impairments that make using preferred meter/test strips difficult.

Per the American Diabetes Association (ADA) 2023 Standards of Care, patients on CGM should have access to BGM for the following reasons/situations:

- CGM accuracy concerns (inclusive of clinical settings where rapidly changing glucose levels (>2 mg/dL/min) may result in inaccurate CGM readings
- CGM calibration (when applicable)
- CGM warnings/alerts
- Glucose levels are changing rapidly

REFERENCE/RESOURCES:

1. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care 2023; 46:Issue Supplement 1. Available at https://diabetesjournals.org/care/issue/46/Supplement_1 (Accessed September 12, 2023).
2. American Diabetes Association. Standards of Medical Care in Diabetes - Diabetes Technology. Available at https://diabetesjournals.org/care/article/46/Supplement_1/S111/148041/7-Diabetes-Technology-Standards-of-Care-in (Accessed September 12, 2023).
3. Centers for Medicare & Medicaid Services (CMS) Medicare Coverage Database. CGS Administrators, LLC Local Coverage Determination (LCD) L33822 “Glucose Monitors”. Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33822&ver=55 (Accessed September 12, 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCTOP035.0623	**TOPICAL PRODUCTS** **DURYSTA®** (bimatoprost intracameral implant)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/21, 07/21, 05/22, 05/23 (JN) P&T Committee Meeting Date: 10/20, 06/21, 08/21, 06/22, 06/23 Original Effective Date: 01/21 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
The following criteria must be met:

1. The patient is not receiving re-treatment of eye(s) previously treated with bimatoprost intracameral implant (Durysta®)
2. Trial and failure, intolerance or contraindication to at least two ophthalmic products (either as monotherapy or as concomitant therapy) from two different pharmacological classes, one of which is an ophthalmic prostaglandin (for example, bimatoprost, latanoprost, or travoprost)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Approved for 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by an ophthalmologist

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCTOP035	TOPICAL PRODUCTS **DURYSTA®** (bimatoprost intracameral implant)

COVERAGE DURATION:

Authorization will be approved for six months. Approval will be for a one-time use in each treated eye (one implant per treated eye, a total of two implants per patient)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Bimatoprost implant (Durysta®) is a novel, prostaglandin analog intracameral biodegradable sustained-release implant. Bimatoprost is also available generically as an ophthalmic solution for the same indication as Durysta®.

FDA APPROVED INDICATIONS:

For the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT)

POSITION STATEMENT:

- Per the American Academy of Ophthalmology, prostaglandin analogs are the most frequently prescribed initial eye drops for lowering IOP in patients with glaucoma because they are most efficacious, well-tolerated, and instilled once daily. If a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy or switching to an alternative therapy may be appropriate.
- Per the National Institute for Health and Care Excellence (NICE): Glaucoma diagnosis and management:
    - For ocular hypertension:
        - Offer a generic prostaglandin analogue (PGA) to people with IOP of 24 mmHg or more (OHT) if they are at risk of visual impairment within their lifetime
        - Offer another pharmacological treatment to people with an IOP of 24 mmHg or more who cannot tolerate their current

treatment. The first choice should be an alternative generic PGA, if available, and if this is not tolerated, offer a beta-blocker. If none of these options are tolerated, offer non-generic PGA, carbonic anhydrase inhibitors, sympathomimetics, miotics or a combination of treatments.

- Offer a drug from another therapeutic class (beta-blocker, carbonic anhydrase inhibitor or sympathomimetic) to people with an IOP of 24 mmHg or more whose current treatment is not reducing IOP sufficiently to prevent the risk of progression to sight loss. Topical drugs from different therapeutic classes may be needed at the same time to control IOP.

- For chronic open angle glaucoma:
  - Offer a generic PGA
  - Ask about adherence to treatment and check the eye drop instillation technique in people who's IOP has not been reduced sufficiently to prevent the risk of progression to sight loss despite pharmacological treatment. If adherence and eye drop instillation technique are satisfactory offer 1 of the following:
    - a drug from another therapeutic class (a beta-blocker, carbonic anhydrase inhibitor or sympathomimetic); topical drugs from different therapeutic classes may be needed at the same time to control IOP
    - laser trabeculoplasty
    - surgery with pharmacological augmentation as indicated.
    - If the drug treatment option is chosen, after trying drugs from 2 therapeutic classes, consider offering surgery with pharmacological augmentation as indicated or laser trabeculoplasty.

- The efficacy of Durysta® was established in two randomized, controlled 20-month studies of Durysta® compared to twice daily topical timolol 0.5% drops, in patients with OAG or OHT.
  - Durysta® demonstrated an IOP reduction of approximately 5 to 8 mmHg in patients with a mean baseline IOP of 24.5 mmHg
- Per the package insert, Durysta® should not be re-administered to an eye that received a prior Durysta® implant.

REFERENCE/RESOURCES:

1. Durysta (bimatoprost) package insert. Madison, NJ: Allergan; Revised November 2020.

2. Durysta In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed May 7, 2023.
3. Durysta In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed May 7, 2023.
4. American Academy of Ophthalmology. Glaucoma. Available at https://www.aao.org/eye-health/diseases/what-is-glaucoma (Accessed July 22, 2020).
5. American Academy of Ophthalmology. Ocular Hypertension. Available at https://www.aao.org/eye-health/diseases/ocular-hypertension-cause (Accessed July 22, 2020).
6. National Institute for Health and Care Excellence. Glaucoma: diagnosis and management. Available at https://www.nice.org.uk/guidance/ng81/chapter/recommendations#treatment (Accessed July 22, 2020).
7. Craven ER, Walters T, Christie W, Bejanian M, Goodkin ML, Guo Q, Zhang J, Robinson MR, Ahmed IK. Phase 3 evaluation of Bimatoprost sustained-release implant in patients with glaucoma or ocular hypertension: results at primary database lock [abstract no. PA054-2019]. Presented at the American Academy of Ophthalmology 2019 meeting, San Francisco, CA, 12–15 October 2019. https://aao.scientificposters.com/epsAbstractAAO.cfm?id=2. Accessed July 22, 2020.
8. Craven ER, et al. 24-Month Phase I/II Clinical Trial of Bimatoprost Sustained-Release Implant (Bimatoprost SR) in Glaucoma Patients. Drugs. 2020;80(2):167-179.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU042.0224	**NEUROMUSCULAR DRUGS** **ELEVIDYS®** (delandistrogene moxeparvovec-rokl suspension, for intravenous infusion)
Effective Date: 4/1/2024	**Review/Revised Date**:
Original Effective Date: 04/24	**P&T Committee Meeting Date**: 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY:

REQUIRED MEDICAL INFORMATION:
Delandistrogene moxeparvovec-rokl is not considered medically necessary for coverage due to insufficient evidence from controlled trial data demonstrating a clinically meaningful benefit.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Delandistrogene moxeparvovec-rokl (Elevidys®), is a adeno-associated virus vector-based gene therapy for treatment of ambulatory pediatric patients aged four through five with Duchenne muscular dystrophy (DMD). Treatment is intended to slow or stabilize progression. Approved under accelerated approval based on the surrogate endpoint of expression of truncated dystrophin (Elevidys micro-dystrophin) in skeletal muscle.

FDA APPROVED INDICATIONS:
Ambulatory pediatric patients aged four through five years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the dystrophin (*DMD*) gene.

This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

POSITION STATEMENT:
Based on all currently available information, there is insufficient evidence to establish a clinical benefit such as improved motor function; therefore, coverage of this therapy is not considered medically necessary.

There is evidence from one phase 1 and one phase 2 study that delandistrogene moxeparvovec increased expression of Elevidys micro-dystrophin in skeletal muscle (surrogate endpoint) in ambulatory males 4-7 years with DMD[11,13]. There is some debate whether the expression of Elevidys micro-dystrophin in muscles (surrogate endpoint used for accelerated approval) is predictive of clinical benefit[4-6]. The primary clinical outcome in the placebo controlled study 102, assessed by the North Star Ambulatory Assessment (NSAA), was found not to be statistically significant. An exploratory subgroup analysis shows a numerical advantage in the NSAA score in those aged 4-5 years, Elevidys = 4.3 (0.7) points [N=8] and placebo = 1.9 (0.7) points [N=8][13].

Duchenne muscular dystrophy is a recessive X-linked genetic muscle disorder. It is a type of muscular dystrophy that affects almost exclusively males, with symptom onset usually between ages two and three with diagnosis usually by the age of five. DMD is characterized by progressive muscle weakness and atrophy which leads to respiratory failure or cardiomyopathy. Lower extremities are affected first and the ability to walk is often lost by the age of 12 or 13. There is a large heterogeneity in the disease and a standardized clinical course is not predictable. Improved respiratory and cardiac care have increased life expectancy into the fourth decade[7,10].

DMD results from mutation in the *DMD* (also known as dystrophin) gene leading to deficiency in the protein dystrophin. Dystrophin is located primarily in the skeletal and cardiac muscles. It helps strengthen muscle fibers and protect them from injury during contraction. Lack of functional dystrophin protein leads to chronic inflammation, atrophy, fibrosis, and fatty infiltration in muscles. The *DMD* (dystrophin) gene is one of the largest known human genes. DMD has a prevalence of approximately seven cases per 100,000 males worldwide. About 400-600 boys are born per year in the USA with DMD[7,10,16].

NSAA is a 17-item rating scale used to measure functional motor abilities in ambulatory children with DMD. It is used to monitor progression of the disease and treatment effects. A score of 0,1 or 2 is given in each of the 17 items. Scores range from 0-34 with higher scores indicate better performance. Highest possible score varies with age. Improvement on the NSAA can occur with standard of care alone in patients aged about four to six years. Peak scores are typically reached at six to seven years of age[4].

There is no curative treatment for DMD. Current treatment includes supportive care and medications such as corticosteroids and exon-skipping therapies.

Corticosteroids, including prednisone and deflazacort (Emflaza®) are a main stay of treatment for patients with DMD. The exact mechanism is unknown, but it is likely due to anti-inflammatory and immunomodulatory effects. Corticosteroids have been shown to slow the decline in muscle strength and function in patients with DMD[9].

Exon-skipping therapies (antisense oligonucleotides [ASOs]) target dystrophin pre-messenger ribonucleic acid (mRNA) and induce skipping of mutated exons of the DMD gene that disrupt downstream protein synthesis and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin that may be beneficial in slowing progression of the disease, though clinical correlation has yet to be established. All four antisense oligonucleotides available were approved under accelerate approval based on a surrogate marker, dystrophin production in skeletal muscle. Confirmatory trials are still pending.

American Academy of Neurology (AAN) Practice Guidelines for DMD include the following:

- Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy 2016 – reaffirmed 2022
- Diagnosis and Management of DMD, Part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and GI and nutritional management - 2018

- Diagnosis and Management of DMD, Part 2: respiratory, cardiac, one health, and orthopedic management - 2018
- Diagnosis and Management of DMD, Part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan - 2018

Guidelines address corticosteroid treatment but do not include exon skipping or gene therapy.

AAN makes the following recommendations regarding corticosteroids[9]:

- prednisone should be offered for improving strength (Level B) and pulmonary function (Level B)
- prednisone may be offered for improving timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C)
- deflazacort may be offered for improving strength and timed motor function and delaying age at loss of ambulation by 1.4–2.5 years (Level C)
- deflazacort may be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5–15 years of follow-up (Level C for each)
- deflazacort and prednisone may be equivalent in improving motor function (Level C)

B = Probably effective (or probably useful/predictive) for the given condition in the specified population
C = Possibly effective (or possibly useful/predictive) for the given condition in the specified population

Micro-dystrophin as a surrogate endpoint and FDA approval[4,5,6]:

- Elevidys micro-dystrophin is a novel, engineered protein designed to function like natural dystrophin. It contains selected portions of the normal, wild type dystrophin. The pharmacologic effect in humans is unclear. There is some debate whether the expression of micro-dystrophin in muscles is predictive of clinical benefit.
- Members of the FDA Review Committee did not consider that the available data supports the use of micro-dystrophin expression as a surrogate endpoint "reasonably likely to predict clinical benefit." They stated, "although Elevidys micro-dystrophin may have a structural effect in muscle cells, its physiological meaningfulness remains unclear.[5]"
- The director of the Center for Biologics Evaluation and Research at the FDA; however, did find expression of micro-dystrophin reasonably likely to predict clinical benefit in the specific population of four to five year olds. This was based on the exploratory subgroup analysis efficacy data in 4- to 5-year-olds (4.3 mean point increase compared to the 1.9 mean point increase which correlated with increased levels of micro-dystrophin protein expression).

- The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) met on May 12, 2023, and voted eight to six in favor of accelerated approval. Some of the members who voted in favor of approval noted compelling data from the four year follow up of study 101 and had reservations regarding the clinical study evidence as well as the use of micro-dystrophin as a surrogate endpoint "reasonably likely to predict clinical benefit.
- The Review Committee found the available data was not adequate to meet the threshold for accelerated approval and did not recommend approval of delandistrogene moxeparvovec. The decision to not approve accelerated approval of delandistrogene moxeparvovec (Elevidys) was overridden by the director of the Center for Biologics Evaluation and Research at the FDA.

On June 22, 2023, the FDA approved delandistrogene moxeparvovec (Elevidys) for the treatment of ambulatory pediatric patients aged four through five years with Duchenne muscular dystrophy (DMD). This indication was approved under accelerated approval based on expression of ELEVIDYS micro-dystrophin in skeletal muscle. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Clinical Trials:

- FDA BLA submission includes data from three interventional clinical trials of delandistrogene moxeparvovec
  Study 101 – phase 1, open label, single arm, N=4, safety was primary endpoint
  Study 102 – phase 2, R, DB, PC
  Study 103 – phase 1, open label, single arm

- Phase 3 confirmatory trial EMBARK is currently active.

Table 1: Summary of clinical trial NCT03769116 and NCT04626674

	Study 102 - Phase 2 (NCT03769116)	**Study 103 - Phase 1 (NCT04626674)**
Study Design	Part 1: R(1:1), DB, PC Part 2: Cross-over with blinding from part 1 Part 3: ongoing open-label follow up	Part 1: open label, single arm, 5 cohorts - focus on cohort 1 only Part 2: 5 year follow up
Study Duration	Part 1: 48 weeks Part 2: 48 weeks	Part 1: 12 weeks

Patient Population	N= 41 Ambulatory (walk independently) males aged 4 -7 with either a confirmed frameshift mutation or a premature stop codon mutation between exons 18 and 58 in the *DMD* gene.	Cohort 1 N=20 Ambulatory males aged 4–7 with a confirmed frameshift mutation, canonical splice site mutation, or premature stop codon mutation in the *DMD* gene (exons 18-79).
Key Inclusion criteria	• On stable dose of corticosteroids for ≥ 12 weeks prior to infusion • Baseline anti-AAVrh74 antibody titers <1:400	• On stable dose of corticosteroids for ≥ 12 weeks prior to infusion • Baseline anti-AAVrh74 antibody titers <1:400
Key exclusion criteria	• Exposure to an investigational or commercial gene therapy product • Exposure to another investigational drug or exon-skipping medication within 6 months of screening	Exposure to gene therapy, investigational medication, or any treatment designed to increase dystrophin expression within protocol-specified time limits.
Intervention	• Peripheral IV infusion of either placebo or Elevidys • Part 1 dose: 1.33×10^{14} vg/kg (N = 8; intended dose), 12 patients received lower doses • Part 2: all received intended dose	Single peripheral IV infusion of 1.33×10^{14} vg/kg
Primary Endpoints	• Change from baseline in quantity of micro-dystrophin expression as measured by western blot at Week 12. • Change from baseline NSAA total score at Week 48.	Change from baseline in quantity of micro-dystrophin expression as measured by western blot at Week 12.
Results		
Baseline Characteristics	• Mean age: 6.3 years (range, 4.34–7.98 years) • Mean weight: 22.4 kg (range, 15.0–34.5 kg)	• Mean age: 5.81 years (range, 4.38–7.94 years) • Mean weight: 21.2 kg (range, 15.2–33.1 kg) • Mean NSAA total score: 22.1 points (range, 18–26 points)

	• Mean time to rise from floor: 4.3 seconds (range, 2.7–10.4 seconds) • Mean NSAA total score: 21.2 points (range, 13–29 points) • Unbalanced scores for NSAA ○ Elevidys group 19.8 (3.3 SD) vs placebo 22.6 (3.3 SD) • Stratified by age not functional status • For sub-group analysis ages 4-5 (N=16) → well matched at baseline • Mean NSAA score: Elevidys group 20.1 (1.9 SD) vs placebo 20.4 (2.7 SD) • For sub-group analysis ages 6-7 (N=25) • Mean NSAA score: Elevidys group 19.6 (4.1 SD) vs placebo 24 (2.9 SD)		• Mean time to rise from floor: 4.2 seconds (range, 2.4–8.2 seconds)
Primary Endpoint			
Western blot (% of Elevidys micro-dystrophin compared to control)[1]	Part 1 (N = 6)	Part 2 (N = 21)	Cohort 1 (N = 20)
Mean change from baseline (SD)	43.4% (48.6)	40.7% (32.3)	54.2 (42.6)
Median change from baseline (min, max)	24.3% (1.6, 116.3)	40.8% (0.0, 92.0)	50.6 (4.8, 153.9)
NSAA Total Score			
Overall	Least-squares (LS) mean treatment difference between Elevidys, and placebo was not statistically significant: Difference = 0.8 (95% CI: −1.0, 2.7; P = 0.37)		N/A

Exploratory sub-group analysis for 4-5 years [LS mean change (SE)]	Elevidys = 4.3 (0.7) points [N=8] Placebo = 1.9 (0.7) points [N=8] *Trend correlating increased micro-dystrophin and improvement in NSAA score	
Exploratory sub-group analysis for 6-7 years [LS mean change (SE)]	Elevidys = -0.2 (0.7) points [N=11] Placebo = 0.5 (0.7) points [N=13]	
Safety From all trials	No deaths, 2 cases immune medicated myositis (1 life threatening), other serious adverse events include rhabdomyolysis, increased transaminases, liver injury, myocarditis, and troponin elevations. Most common reported side effects were nausea, vomiting, acute liver injury, pyrexia, and thrombocytopenia.	

[1]Information from Elevidys package insert.

Press release from Sarepta October 2023 regarding results from confirmatory trial EMBARK[15]:

- "ELEVIDYS-treated patients improved 2.6 points on their North Star Ambulatory Assessment (NSAA) total score 52 weeks after treatment compared to 1.9 points in placebo-treated patients. The difference of 0.65-points between treated and placebo groups did not reach statistical significance (n=125; p=0.24) "
- "All key pre-specified functional secondary endpoints demonstrated robust evidence for a clinically meaningful treatment benefit that was consistent across age groups in ELEVIDYS-treated patients compared to placebo at 52 weeks. These include:

Time to rise (TTR)	Change vs Placebo LSM* Diff in Seconds
Overall (n=124)	-0.64 (p=0.0025)
Ages 4-5 (n=59)	-0.50 (p=0.0177)
Ages 6-7 (n=65)	-0.78 (p=0.0291)

10-meter walk test	Change vs Placebo LSM Diff in Seconds
Overall (n=124)	-0.42 (p=0.0048)
Ages 4-5 (n=59)	-0.33 (p=0.0319)
Ages 6-7 (n=65)	-0.52 (p=0.0363)

"

EMBARK is a phase 3, randomized, two-part crossover, placebo-controlled study in ages 4-7 years. N=125

- Primary outcome: change from baseline in NSAA score at 52 weeks
- Key secondary outcomes: # skills gained or improved (NSAA), 10 meter walk test, time to rise from the floor, stride velocity using wearable device, micro-dystrophin expression at week 12

- Additional results and details from this trial have not been published
- Estimated study completion is November 2024[17]

Safety

- Contraindications to delandistrogene moxeparvovec treatment include patients with any deletion in exon 8 and/or exon 9 in the *DMD* gene due to risk of immune-mediated myositis.
- Warnings and precautions include immune-mediated myositis (possible risk, with deletions in the *DMD* gene in exons 1 to 17 and /or exons 59 to 71), acute serious liver injury, myocarditis and troponin-I elevations, pre-existing immunity against AAVrh74 (baseline testing is required).
- Adverse reactions with an incidence of at least 5% include vomiting and nausea, liver function test increase, pyrexia, and thrombocytopenia.
- Individuals who receive delandistrogene moxeparvovec likely cannot receive future adeno virus-based treatment due to possible immunologic cross-reactivity with other AAV subtypes.

REFERENCE/RESOURCES:

1. Elevidys package insert. Sarepta Therapeutics, Inc. Cambridge, MA: June 2023.
2. Elevidys In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September 6, 2023
3. Elevidys In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed September 6, 2023
4. Food and Drug Administration. Center for Drug Evaluation and Research. STN 125784/0 BLA Clinical Review Memorandum. Available at https://www.fda.gov/media/170230/download?attachment (Accessed September 6, 2023)
5. Food and Drug Administration. Center for Drug Evaluation and Research. Summary basis for regulatory action – Elevidys. BLA STN: 125781/0. Available at https://www.fda.gov/media/169746/download?attachment (Accessed January 8, 2024)
6. Food and Drug Administration. Center for Drug Evaluation and Research. Center director decisional memo. BLA 125781. Available at https://www.fda.gov/media/169707/download?attachment (Accessed January 8, 2024)
7. National Organization for Rare Diseases. Duchenne muscular dystrophy. Available at https://rarediseases.org/rare-diseases/duchenne-muscular-dystrophy/ (Accessed September 6, 2023)
8. Birnkrant DJ, Bushby K, Bann CM, *et al*; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1:

diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018 Mar;17(3):251-267.
9. Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016 Feb 2;86(5):465-72.
10. Muscular dystrophy association. About Duchenne muscular dystrophy. Available at https://www.mda.org/disease/duchenne-muscular-dystrophy (Accessed January 8, 2024)
11. Zaidman CM, Proud CM, McDonald CM, Lehman KJ, Goedeker NL, Mason S, Murphy AP, Guridi M, Wang S, Reid C, Darton E, Wandel C, Lewis S, Malhotra J, Griffin DA, Potter RA, Rodino-Klapac LR, Mendell JR. Delandistrogene Moxeparvovec Gene Therapy in Ambulatory Patients (Aged ≥4 to <8 Years) with Duchenne Muscular Dystrophy: 1-Year Interim Results from Study SRP-9001-103 (ENDEAVOR). Ann Neurol. 2023 Nov;94(5):955-968.
12. Mendell JR, Sahenk Z, Lehman KJ, Lowes LP, Reash NF, Iammarino MA, Alfano LN, Lewis S, Church K, Shell R, Potter RA, Griffin DA, Hogan M, Wang S, Mason S, Darton E, Rodino-Klapac LR. Long-term safety and functional outcomes of delandistrogene moxeparvovec gene therapy in patients with Duchenne muscular dystrophy: A phase 1/2a nonrandomized trial. Muscle Nerve. 2023 Aug 14.
13. Mendell JR, Shieh PB, McDonald CM, Sahenk Z, Lehman KJ, Lowes LP, Reash NF, Iammarino MA, Alfano LN, Sabo B, Woods JD, Skura CL, Mao HC, Staudt LA, Griffin DA, Lewis S, Wang S, Potter RA, Singh T, Rodino-Klapac LR. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. Front Cell Dev Biol. 2023 Jul 11;11:1167762.
14. OSU Drug Use Research & Management Program. Drug class update with new drug evaluation: drugs for Duchenne muscular dystrophy. Available at https://www.orpdl.org/durm/meetings/meetingdocs/2024_02_01/drafts/DMD_ClassUpdateNDE.pdf (Accessed January 8, 2024)
15. Sarepeta therapuetics. Press release. Sarepta therapeutics announces topline results from EMBARK, a global pivotal study of Elevidys gene therapy for muscular dystrophy. Available at https://investorrelations.sarepta.com/node/22976/pdf (Accessed January 8, 2024)
16. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifirò G. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. Orphanet *J Rare Dis*. 2020 Jun 5;15(1):141.

17. A gene transfer therapy study to evaluate the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in participants with Duchenne muscular dystrophy (DMD) (EMBARK).ClinicalTrials.gov identifier: NCT05096221. Updated November 7, 2023. Available from https://classic.clinicaltrials.gov/ct2/show/NCT05096221 (accessed January 8, 2024)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM028.1223	**HEMATOLOGICAL AGENTS** **EMPAVELI®** (pegcetacoplan vial)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/22, 10/23 (JCN)
Original Effective Date: 01/22	**P&T Committee Meeting Date**: 10/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Paroxysmal Nocturnal Hemoglobinuria (PNH):
1. For **initiation of therapy** (patients not established on therapy), all the following must be met:
    a. Documented, confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by Flow Cytometric Immunophenotyping (FCMI) using at least two independent flow cytometry reagents on at least two cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycophosphatidylinositol (GPI)-linked proteins (which may include CD59, CD55, CD14, CD15, CD16, CD24, CD45, and CD64)
    b. Symptomatic hemolytic PNH defined as lactate dehydrogenase (LDH) levels greater than or equal to 1.5 times the upper limit of normal and at least one of the following:
        i. Documented history of thrombosis
        ii. Transfusion dependence (e.g., hemoglobin less than 7 g/dL or symptomatic anemia with hemoglobin less than 9 g/dL)

iii. Disabling fatigue
iv. End-organ complications
v. Frequent pain paroxysms (e.g., dysphagia or abdominal pain)

2. For patients **currently on eculizumab (Soliris®)** or **ravulizumab (Ultomiris®)** switching to pegcetacoplan (Empaveli®) the following must be met:
    a. Confirmed documentation of paroxysmal nocturnal hemoglobinuria (criteria 1a above) and symptomatic disease (criteria 1b above). However, this can be based on patient's history prior to starting eculizumab or ravulizumab.
3. For patients already **established on the requested therapy,** the following must be met for continuation of therapy:
    a. Documentation of reduced LDH levels, reduced transfusion requirements, increase in hemoglobin levels, or improvement in PNH related symptoms

EXCLUSION CRITERIA:
Concurrent therapy with another FDA-approved product for PNH, meaning Soliris® or Ultomiris®, unless the member is in a four-week period of cross-titration between Soliris® and Empaveli®

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older.

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist/oncologist or nephrologist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for up to one year.

QUANTITY LIMIT: 160 mL/ 28 day supply

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM028	HEMATOLOGICAL AGENTS **EMPAVELI®** (pegcetacoplan vial)

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Pegcetacoplan (Empaveli®) is the first self-administered therapy (through being infused through a pump) to be approved for PNH and is the first targeted C3 complement inhibitor for PNH in adults.

FDA APPROVED INDICATIONS:
Indicated for treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

POSITION STATEMENT:
- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life threatening disorder of the blood that develops as a result of somatic mutation of hematopoietic stem cell and is characterized by destruction of red blood cells by the complement system. Symptoms associated with PNH include hemolytic anemia, thrombosis, peripheral blood cytopenia and fatigue. Thrombosis often occurs in unusual locations such as dermal veins, hepatic vein, or other intra-abdominal veins.
- The FDA approval for pegcetacoplan (Empaveli®) for use in the treatment of adult patients with PNH based on one phase 3, multicenter, randomized, head-to-head study (PEGASUS) comparing pegcetacoplan to eculizumab (Soliris®) in PNH patients stable on eculizumab for at least three months (N=80 adults). Pegcetacoplan was found to be superior to eculizumab for the change from baseline in hemoglobin level at week 16 (adjusted mean change from baseline in hemoglobin was 2.37 g/dL with pegcetacoplan vs -1.47 g/dL with eculizumab [mean difference between treatments: 3.84 g/dL; 95% CI, 2.33-5.34; p<0.001).
- A 26-week, phase 3, multicenter, open-label, controlled study (PRINCE) studied pegcetacoplan in 53 complement inhibitor naïve adult patients. Participants had a hemoglobin level below the lower limit of normal and a LDH level ≥ 1.5 times the upper limit of normal. The coprimary endpoint was the avoidance of a greater than 1 g/dL decrease in hemoglobin from baseline and a change in baseline LDH levels. Hemoglobin stabilization occurred in 86% of the pegcetacoplan arm and 0% in the control arm and difference in change from baseline in LDH was -1470 (-2113.4, -827.3) p<0.0001.[6] Secondary endpoints included change from baseline hemoglobin 2.7 (0.99, 4.35) p = 0.0019 and transfusion avoidance 72% (56%, 89%) p<0.0001.
- Pegcetacoplan is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to risk of serious infection.

- The recommended dose of pegcetacoplan is 1080 mg by subcutaneous infusion twice weekly through a commercially available infusion pump with a reservoir of at least 20mL.
    - Usual infusion time is 60 minutes if using 1 infusion site and 30 minutes if using 2 infusion sites.
- To reduce the risk of hemolysis associated with abrupt treatment discontinuation, the following are recommendations for switching to alternative products:
    - If changing from eculizumab: pegcetacoplan should be started and eculizumab should be continued at its current dose. After four weeks of concomitant therapy, eculizumab can be discontinued.
    - If changing from ravulizumab: pegcetacoplan should be started within four weeks of discontinuing treatment with ravulizumab.
- Similar products by indication:
    - Eculizumab (Soliris®) is FDA approved for the treatment of PNH, atypical hemolytic uremic syndrome, generalized myasthenia gravis and Neuromyelitis Optica Spectrum Disorder (NMOSD)
    - Ravulizumab (Ultomiris®) is FDA approved for the treatment of PNH in adult patients and hemolytic uremic syndrome.

REFERENCE/RESOURCES:

1. Empaveli package insert. Apellis Pharmaceuticals. Waltham, MA. September 2023.
2. Empaveli In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September 10, 2021
3. Empaveli In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed September 10, 2021
4. Cançado RD, Araújo ADS, Sandes AF, *et al*. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021 Jul-Sep;43(3):341-348.
5. Sahin F, Akay OM, Ayer M, Dal MS, Ertop S, Ilhan O, Karakus V, Ozcan MA, Ozkocaman V, Ozsan H, Salim O, Tobu M, Tombak A, Tuglular TF, Yilmaz M, Unal A, Yenerel MN, Saydam G. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016 Aug 5;6(2):19-27.
6. Wong RSM, Navarro-Cabrera JR, Comia NS, *et al*. Pegcetacoplan controls hemolysis in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023 Jun 13;7(11):2468-2478.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM031.1223	**HEMATOLOGICAL AGENTS** **ENJAYMO®** (sutimlimab-jome injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 10/22, 04/23, 10/23 (JCN)
Original Effective Date: 08/22	**P&T Committee Meeting Date**: 06/22, 12/22, 04/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy** (new start), all the following must be met (supporting documentation is required):

1. Diagnosis of primary cold agglutinin disease (CAD) by all the following:
    a. Chronic hemolysis, confirmed by low levels of haptoglobin, and high levels of unconjugated bilirubin and lactate dehydrogenase
    b. Positive direct antiglobulin (Coombs) test for C3d. (Note: a positive is graded as a 1+, 2+, or 3+)
    c. Cold agglutinin titer of 1:64 or higher at 4 degrees Celsius
    d. Presence of one or more symptom associated with CAD such as symptomatic anemia, acrocyanosis, Raynaud's phenomenon, hemoglobinuria
2. Hemoglobin of 10 g/dL or less
3. Dose and frequency are in accordance with FDA-approved labeling

For patients that are **established on therapy,** all the following must be met (Note: Medications obtained as samples, coupons, or any other method of obtaining

medications outside of an established health plan benefit are NOT considered established on therapy)**:**

1. Diagnosis of cold agglutinin disease
2. Documentation of successful response to therapy defined as an increase in hemoglobin level, improvement in markers of hemolysis (such as haptoglobin, unconjugated bilirubin, lactate dehydrogenase), improvement in the signs and symptoms (such as fatigue, shortness of breath) or reduced transfusion requirements
3. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
Intended use is for treatment of cold-induced symptoms of cold agglutinin disease such as Raynaud phenomenon, acrocyanosis

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist or an oncologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for a year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Sutimlimab-jome (Enjaymo®) is the first FDA-approved drug for cold agglutinin disease. It is a humanized monoclonal antibody complement inhibitor of C1s.

Inhibition of C1 leads to the prevention of deposition of complement opsonins on red blood cell (RBC) surfaces, resulting in inhibition of hemolysis.

FDA APPROVED INDICATIONS:
Treatment of hemolysis in adults with cold agglutinin disease (CAD).

POSITION STATEMENT:
Cold agglutinin disease (CAD) is a rare form of autoimmune hemolytic anemia caused by cold-reacting autoantibodies. The autoantibody reacts at temperatures lower than body temperature. Most often the autoantibody in CAD is immunoglobulin M (IgM). CAD is primarily characterized by chronic hemolysis. Anemia in CAD can be mild to severe, and some individuals may become transfusion dependent. Exacerbation of hemolysis can be triggered by cold temperature, acute illness, trauma, or surgery. Additional clinical symptoms are often related to RBC agglutination in cooler parts of the body (for example, Raynaud's phenomenon, acrocyanosis, livedo reticularis). Individuals may also be at increased risk for thromboembolic events. As with other autoimmune hemolytic anemias, it can be classified as primary or secondary. Secondary cold agglutinin syndrome is most often caused by an infection or malignancy. Treatment for secondary cold agglutinin syndrome involves treating the underlying condition.[5,7,9,11]

General measures for cold agglutinin disease include avoiding cold exposure and, if applicable, prewarming any infusions. Supportive therapies for anemia may include erythropoietin and folic acid while emergency therapies may include transfusions, plasmapheresis, or eculizumab. Corticosteroids and splenectomy are generally not recommended therapies.[5,7,10]

Treatment recommendations from the *First International Consensus Meeting* for the diagnosis and treatment of autoimmune hemolytic anemia in adults (2019) include:[5]
- Rituximab or (rituximab + bendamustine for fit patients) as first line for symptomatic disease (i.e., symptomatic anemia, transfusion dependence, circulatory symptoms)
- Second line options include rituximab + bendamustine, clinical trials/experimental treatment, rituximab + fludarabine or bortezomib

British Society for Haematology (2016) working group recommendations include:[10]
- Rituximab as first line treatment for symptomatic disease
- The addition of fludarabine can be considered if clonality has been demonstrated
- Rituximab in prospective uncontrolled trials has a response rate of about 50% with a median Hgb increase of 4 g/dL, median time to response of 1.5 months and response duration of approximately one year.[9,13]
- Rituximab + bendamustine in an observation prospective study demonstrated a 70% response rate, median Hgb increase of 4.4 g/dL in complete responders,

median time to response of 1.9 months (upper range 12 months), with less than 10% of responders relapsing by 32 months. However, grade 4 neutropenia occurred in 20% of patients.[13]

- Bortezomib single cycle dosing in a study of 21 patients for whom at least one prior therapy was ineffective, had a responder rate of (32%). Median duration of response was 16 months.[12]

Approval of Enjaymo® was based on a phase 3 open-label, single arm study of 24 patients with primary CAD with chronic hemolysis and a Hgb ≤10 g/dL that received a blood transfusion within the previous six months[4].

- Intervention: sutimlimab 6.5 g or 7.5 g (for patients 75 kg or greater), once per week for the first two doses followed by every other week dosing
    - Transfusions were performed if Hgb less than 9 g/dL and was symptomatic or Hgb less than 7 g/dL with or without symptoms
- Primary endpoint: Composite of the percentage of patients that had Hgb of at least 12 g/dL or Hgb increase of at least 2 g/dL from baseline without red-cell transfusion from week 5 through week 26 or medications for cold agglutinin disease prohibited by the protocol (rituximab monotherapy or rituximab combination therapies)
- Efficacy:
    - 13 of 24 patients (54%; 95% confidence interval, 33 to 74) met the composite primary endpoint
        - Clinically meaningful if responder rate at least 30% of patients
    - 17 patients (70.8%) were transfusion free from week 5-26
    - Three patients did not have any hematologic response
    - Mean Hgb levels started to rise within first week (1.2 g/dL) and was a mean increase of 2.3 g/dL by the third week
    - Mean bilirubin level normalized within three weeks
- Safety:
    - Warnings & precautions: May increase susceptibility to serious infections, may potentially increase the risk for developing autoimmune diseases such as systemic lupus erythematosus (SLE), infusion related reactions, recurrent hemolysis after discontinuation
    - Most common adverse reactions include infections (such as respiratory, skin, viral) and gastrointestinal (diarrhea and dyspepsia)

The Cadenza trial[16] was a phase 3 randomized, placebo-controlled, double-blind study to assess safety and efficacy of sutimlimab in patients with CAD with Hgb ≤10 g/dL without recent (within 6 months prior to enrollment) transfusion history.

- Intervention: 42 patients were randomized to receive 26 weeks of either sutimlimab or placebo once per week for the first two doses followed by every other week dosing

    - Transfusions were performed if Hgb less than 9 g/dL and symptomatic or Hgb less than 7 g/dL with or without symptoms
- Primary endpoint: Composite of Hgb increase from baseline of ≥1.5 g/dL at the treatment assessment timepoint (mean values from weeks 23, 25, and 26), absence of blood transfusions from week 5 to week 26, and avoidance of protocol-prohibited CAD medications from week 5 to week 26.
- Efficacy:
    - Composite primary endpoint was met by 16/22 patients (72.7%) treated with sutimlimab and 3/20 patients (15.0%) who received placebo (odds ratio, 15.9 [95% confidence interval, 2.9, 88.0; P<.001])
        - At treatment assessment timepoint, 16 patients (72.7%) treated with sutimlimab vs 3 patients (15.0%) with placebo had an increase in Hgb levels ≥1.5 g/dL from baseline
        - Between weeks 5 and 26, 18 patients (81.8%) in the sutimlimab arm and 16 patients (80.0%) in the placebo arm did not receive blood transfusions
        - 19 patients (86.4%) of sutimlimab patients did not require use of protocol-prohibited CAD medications from week 5 to week 26, versus 20 (100%) of placebo-treated patients
    - Secondary Endpoints:
        - 15 (88.2%) in the sutimlimab arm and 4 (22.2%) of patients in placebo arm achieved normal total bilirubin levels at treatment assessment endpoint
        - Sutimlimab treatment led to clinically meaningful improvement in fatigue, versus no change for placebo-treated patients
- Safety:
    - 21 (96%) of sutimlimab patients and 20 (100%) of placebo patients experienced ≥1 treatment-emergent adverse event.
        - Headache, hypertension, rhinitis, Raynaud phenomenon, and acrocyanosis were more frequent with sutimlimab vs placebo
    - 3 sutimlimab patients discontinued owing to adverse events; no placebo patients discontinued
- There is an ongoing open-label extension period to this study in which patients continue to receive sutimlimab for a minimum of 1 year after the initial period of the study

Sutimlimab is not expected to help cold-induced symptoms such as Raynaud phenomenon and acrocyanosis as these symptoms are caused by RBC agglutination and are not complement mediated[1,5].
Other possible areas of future research and use include acute life-threatening hemolysis in patients with CAD, pre-op use in cardiac surgery patients to prevent

CAD-exacerbation associated with hypothermia, and to increase platelet counts in patients with chronic immune thrombocytopenia[14,15].

REFERENCE/RESOURCES:

1. Enjaymo package insert. Bioverativ USA Inc. Waltham, MA: February 2023.
2. Sutimlimab: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed February 1, 2023.
3. Sutimlimab: In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed February 1, 2023.
4. Röth A, Barcellini W, D'Sa S, *et al*. Sutimlimab in Cold Agglutinin Disease. N Engl J Med. 2021 Apr 8;384(14):1323-1334.
5. 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
6. Jäger U, D'Sa S, Schörgenhofer C, et al. Inhibition of complement C1s improves severe hemolytic anemia in cold agglutinin disease: a first-in-human trial. *Blood*. 2019;133(9):893-901.
7. National Organization for Rare Diseases. Cold agglutinin disease. Available at https://rarediseases.org/rare-diseases/cold-agglutinin-disease/ (Accessed April 17, 2022).
8. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 761164Orig1s000 Summary Review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761164Orig1s000TOC.cfm (Accessed May 1, 2022)
9. UptoDate: Cold agglutinin disease. (Accessed November 2, 2023)
10. Hill QA, Stamps R, Massey E, et al on behalf of the British Society for Haematology. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol 2017; 176:395.
11. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. Blood. 2013 Aug 15;122(7):1114-21.
12. Rossi G, Gramegna D, Paoloni F, *et al*. Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study. Blood. 2018 Aug 2;132(5):547-550.
13. Berentsen S, Barcellini W, D'Sa S, *et al*. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. Blood. 2020 Jul 23;136(4):480-488.
14. Tvedt THA, Steien E, Øvrebø B, *et al*. Sutimlimab, an investigational C1s inhibitor, effectively prevents exacerbation of hemolytic anemia in a patient with cold agglutinin disease undergoing major surgery. Am J Hematol. 2022 Feb 1;97(2):E51-E54.

15. Catherine M. Broome, Alexander Röth, David J Kuter, Marie Scully, Roy Smith, Jennifer Wang, Caroline Reuter, William Edward Hobbs, Ahmed Abd Almalik Daak; Safety and Efficacy of Classical Complement Pathway Inhibition with Sutimlimab in Chronic Immune Thrombocytopenia. Blood Adv 2022; bloodadvances.2021006864. doi: https://doi.org/10.1182/bloodadvances.2021006864
16. Alexander Röth, Sigbjørn Berentsen, Wilma Barcellini, Shirley D'Sa, Bernd Jilma, Marc Michel, Ilene C. Weitz, Masaki Yamaguchi, Jun-ichi Nishimura, Josephine M. I. Vos, Michael Storek, Nancy Wong, Parija Patel, Xiaoyu Jiang, Deepthi S. Vagge, Marek Wardęcki, Frank Shafer, Michelle Lee, Catherine M. Broome; Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. Blood 2022; 140 (9): 980–991. doi: https://doi.org/10.1182/blood.2021014955

Brand Name	Generic Name	HCPCS Code
Enjaymo®	sutimlimab-jome	J1302

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY CRITERIA POLICY AND CRITERIA ORPTCEND082.1023	**ENDOCRINE & METABOLIC DRUGS** **ENZYME REPLACEMENT THERAPY** See Table 1 for Medications
Effective Date: 1/1/2024  **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 10/23 (JCN) P&T Committee Meeting Date: 06/23, 10/23 Original Effective Date: 08/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 25

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts to therapy) all the following criteria must be met:

1. Documentation of FDA-labeled indication (See Appendix 1) for the requested product
2. Dosing is within FDA-labeled guidelines (See Appendix 1).
3. For avalglucosidase alfa (Nexviazyme®) only: Patients weighing less than 30 kg must have a documented trial, failure, intolerance or contraindication to alglucosidase alfa (Lumizyme®)
4. For olipudase alfa (Xenpozyme®) only, the following additional criteria must be met:
    a. Clinical presentation must be consistent with acid sphingomyelinase deficiency (ASMD) type B OR ASMD type A/B
    b. Spleen volume of six multiples of normal (MN) or more for adults OR five MN or more for those less than 18 years old
    c. For adults only, diffusing capacity of the lungs for carbon monoxide (DLco) equal to 70% or less of predicted normal value
    d. The following are excluded from coverage:

i. Use of invasive ventilatory support, or noninvasive ventilatory support while awake for greater than 12 hours a day
ii. Acute or rapidly progressive neurological abnormalities and/or genotypes associated with ASMD type A, meaning homozygous for SMPD1 gene mutations R496L, L302P, and fs330 or any combination of these three mutations

5. For cerliponase alfa (Brineura®) only, the following additional criteria must be met:
    a. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2) confirmed by both of the following:
        i. Deficiency of tripeptidyl peptidase 1 (TPP1) enzyme activity (in a sample of leukocytes, fibroblasts, dried blood spot or saliva)
        ii. Genetic testing revealing one pathogenic mutation on each parental allele of TPP1/CLN2 gene
    b. Documentation of symptomatic disease (such as, seizures, changes in gait, falls, difficulty in ambulating, loss of language/delay in language development, visual failures)
    c. Baseline Motor Domain of the CLN2 Clinical Rating Scale score of at least one (See Appendix 2)
6. For velmanase alfa only, the following additional criteria must be met:
    a. Confirmed diagnosis of alpha-mannosidosis as defined by alpha-mannosidase activity less than 10% of normal activity in blood leukocytes
    b. Documented baseline serum oligosaccharide level
    c. Documented baseline value of either 6-minute walk test, 3-minute stair climb or forced vital capacity. Note: This may be waved for children under the age of three. Improvement or stabilization is required for reauthorization.
    d. Therapy is being used to treat non-central nervous system manifestations of alpha mannosidosis such as skeletal abnormalities, myopathy, motor function disturbances, immune deficiency
    e. No prior history of bone marrow transplant

Note: If request is for a non-FDA approved dose, medical rational must be submitted in support of therapy with a higher dose for the intended diagnosis such as high-quality peer reviewed literature, accepted compendia or evidence-based practice guidelines and exceptions will be considered on a case-by-case basis.

For patients currently established on the requested therapy, all the following criteria must be met. Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

1. Documentation of successful response to therapy (e.g., disease stability or improvement in symptoms).
    a. For olipudase alfa (Xenpozyme®) only, documentation of improvement in at least one of the following: spleen volume, liver volume, platelet count, DLco or forced vital capacity (FVC)
    b. For cerliponase alfa (Brineura®) only, documentation of both of the following:
        i. No more than a 1-point decline in the Motor Domain of the CLN2 Clinical Rating Scale
        ii. Motor Domain of the CLN2 Clinical Rating Scale score remains above zero
    c. For velmanase alfa (Lamzede®) only, documentation of one of the following:
        i. For initial reauthorization: a decrease of serum oligosaccharides of 3 micromoles per liter or at least 30%
        ii. For subsequent reauthorizations: stabilization or improvement in either the 6-minute walk test, 3-minute stair climb or forced vital capacity
2. Dosing is within FDA-labeled guidelines

Note: If request is for a non-FDA approved dose, medical rational must be submitted in support of therapy with a higher dose for the intended diagnosis (such as high-quality peer reviewed literature, accepted compendia or evidence-based practice guidelines) and exceptions will be considered on a case-by-case basis.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hepatologist, endocrinologist, medical geneticist, cardiologist, pulmonologist, neurologist, or bone and mineral specialist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

QUANTITY LIMIT:
Initial dose approval will be based on patient's current weight (See Appendix 1). Increases in dose will require new authorization with patient's weight and relevant chart notes

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Enzyme replacement therapy is used to replace absent or defective enzymes in several different lysosomal storage diseases. Lysosomal storage diseases are genetically inherited rare disorders causes by deficient activity of a distinct lysosomal enzyme. This results in accumulation of undegraded substrates leading to cellular and organ dysfunction. There are currently over fifty identified lysosomal storage diseases that affect different parts of the body with varying degrees of severity. Other treatment options for lysosomal storage diseases may include bone marrow transplant, gene therapy, substrate reduction therapy (for Gaucher disease), a pharmacologic chaperone (stabilizes and increases activity of a deficient enzyme in Fabry disease) and symptomatic treatments for the underlying disease.

Aldurazyme® (laronidase) is a recombinant form of human alpha-L-iduronidase. It provides exogenous enzyme for uptake into lysosomes and increase the catabolism of glycosaminoglycans (GAG). Laronidase uptake by cells into lysosomes is probably mediated by the mannose-6-phosphate receptors. Aldurazyme is approved for Mucopolysaccharidosis I (MPS I) and has been shown to improve pulmonary function (forced vital capacity) and walking capacity.

Elaprase® (idursulfase) is a purified form of human iduronate-2-sulfatase lysosomal enzyme. It provides an exogenous enzyme source to allow for catabolism of GAG in patients with Mucopolysaccharidosis II (MPS II) or Hunter Syndrome, where a deficiency of this enzyme results in GAG accumulation and subsequent organ dysfunction. Boxed warning includes higher incidence of hypersensitivity, serious adverse reactions, and antibody development in Hunter Syndrome patients aged seven years and younger with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations.

Mepsevii® (vestronidase alfa) is indicated for MPS VII, also known as Sly Syndrome, is caused by mutations in the gene that encodes for beta-glucuronidase, located on chromosome 7q21.11. It is associated with significant soft tissue and skeletal abnormalities. A common presentation is hydrops fetalis. Heart disease and airway obstruction are major causes of death in people with MPS VII

Naglazyme® (galsulfase) is the first FDA approved treatment for patients with Mucopolysaccharidosis VI (MPS VI). Naglazyme® (galsulfase) is a hydrolytic lysosomal GAG-specific enzyme that decreases urinary GAG excretion and improves patient function and survival.

Vimizim® (elosulfase alfa) is the first FDA approved drug for Morquio A syndrome (MPS IVA), a rare autosomal recessive lysosomal storage disease. This condition results from the absence of the enzyme N-acetylgalactosamine-6-sultae sulfatase (GALNS) which normally clears out long chains of sugar molecules. About 800 people suffer from the disease in the U.S., with 3,000 patients in the developed world. Vimizim® is intended to provide the exogenous GALNS enzyme.

Black Box Warning for enzyme replacement therapies for MPS:
These agents contain boxed warning for risk of life-threatening anaphylactic reactions. Patients with compromised respiratory and/or cardiac function or acute respiratory and/or cardiac disease may be at risk of serious acute exacerbation due to infusion reactions. Appropriate medical support should be readily available when infusions of enzyme replacement therapies are administered.

Cerezyme® (imiglucerase), Elelyso® (taliglucerase alfa) and Vpriv® (velaglucerase alfa) are all indicated for the treatment of Gaucher's Disease. Cerezyme® is a human enzyme beta-glucocerebrosidase analog which catalyzes the hydrolysis of the lipid glucocerebroside to glucose and ceramide which prevents its accumulation in macrophages. Elelyso™ is a hydrolytic lysosomal glucocerebroside-specific enzyme which catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In patients with type 1 Gaucher's disease, treatment with taliglucerase alfa reduced spleen and liver size, and stabilized hematologic parameters. Vpriv® is an enzyme created by gene activation technology in human fibroblast cells it catalyzes hydrolysis of glucocerebroside.

Fabrazyme® and Elfabrio® are used for patients with Fabry disease. These enzymes reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. In adults, Elfabrio® was found to be non-inferior to Fabrazyme® in slowing kidney function decline. Elfabrio® has a longer

half-life than Fabrazyme® and is currently being studied for every four week dosing.

Kanuma® (sebelipase alfa) binds to cell surface receptors via glycans expressed on the protein and is subsequently internalized into lysosomes. Sebelipase alfa catalyzes the lysosomal hydrolysis of cholesteryl esters and triglycerides to free cholesterol, glycerol, and free fatty acids. In patients with lysosomal acid lipase (LAL) deficiency, replacement with sebelipase alfa, a recombinant form of LAL, results in improvement in disease-related hepatic and lipid parameters.

Lumizyme® (alglucosidase alfa) is a recombinant human enzyme, acid alpha-glucosidase (GAA), produced in a Chinese hamster ovary cell line. Alglucosidase alfa provides an exogenous source of GAA, the enzyme that is absent or deficient in Pompe disease (glycogen storage disease type II). It contains a boxed warning for risk of life-threatening anaphylactic reactions and severe hypersensitivity have occurred during and after infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following treatment. Therefore, patients need to be closely observed during and after administration. Patients must be informed about the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and be advised to seek immediate medical attention should signs/symptoms occur. Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious exacerbation due to fluid overload and require additional monitoring.

Nexviazyme® (avalglucosidase alfa-ngpt) also provides an exogenous source of GAA for patients with Pompe disease. It carries similar warning and precautions as Alglucosidase alfa.

Xenpozyme® (olipudase alfa) provides an exogenous source of the enzyme acid sphingomyelinase (ASM), the enzyme that is deficient in acid-sphingomyelinase deficiency (ASMD). Olipudase alfa degrades sphingomyelin to ceramide and phosphocholine. Olipudase alfa is not expected to cross the blood-brain barrier or alter CNS manifestations of ASMD.[18,22,23]

Velmanase alfa-tycv (Lamzede®) provides an exogenous source of alpha-mannosidase. Velmanase alfa binds to extracellular mannose-6-phosphate receptors on the cell surface and is transported into lysosomes where it exerts enzyme activity. Alpha-mannosidase catalyzes the degradation of accumulated mannose-containing oligosaccharides. Velmanase alfa is not expected to cross the blood-brain barrier or alter CNS manifestations of alpha-mannosidosis[1,29].

Cerliponase alfa, a proenzyme, is taken up by target cells in the central nervous system and is translocated to the lysosomes through the Cation Independent Mannose-6-Phosphate Receptor (CI-MPR, also known as M6P/IGF2 receptor). Cerliponase alfa is activated in the lysosome and cleaves from the N-terminus of proteins to minimize accumulation of lysosomal storage materials.

FDA APPROVED INDICATIONS: See Appendix 1

POSITION STATEMENT:
Mucopolysaccharidoses (MPS) is a group of inherited diseases in which a defective or absence of an enzyme causes large amounts of complex sugar molecules to accumulate in harmful amounts in the body's cells and tissues. This accumulation causes permanent, progressive cellular damage that affects appearance, physical abilities, organ and system function, and in most cases, mental development.

There are distinct types and subtypes of MPS. Deficiencies are in the following enzymes:

MPS I (Hurler – most severe form, Hurler-Scheie – intermediate, Scheie – least severe form): alpha-L-iduronidase
MPS II (Hunter syndrome): iduronate sulfatase
MPS IIIA: heparan N-sulfatase
MPS IIIB: alpha-N-acetylglucosaminidase
MPS IIIC: acetyl-CoA:alpha-glucosaminide acetyltransferase
MPS IIID: N-acetylglucosamine 6-sulfatase
MPS IV (Morquio syndrome): N-acetylgalactosamine 6-sulfatase (Type A) or beta-galactosidase (Type B)
MPS VI (Maroteaux-Lamy syndrome): N-acetylgalactosamine 4-sulfatase
MPS VII (Sly syndrome): beta-glucuronidase

Clinical examination and urine tests (excess mucopolysaccharides are excreted in the urine) are the first steps in the diagnosis of an MPS disease but enzyme assays testing a variety of cells or blood in culture for enzyme deficiency or genetic testing are used to provide definitive diagnosis of one of the mucopolysaccharidoses. Urine glycosaminoglycan (GAG) concentrations vary based on age and are subject to dilution effects so may not be a reliable confirmatory measure.

Gaucher disease (GD) is an inborn error of metabolism in which deficiency of the enzyme glucocerebrosidase results in the glycolipid glucocerebroside, throughout the body especially within the bone marrow, spleen and liver. There are different presentations (types) of Gaucher disease and the symptoms and physical findings

can vary greatly with some patients being asymptomatic with others suffering serious consequences. Enzyme replacement therapy (ERT) in patients with non-neuronopathic Gaucher disease Type 1 is usually reserved for patients with clinically significant manifestations of the disease.

Fabry Disease is an X-linked genetic disorder caused by a mutation in lysosomal enzyme alpha-galactosidase A leading to a buildup of globotriaosylceramide, or Gb3, which is an intermediate metabolite of globoside, a major glycosphingolipid. Gb3 is suspected to have cytotoxic, proinflammatory, and profibrotic effects and classical presentation of the disease often involves renal and cardiac dysfunction, neuropathies, and gastrointestinal symptoms. Both males and females can have varying symptoms and severity of the disease.

Pegunigalsidase alfa (Elfabrio®) may have a favorable immunogenicity profile over agalsidase beta as the proportion of patients with neutralizing anti-drug antibodies declined over time with pegunigalsidase alfa but not with agalsidase beta (Fabrazyme®) in unpublished BALANCE trial[34]. Evidence from one published phase 1/2 trial that pegunigalsidase alfa reduces the number of renal Gb3 inclusions (a surrogate marker) in adult patients with Fabry disease not currently on enzyme replacement therapy. Prespecified noninferiority margin was met in one unpublished phase 3 trial comparing pegunigalsidase alfa to agalsidase beta. The median eGFR slope in the pegunigalsidase alfa arm was -2.514 mL/min/1.73 m2/year and -2.155 mL/min/1.73 m2/year in the agalsidase beta arm. Migalastat (Galafold®) is currently approved under accelerated approval for only patients with an amenable mutation (~30% of those with Fabry disease).

Lysosomal acid lipase deficiency (LALD) is a metabolic storage disease that includes Wolman disease (early-onset, severe) and Cholesteryl ester storage disease ([CESD] late-onset, less severe). LALD is caused by mutations in the LIPA gene, which provides instructions to produce the lysosomal acid lipase enzyme. When there is not enough of this enzyme, the body cannot break down certain fats and this leads to a toxic buildup of fatty substances in the body's cells and tissues.

Rapidly Progressive LAL Deficiency Presenting within the First 6 Months of Life (Wolman disease)
A multicenter, open-label, single-arm clinical study of sebelipase alfa was conducted in nine infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to six months of age. The age range at entry was one to six months. Patients received sebelipase alfa at 0.35 mg/kg once weekly for the first two weeks and then 1 mg/kg once weekly. Due to suboptimal clinical response, doses in all six surviving patients were escalated to 3 mg/kg once weekly, between four and 88 weeks (median 11 weeks) after starting treatment at 1 mg/kg.

In one patient, the dose was escalated to 5 mg/kg once weekly at Week 88 due to decreased growth velocity in a setting of positive neutralizing anti-drug antibodies to sebelipase alfa. The recommended dosage for these patients is 1 mg/kg to 3 mg/kg once weekly.

Efficacy of sebelipase alfa was assessed by comparing the survival of nine sebelipase alfa-treated patients at 12 months of age with an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics. Of the nine sebelipase alfa-treated infants, six patients survived beyond 12 months of age, compared to 0 of 21 patients in the historical cohort, all of whom died by eight months of age. The median age of the six surviving sebelipase alfa-treated patients was 18.1 months (range 12 to 42.2 months). Following initiation of treatment with sebelipase alfa 1 mg/kg once weekly, weight-for-age z-scores improved in three of five surviving patients with growth failure, and all six surviving patients demonstrated improvements in weight-for-age z-scores following dose escalation to 3 mg/kg once weekly.

Pediatric and Adult Patients with LAL Deficiency (Cholesteryl ester storage disease)
The safety and efficacy of sebelipase alfa were assessed in 66 pediatric and adult patients with LAL deficiency, aged four to 58 years (71% were less than 18 years old), in a multicenter, double-blind, placebo-controlled trial. Patients were randomized to receive sebelipase alfa at a dosage of 1 mg/kg (n=36) or placebo (n=30) once every other week for 20 weeks in the double-blind period. Sixty-two of the 66 (94%) patients had LDL-c of 130 mg/dL or greater at study entry. The majority of patients (58%) had LDL-c above 190 mg/dL at study entry, and 24% of patients with LDL-c above 190 mg/dL remained on lipid lowering medications. At the completion of the 20-week double-blind period of the trial, a statistically significant improvement in percent change from baseline in LDL-c was observed in the sebelipase alfa-treated group as compared to the placebo group (mean difference and 95% C.I.: -22%, [-33%, -15%]; p<0.0001). LDL-c of less than 130 mg/dL was achieved in 13 of 32 (41%; 95% C.I.: [24%, 58%]) sebelipase alfa-treated patients and in only two of 30 (7%; 95% C.I.: [0%, 16%]) placebo-treated patients with baseline LDL-c of 130 mg/dL or greater. A statistically significant improvement in percent change from baseline at 20 weeks was also observed in the sebelipase alfa-treated group, compared to the placebo group for other parameters related to LAL deficiency, including decreases in non-HDL-c (mean difference and 95% C.I.: -21%, [-30%, -15%]; p<0.0001) and triglycerides (mean difference and 95% C.I.: -14%, [-28%, -1%]; p=0.0375), and increases in HDL-c (mean difference and 95% C.I.: 20%, [12%, 26%]; p<0.0001). The effect of sebelipase alfa on cardiovascular morbidity and mortality has not been established.

Patients treated with sebelipase alfa had larger reductions from baseline in ALT values and liver fat content (measured by MRI), compared to patients treated with placebo. The significance of these findings as they relate to progression of liver disease in LAL deficiency has not been established.

Open-label Extension
Pediatric and adult patients who participated in the randomized, placebo-controlled trial were eligible to continue treatment in an open-label extension. Sixty-five of 66 patients (98%) entered the open-label period in which all patients received sebelipase alfa at a dosage of 1 mg/kg once every other week. During the open-label extension, patients treated with sebelipase alfa for up to 36 weeks demonstrated improvements in lipid parameters, including LDL-c and HDL-c levels, and ALT.

Pompe Disease is a rare condition with two available enzyme therapies approved for treatment alglucosidase alfa (Lumizyme®) and avalglucosidase alfa (Nexviazyme®). Previously, alglucosidase alfa was also available as Myozyme® but it is no longer available in the U.S.

Myozyme® (alglucosidase alfa) has been used in the treatment of infantile-onset Pompe disease in open-label clinical trials, resulting in improvements in ventilator-free survival compared to untreated historical controls in one trial and no improvements in survival versus untreated historical controls in another trial. The safety and efficacy of Lumizyme® (alglucosidase alfa) was assessed in one 18 month pivotal, randomized, double-blind, placebo-controlled, multicenter study in 90 patients with late onset Pompe disease. Lumizyme-treated patients had an increase in the distance walked on 6-minute walk test (6MWT) as well as an increase in the predicted forced vital capacity (FVC). For patients treated with Lumizyme®, the mean increase in 6MWT was 25.1 meters (average baseline 332.2 meters); the placebo group experienced a 3.0 meter (average baseline 317.9 meters) reduction in 6MWT distance (P = 0.03, for the difference). The estimated change in FVC expressed as a percentage of each patients predicted value, was an increase of 1.2 percentage points for the patients treated with Lumizyme® and a decrease of 2.2 percentage points for the patients who received placebo (P = 0.006, for the difference).

Avalglucosidase alfa (Nexviazyme® and alglucosidase alfa (Lumizyme®) are structurally and mechanistically similar. Nexviazyme® was designed to increase cellular uptake of the enzyme through a 15-fold increase in M6P content compared to Lumizyme®, the clinical implications of this have not been demonstrated in clinical trials. In the Phase 3 COMET trial, Nexviazyme® was found to be noninferior to

Lumizyme® and did not meet the threshold for superiority. In addition, patients previously treated with Lumizyme® were excluded from the COMET trial.

Acid-sphingomyelinase deficiency (ASMD) is an autosomal recessive lysosomal disease caused by mutations in the *SMPD1* gene. It is also known as ASM-deficient Niemann-Pick disease. The enzyme acid sphingomyelinase metabolizes sphingomyelin into ceramide and phosphocholine. A deficiency in ASM leads to accumulation of sphingomyelin in organ systems such as liver, spleen, lymph nodes, adrenal cortex, lung airways, bone marrow and central nervous system (CNS). There is a spectrum of disease with ASMD ranging from severe (Type A) to milder form (Type B). Individuals with ASMD Type A experience hepatosplenomegaly, pathologic changes to the lungs in infancy and severe CNS involvement. ASMD Type A is a fatal neurodegenerative disease that presents in infancy and individuals rarely survive beyond two to three years of age. Individuals with ASMD Type B have less severe disease and little to no CNS involvement with most having later onset of symptoms and can survive into adulthood. Individuals with AMSD Type A/B can have vastly different disease presentation and progression rate but all have some CNS manifestation. Prior to olipudase alfa, treatment was supportive therapy. [18,19] Olipudase alfa is not expected to treat CNS manifestations of ASMD as it does not cross the blood brain barrier.[1,18]

Olipudase alfa was studied in adults (ASCEND) and pediatrics (ASCEND-Peds) with ASMD type B or type A/B. No individuals with ASMD type A were enrolled in the trials. Key inclusion criteria included spleen volume ≥6 multiples of normal (MN) measured by MRI or ≥5 MN for patients less than 18 years old and for adults only, diffusing capacity of the lungs for carbon monoxide (DLco) equal to 70% or less of predicted normal value. Individuals with acute or rapidly progressive neurological abnormalities and/or genotypes associated with ASMD type A as well as those dependent on ventilatory support were excluded from the trials.
Olipudase alfa showed improvement in the primary efficacy endpoint spleen volume and in the ASCEND trial, diffusing capacity of the lung (DLco). Improvements in other key endpoints, liver volume and platelet count, were also observed.

CLN2 is a rare (0.22 to 9 per 100,000 live births), autosomal recessive neurodegenerative disorder caused by mutations in the TPP1/CLN2 gene and the resulting TPP1 enzyme deficiency. With TPP1 enzyme deficiency, there is accumulation of ceroid and neuronal loss. Presentation is often with seizures and ataxia, usually at age 2-4 (late-infantile onset).

The expert recommended gold standard for diagnosis of CLN2 is deficient TPP1 enzyme activity (in leukocytes, fibroblasts, or dried blood spots) in the setting of normal activity of a control enzyme such as palmitoyl-protein thioesterase 1 (PPT1)

and/or β-galactosidase and the identification of causative mutations in each allele of the TPP1/CLN2 gene. Alternatively, if this is not possible to obtain both analyses, CLN2 can be diagnosed with demonstration of either:

- Deficient TPP1 enzyme activity in leukocytes or fibroblasts
- Detection of two pathogenic mutations in trans of the TPP1/CLN2 gene.

Cerliponase alfa was studied in a single arm, Phase I/II, open-label, dose escalation (initial dose of 30-300 mg every 14 days, then 300 mg every 14 days) 48-week clinical trial. Patients (N=24 treated, N=42 in historical control) aged 3-15 years with confirmed diagnosis of early to moderate CLN2 with TPP1 activity (dried blood spot) and CLN2 genotype analysis were enrolled in the trial. Early to moderate disease was defined as a score 3-5 on adapted two domain CLN2 disease rating scale, including a score of at least one in each domain. The CLN2 Clinical Rating Scale has a Motor and Language domain, each with a 0 to 3 score (the highest possible combined score is 6). However, only the Motor domain was used to assess disease progression in clinical studies. Decline was defined as a sustained 2-point loss or unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale. Of note, patients with previous stem cell, gene therapy, or enzyme replacement therapy for CLN2 disease were excluded from the trial. The primary endpoint was the response rate (defined as the absence of an unreversed two-point decline or score of zero in the CLN2 score) at 48 weeks, separately assessed as matched controls based on age and motor function. 87% (20/23) of treated patients responded to treatment at week 48 and 96 compared to the expected response rate of 50% from the historical control group (P-value=0.0002). All patients treated with cerliponase alfa had less than 2 point reduction in the motor and language domains compared to 43% of matched historical controls (P-value <0.001). This trial was limited by the small sample size due to rarity of condition and inconsistent treatment regimens.

Alpha-mannosidosis (AM) is a very rare (prevalence 1 in 500 000) lysosomal storage disorder that results from reduced activity of the enzyme alpha-mannosidase, caused by gene variants in the *MAN2B1* gene, resulting in progressive accumulation of mannose-rich oligosaccharides in various organs and tissues. There is a spectrum of disease with AM ranging from mild (Type 1) to severe form (Type 3). Symptoms vary widely in type and severity. Symptoms can include immunodeficiency (recurrent infections), facial and skeletal abnormalities, hearing impairment, impairment of speech, intellectual disability, muscular weakness, joint abnormalities and ataxia. Prior to velmanase alfa, treatment was primarily with supportive therapy. Varying success has been seen with bone marrow transplant in patients with AM.[31,33] Velmanase alfa is not expected to treat CNS manifestations of AM as it does not cross the blood brain barrier.[1,31]

Velmanase alfa was studied in a 52-week double blind placebo-controlled phase 3 trial. Twenty-five patients aged 6-35 years of age were enrolled. Individuals with a history of bone marrow transplant were excluded from the trial. The trial's primary endpoints were change in baseline serum oligosaccharides and 3-minute stair climb test. Change in serum oligosaccharides was statistically significantly reduced at 52 weeks. Absolute change from baseline in serum oligosaccharides was -3.5 µmol/L (-4.4, -2.6) p<0.001. The other primary endpoint, 3-minute stair climbing test as well as the secondary endpoints, forced vital capacity and 6-minute walk test, were not statistically significant but favored velmanase alfa.[32]

REFERENCE/RESOURCES:

1. Relevant package inserts
2. National Institute of Neurological Disorders and Stroke. Mucopolysaccharidoses Fact Sheet. Available at https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Mucopolysaccharidoses-Fact-Sheet. Accessed 2021 March 3.
3. Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.
4. National Institutes of Health Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov. Accessed March 3, 2021.
5. Van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of aglucosidase alfa in late-onset Pompe's disease. *N Engl J Med.* 2010;362(15):1396-1406.
6. Kishnanai PS, Steiner RD, Bali D, et al; ACMG work group on management of Pompe disease. *Genet Med.* 2006;8(5):267-288.
7. Strothotte S, Strigl-Pill N, Grunert C, et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12 month results of an observational clinical trial. *J Neurol*. 2010;257:91-97.
8. Myozyme becomes Lumizyme after biologics scale-up. [press release]. February 16, 2009. Accessed June 13, 2010. Available at: http://www.in-pharmatechnologist.com/Materials-Formulation/Myozyme-becomes-Lumizyme-after-biologics-scale-up.
9. Kishnani PS, Howell RR. Pompe disease in infants and children. J Pediatr. 2004 May;144(5 Suppl):S35-43.
10. Winkel LP, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. J Neurol. 2005 Aug;252(8):875-84.
11. Van der Ploeg AT, Reuser AJ. Lysosomal storage disease 2. Pompe's disease. *Lancet*. 2008;372:1342-1353.

12. Case LE, Bjartmar C, Morgan C et al. Safety and efficacy of alternative alglucosidase alfa regimens in pompe disease. Neuromuscul Disord. 2015;25(4):321-32.
13. Genetics Home Reference website. https://ghr.nlm.nih.gov. Updated periodically. Accessed February 11, 2020.
14. Genetic Testing Registry. https://www.ncbi.nlm.nih.gov/gtr/. Updated periodically. Accessed February 11, 2020.
15. National organization for rare disorders. Lysosomal storage disorders. https://rarediseases.org/rare-diseases/lysosomal-storage-disorders/ Accessed March 6, 2021.
16. Safary A, Akbarzadeh Khiavi M, Mousavi R, Barar J, Rafi MA. Enzyme replacement therapies: what is the best option?. *Bioimpacts*. 2018;8(3):153-157.
17. Bruni S, Loschi L, Incerti C, Gabrielli O, Coppa GV. Update on treatment of lysosomal storage diseases. *Acta Myol*. 2007;26(1):87-92.
18. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 761261Orig1s000 Integrated Review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000TOC.cfm (Accessed October 23, 2022)
19. National Organization for Rare Disorders (NORD). Acid Sphingomyelinase Deficiency. Available at https://rarediseases.org/rare-diseases/acid-sphingomyelinase-deficiency/ (Accessed October 23, 2022).
20. McGovern MM, Dionisi-Vici C, Giugliani R, *et al*. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. *Genet Med*. 2017 Sep;19(9):967-974.
21. Jones SA, McGovern M, Lidove O, *et al*. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. *Mol Genet Metab*. 2020 Sep-Oct;131(1-2):116-123.
22. Wasserstein M, Lachmann R, Hollak C, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. *Genet Med*. 2022;24:1425-36.
23. 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;23:1543-1550.
24. Cerliponase (Brineura) package insert. Novato, CA; BioMarin Pharmaceutical Inc. 2020 July.
25. Cerliponase (Brineura) In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed Feb 03, 2022.
26. Cerliponase (Brineura) In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed Feb 06, 2020.

27. Fietz M, AlSayed M, Burke D. Diagnosis of neuronal ceroid lipofuscinosis type 2 (CLN2 disease): Expert recommendations for early detection and laboratory diagnosis. Mol Genet Metab. 2016;119(1-2):160-7.
28. Brineura dossier provided by Biomarin Pharmaceutical. May 2017.
29. Lamzede In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 19, 2023
30. Lamzede In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed April 19, 2023
31. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 761278Orig1s000 Integrated Review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761278Orig1s000TOC.cfm (Accessed April 4, 2023)
32. 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 Nov;41(6):1215-1223.
33. National Organization for Rare Disorders (NORD). Alpha-mannosidosis. Available at https://rarediseases.org/rare-diseases/alpha-mannosidosis/ (Accessed April 4, 2023).
34. Clinicaltrials.gov. Study of the Safety and Efficacy of PRX-102 Compared to Agalsidase Beta on Renal Function (BALANCE). NCT02795676. Available at https://clinicaltrials.gov/study/NCT02795676 (Accessed September 5, 2023)
35. Bernat J, Wallace E, Goker-Alpan O, et al. Abstract P005: Head-to-head trial of pegunigalsidase alfa vs agalsidase beta in Fabry disease: Phase 3 randomized, double-blind, BALANCE Study 2-year results. GIM Open. Volume 1, Issue 1, Supplement, 2023, 100015.
36. National Institute for Health and Care Excellence. Final Draft Guidance. Pegunigalsidase alfa for treating Fabry disease. Available at https://www.nice.org.uk/guidance/gid-ta10790/documents/674 (Accessed September 5, 2023).

Table 1: Products associated with this policy and coding considerations

Brand Name	Generic Name/Dosage Form	HCPCS code
Aldurazyme®	Injection, laronidase, 0.1mg	J1931
Brineura®	injection, cerliponase alfa, 1mg	J0567/C9014
Cerezyme®	Injection, imiglucerase, 10 units	J1786
Elaprase®	Injection, idursulfase, 1mg	J1743
Elelyso®	Injection, taliglucerase alfa, 10 units	J3060
Elfabrio®	Injection, pegunigalsidase alfa-iwxj, 20 mg	
Fabrazyme®	Injection, agalsidase beta, 1 mg	J0180
Kanuma®	Injection, sebelipase alfa, 1mg	J2840
Lamzede®	Injection, velmanase alfa, 10 mg	
Lumizyme®	Injection, alglucosidase alfa (Lumizyme), 10mg	J0221
Mepsevii®	Injection, vestronidase alpha-vjbk, 10 mg	J3397
Naglazyme®	Injection, galsulfase, 1mg	J1458
Nexviazyme®	Injection, avalglucosidase alfa-ngpt, 10 mg	J0219
Vimizim®	Injection, elosulfase alfa, 1mg	J1322
Vpriv®	Injection, velaglucerase alfa, 100 units	J3385
Xenpozyme®	Injection, olipudase alfa, 20 mg	J0218

PHARMACY PRIOR AUTHORIZATION POLICY AND STEP THERAPY CRITERIA ORPTCEND	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Appendix 1.

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
Laronidase (Aldurazyme®)	MPS I (Hurler, Scheie, and Hurler-Scheie forms)	• Molecular genetic testing of mutation in the alpha-L-iduronidase (*IDUA)* gene • Deficiency or absence of fibroblast or leukocyte enzyme activity of alpha-L-iduronidase	Developmental delay, severe coarse facies, hepatosplenomegaly, airway obstruction, joint disease, corneal clouding, aortic valve disease	0.58 mg/kg IV every week	2.9mg/5ml vial
Idursulfase (Elaprase®)	MPS II (Hunter syndrome) For 16 months and older	• Deficiency in iduronate 2-sulfatase (IDS) activity as measured in fibroblasts/leukocytes combined with normal enzyme activity level of another sulfatase • Molecular genetic testing for deletion or mutations in the *IDS* gene (Xq28) Also known as: ID2S, MPS2, SIDS	Abnormal facial features, macrocephaly, hepatosplenomegaly, cardiovascular disorders, neurocognitive decline, deafness	0.5 mg/kg IV every week	6mg/3ml vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY CRITERIA POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
Vestronidase alpha-vjbk (Mepsevii®)	MPS VII (Sly Syndrome)	• Leukocyte or fibroblast glucuronidase enzyme assay or genetic testing. Urinary glycosaminoglycan (uGAG) excretion at a minimum of 3-fold over the mean normal for age • Molecular genetic testing of mutations in the *GUSB* gene	Variable from very sever to attenuated: Hydrops fetalis (fluid retention throughout body) in severe cases, slower height growth, slow cognitive development by 1-3 years with regression of skills until death, coarse facial features, respiratory weakness, thick lips/enlarged tongue, valvular heart disease, enlarged liver/spleen, skeletal malformation	4 mg/kg IV every two weeks	10 mg/5 mL vial
Galsulfase (Naglazyme®)	MPS VI (Maroteaux-Lamy syndrome)	• Absence or deficiency of fibroblast or leukocyte enzyme activity of N-acetylgalactosamine 4-sulfatase (arylsulfatase) • Molecular genetic confirmation of mutations in the *ARSB* gene (5q13-q14). Gene also known as: *ASB, G4S, MPS6*	Coarse facial features, severe skeletal disease, joint abnormalities, respiratory disease, cardiac abnormalities, obstructive sleep apnea, pulmonary hypertension	1mg/kg IV every week	5mg/5ml vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY CRITERIA POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
Elosulfase alfa (Vimizim®)	MPS IVA (Morquio A syndrome) For ages 5 years and older	• Absence or deficiency of fibroblast or leukocyte GALNS enzyme activity • Molecular genetic testing for mutations in the *GALNS* gene (16q24.3). Gene also known as: *GALNAC6S, GAS, GalN6S, MPS4A*	Skeletal disease, short stature, corneal opacities, ligamentous laxity	2mg/kg IV every week	5mg/5ml vial
Imiglucerase (Cerezyme®)	Gaucher Disease Type 1 For ages 2 years and older	• Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values • DNA testing showing a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	2.5 units/kg 3 times per week, up to 60 units/kg every 2 weeks For Type 3 (off-label): doses up to 120 units/kg every 2 weeks have been safely administered	400 Units per vial
Taliglucerase alfa (Elelyso®)	Gaucher Disease Type 1	• Biochemical assay of beta-glucocerebrosidase activity (in leukocytes	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	60 Units/kg IV every other week	200 Units per vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	For ages 4 years and older	or skin fibroblasts) of less than 30% of normal values • DNA testing showing a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA		Patients switching from imiglucerase: Begin at the same unit/kg dose as the patient's previous imiglucerase dose	
Velaglucerase alfa (Vpriv®)	Gaucher Disease Type 1 For ages 4 years and older	• Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values • DNA testing showing a mutation in the *GBA* gene. Also known as: GBA1, GCB, GLUC, GBA	Hepatosplenomegaly, anemia, thrombocytopenia, skeletal abnormalities, lung disease	60 Units/kg IV every other week Patients switching from imiglucerase (on a stable dose): start treatment with previous imiglucerase dosage two weeks after the last imiglucerase dose	400 Units per vial
Agalsidase beta (Fabrazyme®)	Fabry disease For ages 2 years and older	• Absence or deficiency (<1%) of alpha-galactosidase activity in leukocytes, dried blood spots, or serum analysis	Acroparesthesias, anhidrosis or hypohidrosis, angiokeratomas, corneal dystrophy, renal dysfunction and heart manifestations	1 mg/kg IV every 2 weeks	35 mg vial 5 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
		○ For biological males only ○ Often included in male newborn screening • Molecular genetic testing for deletion or mutations in galactosidase alpha (*GLA)* gene, also known as *GALA*	Other symptoms: chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers.		
Pegunigalsidase alfa (Elfabrio®)	Fabry disease For ages 18 years and older	• Absence or deficiency (<1%) of alpha-galactosidase activity in leukocytes, dried blood spots, or serum analysis ○ For biological males only ○ Often included in male newborn screening • Molecular genetic testing for deletion or mutations in galactosidase alpha	Acroparesthesias, anhidrosis or hypohidrosis, angiokeratomas, corneal dystrophy, renal dysfunction and heart manifestations Other symptoms: chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers.	1 mg/kg every 2 weeks	20 mg/10 mL vial

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY CRITERIA POLICY AND CRITERIA ORPTCEND082	ENDOCRINE & METABOLIC DRUGS ENZYME REPLACEMENT THERAPY See Table 1 for Medications

Drug name Generic (Brand®)	**Indication**	**Confirmatory Tests**	**Symptoms**	**Dosing schedule**	**How Supplied**
		(*GLA)* gene, also known as *GALA*			
Sebelipase alfa (Kanuma®)	Lysosomal acid lipase deficiency (Wolman Disease)	• Absence or deficiency of lysosomal acid lipase activity by dried blood spot test • Molecular genetic testing for deletion or mutation of the lipase A, lysosomal acid type (*LIPA*) gene	Abdominal distention, hepatosplenomegaly, liver fibrosis, ascites, malabsorption, steatorrhea, hernia, hypotonia, delays in motor skill development, adrenal gland calcification, anemia.	Rapidly progressive LAL deficiency presenting within first 6 months of age: 1 mg/kg/dose once weekly; may increase to 3 mg/kg IV every week Pediatric and adults: 1 mg/kg IV every two weeks	20 mg/10mL vial
Alglucosidase alfa (Lumizyme®)	Pompe disease [acid α-glucosidase (GAA) deficiency]	• Absence or deficiency of GAA activity in skin fibroblast • Molecular genetic testing for deletion or mutations in *GAA* Gene also known as *LYAG*	Respiratory distress, skeletal muscle weakness, cardiac hypertrophy	20mg/kg IV every 2 weeks	50 mg vial
Avalglucosidase alfa (Nexviazyme®)	Patients 1 year of age and older	Same as Lumizyme®	Same as Lumizyme®	≥30 kg: 20 mg/kg every 2 weeks	100 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	with late-onset Pompe disease			<30 kg: 40 mg/kg every 2 weeks	
Olipudase alfa (Xenpozyme®)	Acid-sphingomyelinase deficiency (ASMD) – treatment of non-CNS manifestations	• Genetic testing for mutation in the sphingomyelin phophodiesterase-1 (*SMPD1*) gene • Reduced AMS activity in peripheral blood leukocytes or cultured skin fibroblasts[20]	Type B or A/B: hepatosplenomegaly, thrombocytopenia, interstitial lung disease, short stature, delayed skeletal maturation, hyperlipidemia Type A: feeding difficulties, loss of early motor skills, interstitial lung disease withing first few months of life, profound loss of neurological function, hepatosplenomegaly	Maintenance dose of 3 mg/kg IV every 2 weeks Specific dose escalation regimens for pediatrics and adults	20 mg vial
Cerliponase alfa injection (Brineura®)	Neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency For ages 3 years and older	Deficiency of tripeptidyl peptidase 1 (TPP1) enzyme activity (in a sample of leukocytes, fibroblasts, dried blood spot or saliva) AND Genetic testing revealing one pathogenic mutation on each parental allele of TPP1/CLN2 gene	seizures, changes in gait, falls, difficulty in ambulating, loss of language/delay in language development, visual failures	300 mg IV once every other week	150 mg/5ml vial
Velmanase alfa (Lamzede®)	Alpha-mannosidosis (AM) – treatment	• Alpha-mannosidase activity less than 10%	Symptoms vary widely in type and severity. Symptoms can include immunodeficiency (recurrent	1 mg/kg (actual body weight) IV once weekly	10 mg vial

Drug name Generic (Brand®)	Indication	Confirmatory Tests	Symptoms	Dosing schedule	How Supplied
	of non-CNS manifestations	of normal activity in blood leukocytes • Genetic testing revealing biallelic pathogenic variants in *MAN2B1* There is no clear relationship between genotype and severity of disease.	infections), facial and skeletal abnormalities, hearing impairment, impairment of speech, intellectual disability, muscular weakness, joint abnormalities, ataxia. Mild form (type 1): usually recognized after age ten with slow disease progression Moderate form (type 2): Usually recognized before age ten with slow disease progression Severe form (type 3): usually begins within first year of life with rapid disease progression		

Appendix 2: CLN2 Clinical Rating Scale (Motor Domain)

MOTOR FUNCTION[1,3]		
3	**Normal***	Grossly normal gait. No prominent ataxia, no pathologic falls.
2	**Abnormal**	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability, and may have intermittent falls.
1	**No unaided walking**	Requires assistance to walk, or can crawl only.
0	**Immobile**	Can no longer walk or crawl.

Decline was defined as a sustained (unreversed) 2-point loss or an unreversed score of 0 in the Motor domain of the CLN2 Clinical Rating Scale

Adapted from: Steinfeld R, et al. *Am J Med Genet*. 2002:112:347-354.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM024.1223	**HEMATOLOGY** **ERYTHROPOIESIS STIMULATING AGENTS** See Appendix A for medications covered by policy
Effective Date: 2/1/2024	**Review/Revised Date**: 06/02, 02/05, 02/06, 12/06, 04/07, 04/08, 08/08, 12/08, 02/09, 02/10, 12/10, 10/11, 02/12, 10/12, 04/13, 12/13, 10/14, 10/15, 08/16, 09/17, 07/18, 09/18, 05/19, 11/19, 03/20, 10/20, 10/21, 10/22, 11/23 (JN)
Original Effective Date: 07/08	**P&T Committee Meeting Date**: 02/05, 02/06, 12/06, 04/07, 04/08, 08/08, 12/08, 02/09, 02/10,12/10, 10/11, 02/12, 04/13, 12/13, 10/14, 10/15, 10/16, 10/17, 08/18, 09/18, 10/18, 04/19, 06/19, 12/19, 06/20, 12/20, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit and medically accepted indications outlined below.

Coverage criteria for oncologic conditions are based on the National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (110.21) and the Medicare Benefit Manual, Chapter 15.

REQUIRED MEDICAL INFORMATION:
For patients initiating therapy:
1. All diagnoses, with the exception of 2d (preoperative use in patients scheduled for elective non-cardiac, nonvascular surgery) and 2e (preoperative use in patients scheduled for cardiac surgery), must have **documented Hemoglobin (HGB) levels of less than 10 g/dl (or hematocrit less than 30%) within the 45 days prior** to initiation of therapy

AND

2. Must meet all of the listed criteria below for each specific diagnosis:
    a. **Treatment of Anemia in Chronic Kidney Disease (CKD)**
        i. If the patient is undergoing dialysis, these agents will be covered as a Part B bundle payment
        ii. For patients not on dialysis: Adequate iron stores as indicated by current (within the last three months) serum ferritin level more than

or equal to 100 mcg/L or serum transferrin saturation more than or equal to 20%

b. **Treatment of anemia secondary to chemotherapy in patients with cancer:**
    i. Documentation that anemia is secondary to myelosuppressive chemotherapy in solid tumors, multiple myeloma, lymphoma, or lymphocytic leukemia (other cancer types are not covered – see exclusion criteria)
c. **Anemia associated with zidovudine-treated HIV-infection patients**
    i. Documented current (within last three months) endogenous serum erythropoietin level is less than or equal to 500 mU/ml
    ii. Zidovudine dose is less than or equal to 4200mg/week
d. **Preoperative use in patients scheduled for elective noncardiac and nonvascular surgery, all of the following criteria must be met:**
    i. Documentation that the patient will be undergoing hip or knee surgery
    ii. Documentation that anemia is due to chronic disease
    iii. Member has preoperative HGB between 10 and 13 g/dL
    iv. The surgery has a high-risk for perioperative blood loss (for example, expected to lose more than two units of blood)
    v. Patient is unwilling or unable to donate autologous blood pre-operatively
e. **Preoperative use in patients scheduled for cardiac surgery (including elective cardiac surgery), one of the following criteria must be met:**
    i. Documentation that the patient will be undergoing cardiac surgery
    ii. Documentation that anemia is due to chronic disease
    iii. One of the following criteria:
        1) Patient has preoperative anemia, defined as HGB less than 13 g/dL for adult males or less than 12 g/dL for non-pregnant adult females
        2) Patient refuses blood transfusions
        3) Patient is deemed high-risk for postoperative anemia
f. **Treatment of Anemia in Myelodysplastic Syndromes (MDS) or with myelofibrosis:**
    i. Adequate iron stores as indicated by current (within the last three months) serum ferritin level more than or equal to 100 mcg/L or serum transferrin saturation more than or equal to 20%
    ii. Must have documented current (within last three months) endogenous serum erythropoietin levels less than or equal to 500 mU/mL

g. **Mircera only: For the treatment of pediatric patients 5 to 17 years of age who are on hemodialysis and converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA:**
   i. Documented hemodialysis for at least eight weeks
   ii. Documented stable maintenance treatment with epoetin alfa, epoetin beta, or darbepoetin alfa for at least eight weeks prior to initiation of therapy
   iii. Documented stable hemoglobin (HGB) levels for at least eight weeks prior to initiation of therapy.

For patients established on therapy
(Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy)**:**
1. Documentation of continued medical necessity (such as ongoing chronic kidney disease)
2. Documented HGB levels of less than or equal to 12 g/dl within previous 45 days

EXCLUSION CRITERIA:
- Patients with uncontrolled hypertension
- Anemia in cancer or cancer treatment patients due to folate deficiency (ICD-10: D52.0, D52.1, D52.8, or D52.9), B-12 deficiency (ICD-10: D51.1, D51.2, D51.3, D51.8, D51.9, or D53.1), iron deficiency (ICD-10: D50.0, D50.1, D50.8, and D50.9), hemolysis - (ICD-10: D55.0, D55.1, D58.0, D58.9, D59.0, D59.1, D59.2, D59 4, D59.5, D59.6, D59.8, or D59.9), or active bleeding (ICD-10D50.0, D62)
- Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML) (ICD-10: C92.00, C92.01, C92.02, C92.10, C92.11, C92.12, C92.20, C92.21, C92.40, C92.41, C92.42, C92.50, C92.51, C92.52, C92.60, C92.61, C92.62, C92.90, C92.91, C92.A0, C92.A1, C92.A2, C92Z0, C92Z1, or C92Z2), or
- Anemia associated with the treatment of erythroid cancers (ICD-10: C94.00, C94.01, C94.02, C94.20, C94.21, C94.22, C94.30, C94.31, C94.80, C94.81, D45).
- Anemia in cancer or cancer treatment patients due to bone marrow fibrosis
- Anemia of cancer not related to cancer treatment
- Any anemia associated only with radiotherapy
- Prophylactic use to prevent chemotherapy-induced anemia
- Prophylactic use to reduce tumor hypoxia
- Patients with erythropoietin-type resistance due to neutralizing antibodies

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM024	HEMATOLOGY ERYTHROPOIESIS STIMULATING AGENTS (ESAs) See Appendix A for medications covered by policy

PRESCRIBER RESTRICTIONS: N/A

AGE RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization and reauthorization will be for one year. For use during chemotherapy, therapy should be discontinued eight weeks following the final dose of myelosuppressive chemotherapy (subject to audit).

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Erythropoietin is a glycoprotein that stimulates red blood cell production. It is produced in the kidney and stimulates the division and differentiation of erythroid progenitors in the bone marrow. The level of tissue oxygenation regulates endogenous production of erythropoietin. Hypoxia and anemia generally increase the production of erythropoietin, which in turn stimulates erythropoiesis. Production of endogenous erythropoietin is impaired in patients with CKD and erythropoietin deficiency is the primary cause of their anemia. There are three commercially available Erythropoietin Stimulating Agents (ESAs) that are structurally identical to endogenous erythropoietin; Epogen®, Procrit®, and Retacrit®.

Darbepoetin alfa (Aranesp®) is an ESA that is an epoetin analog that stimulates erythropoiesis by the same mechanism as epoetin. Darbepoetin was created to increase the serum half-life of epoetin by increasing the amount of sialic acid-containing carbohydrate content. This modification also results in a product with a three-fold longer half-life which allows for less frequent dosing.

Mircera® (methoxy polyethylene glycol – epoetin beta for injection) is an erythropoietin receptor activator with greater in vivo activity and a longer half-life than endogenous erythropoietin. In adult patients, Mircera® is administered either intravenously or subcutaneously and patients may be taught to self-administer. In pediatric patients, Mircera® is administered intravenously.

FDA APPROVED INDICATIONS:

Darbepoetin alfa (Aranesp®)

1. Anemia due to chronic kidney disease in patients on dialysis and patients not on dialysis
2. Anemia in patients with non-myeloid malignancies where anemia is due to the effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy

   Limitations of Use: has not been shown to improve quality of life, fatigue, or patient well-being. Aranesp® is not indicated for use:
   - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy
   - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
   - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
   - As a substitute for RBC transfusions in patients who require immediate correction of anemia

Epoetin alfa (Epogen®/Procrit®/Retacrit®)

1. Anemia due to chronic kidney disease, including patients on dialysis and not on dialysis to decrease the need for red blood cell (RBC) transfusion
2. Anemia due to chemotherapy for non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy.
3. Anemia associated with zidovudine administered at less than or equal to 4200 mg/week in patients with HIV-infection with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL
4. Reduction of allogeneic red blood cell transfusions among patients with perioperative hemoglobin more than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, non-cardiac, nonvascular surgery.

Limitations of Use: has not been shown to improve quality of life, fatigue, or patient well-being. Epogen®/Procrit® are not indicated for use:

- In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
- In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion
- In patients scheduled for surgery who are willing to donate autologous blood.
- In patients undergoing cardiac or vascular surgery.
- As a substitute for RBC transfusions in patients who require immediate correction of anemia

Mircera® (methoxy polyethylene glycol – epoetin beta)

1. Treatment of anemia associated with chronic kidney disease (CKD) in:
    - Adult patients on dialysis and patients not on dialysis
    - Pediatric patients five to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

Limitations of use:

- has not been shown to improve symptoms, physical functioning, or health-related quality of life.
- Mircera® is not indicated and is not recommended:
    - In the treatment of anemia due to cancer chemotherapy
    - As a substitute for RBC transfusions in patients who require immediate correction of anemia

POSITION STATEMENT:

Coverage of ESAs for Medicare is mandated through the Medicare Benefit Manuals and National Coverage Determinations (NCDs) from CMS. The current NCD indicates that ESA treatment is not reasonable and necessary for beneficiaries with certain clinical conditions, either because of a deleterious effect of the ESA on their underlying disease or because the underlying disease increases their risk of adverse effects related to ESA use. These conditions include:

Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;

The anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;
The anemia of cancer not related to cancer treatment;
Any anemia associated only with radiotherapy;
Prophylactic use to prevent chemotherapy-induced anemia;
Prophylactic use to reduce tumor hypoxia;
Patients with erythropoietin-type resistance due to neutralizing antibodies; and
Anemia due to cancer treatment if patients have uncontrolled hypertension.[1-2]

For all ESAs (Aranesp®, Epogen®, Procrit®, Retacrit®, Mircera®), all diagnoses, the product labeling dosing and administration section recommends that the following criteria for iron stores must be met prior to initiation of therapy:

- Iron stores should be repleted to TSAT> 20% or serum ferritin > 100mcg/L
    - If iron levels are not adequate, oral iron therapy is preferred, but if patient is intolerant, IV iron therapy is an alternative
    - Iron stores should be monitored periodically throughout therapy

Additionally, the product labeling for all ESAs also recommends that the following also be met prior to initiation of therapy:

- For patients with hypertension, blood pressure should be adequately controlled before initiation and closely monitored and controlled during therapy
- All other causes of anemia need to be ruled out and corrected prior to starting ESA treatment including folate deficiency, B-12 deficiency, iron deficiency (see above), hemolysis, bleeding, or bone marrow fibrosis

Anemia in chronic kidney disease (CKD)
These products carry a **FDA boxed warning** in this indication that states “in controlled trials with CKD patients, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target hemoglobin (Hgb) level of greater than 11 g/dL.”[3-5]

Additionally, the FDA issued recommendations in 2011 for initiation of ESA therapy in this indication:

- Consider starting ESA treatment when the Hgb level is less than 10 g/dL. This advice does not define how far below 10 g/dL is appropriate for an individual to initiate. This advice also does not recommend that the goal is to achieve a Hgb of 10 g/dL or a Hgb more than 10 g/dL.
- Individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. Target Hgb levels have been removed from product labeling.[1-5]

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for anemia in CKD follow these FDA recommendations. They recommend a full workup, including performing iron studies, to determine any treatable causes of anemia before initiating ESA therapy (for example, iron deficiency). They state that ESA therapy should only be used when Hgb < 10 g/dL, to avoid falling below 9 g/dL, and the benefits are determined to outweigh risks.[6]

The KDIGO guidelines do not recommend maintaining Hgb levels > 11.5 g/dL and strongly recommend against intentionally increasing the Hgb > 13 g/dL.[6]

In addition, the KDIGO guidelines state that untreated iron deficiency is an important cause of hyporesponsiveness to ESA treatment. They recommend that for all adult patients both on ESA therapy and not on ESA therapy who are not receiving iron supplementation to receive a trial of IV iron (or in CKD nondialysis patients alternatively a 1-3 month trial of oral iron therapy) if their TSAT is ≤30% and ferritin is ≤500 ng/ml. They also recommend that for all pediatric CKD patients with anemia both on ESA therapy and those not on ESA therapy who are not receiving iron supplementation to receive oral iron (or IV iron in CKD hemodialysis patients) when TSAT is ≤20% and ferritin is ≤100 ng/mL.[6]

Anemia in patients with cancer

These products carry **FDA boxed warnings** for this indication:

- ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers
- Use the lowest dose to avoid RBC transfusions.
- Use ESAs only for anemia from myelosuppressive chemotherapy.
- ESAs are not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
- Discontinue following the completion of a chemotherapy course.[3-5]

The National Comprehensive Cancer Network (NCCN) guidelines for use of Hematopoietic Growth Factors in patients with cancer recommend a full workup of anemia to identify possible causes. This includes evaluation for possible iron deficiency and underlying comorbidities (such as bleeding, hemolysis, nutritional deficiencies, renal insufficiency). If patients have symptomatic anemia, the decision to use ESA is based on a risk/benefit evaluation, as both ESAs and red blood cell transfusions carry inherent risks. The guideline recommends to "consider the use of ESAs for select patients by FDA dosing/dosing adjustments, given there is no option for transfusion7". If ESAs are initiated, NCCN recommends adjusting doses to maintain an Hgb level that avoids red blood cell transfusions.[4]

Treatment of anemia in patients with myelodysplastic syndrome (MDS)
NCCN guidelines outline that the treatment of symptomatic anemia with ESAs for patients with MDS should be reserved to patients with low basal serum erythropoietin as this is a predictor of positive response. Other predictors of positive response include low percentage of marrow blasts and few prior red blood cell transfusions.[11]

Reduction of allogeneic blood transfusion in surgery patients
Due to increased risk of deep venous thrombosis (DVT) seen in clinical trials of patients on ESAs undergoing surgical orthopedic procedures, DVT prophylaxis is strongly recommended.

Anemia secondary to Hepatitis C therapy
The American Association for the Study of Liver Disease practice guidelines do not recommend use of growth factors for the treatment of anemia, but instead taking into account the risks of anemia associated with treatment regimens containing ribavirin. Recommendations are made to reduce the dose of ribavirin for those patients that do develop significant anemia (hemoglobin < 10 g/dL). The newer treatments currently available without ribavirin do not have a large risk of anemia.[8]

Anemia in Cardiac Operations
The 2021 STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management, recommend (class IIA recommendation), that in patients who have preoperative anemia, refuse blood transfusions or are deemed high-risk for postoperative anemia, it is reasonable to administer preoperative erythropoietin stimulating agents (ESAs) and iron supplementation several days prior to cardiac operations to increase red cell mass.[12] Anemia in preoperative patients is defined as a hemoglobin level of less than 13g/dL in adult males and less than 12g/dL in adult non-pregnant females.[13] The 2021 STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management states that treatment of anemia is warranted in the elective surgical patient.[12] Additionally, a meta analysis by Ali et al. reviewed eight clinical studies regarding the role of preoperative erythropoietin in the optimizations of preoperative anemia among surgical patients and concluded that preoperative erythropoietin provides better outcomes considering the optimization of preoperative anemia for elective surgical procedures.[13] Of note, epoetin alfa (Epogen®/Procrit®/Retacrit®) carries a boxed warning for perisurgery stating “due to increased risk of deep venous thrombosis (DVT), DVT prophylaxis is recommended.”[4,5,9] Darbepoetin alfa (Aranesp®) and Mircera® (methoxy polyethylene glycol – epoetin beta) do not contain the same boxed warning.[2,4,5,9]

REFERENCE/RESOURCES:

1. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD): Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (NCD 160.26). Available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part2.pdf (Accessed October 12, 2022).
2. Centers for Medicare & Medicaid Services. Medicare Benefit Policy Manual, Chapter 15 (Rev 259, 07-12-19). Available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf (Accessed May 14, 2020)
3. Aranesp® (darbepoetin alfa) prescribing information. Thousand Oaks, CA: Amgen, Inc.; 2019 Jan.
4. Epogen® (epoetin alfa) prescribing information. Thousand Oaks, CA: Amgen, Inc. 2018 July.
5. Procrit® (epoetin alfa) prescribing information. Horsham, PA: Janssen products, LP. 2020 May.
6. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Supp*. 2012;2(4):288–98.
7. National Comprehensive Cancer Network (NCCN). Hematopoietic Growth Factors version 12.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf (Accessed October 26, 2022)
8. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD): Erythropoiesis Stimulating Agents (ESAs) in Cancer and Related Neoplastic Conditions (NCD 110.21). Available at https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part2.pdf (Accessed May 14, 2020).
9. Retacrit® (epoetin alfa) prescribing information. Lake Forest, IL: Prizer; 2020 July**.**
10. Hoffman-La Roche, Inc. Full prescribing information (US): Mircera (methoxy polyethylene glycol-epoetin beta). Nutley (NJ): Hoffman – La Roche Inc., 2014. Updated August 2019.
11. National Comprehensive Cancer Network (NCCN). Myelodysplastic Syndromes version 1.2023. Available at

https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf (Accessed October 12).

12. Tibi P, Mclure S, Huang J, et al. STS/SCA/AmSECT/SABM update to the clinical practice guidelines on patient blood management. Annals of Thoracic Surgery. 2021: 112(3): 981-1004. Available at: https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0003497521005567?scrollTo=%23hl0000841 (Accessed November 9, 2023).
13. Ali S, Hafeez M, Nisar O, et al. Role of preoperative erythropoietin in the optimization of preoperative anemia among surgical patients – a systematic review and meta-analysis. *Hematology, Transfusion and Cell Therapy*. January-March 2022. 44(1):76-84. Available at: https://www.sciencedirect.com/science/article/pii/S2531137921000067.

APPENDIX A.

Brand Name	Generic Name
Aranesp®	darbepoetin alfa injection
Epogen®/Procrit®/Retacrit®	epoetin alfa injection
Mircera®	methoxy polyethylene glycol – epoetin beta injection

HCPCS CODES

Prior Authorization Required	
HCPCS Code	**Description**
J0881	Injection, darbepoetin alfa, 1 microgram (non-ESRD use)
J0885	Injection, epoetin alfa, (for non-ESRD use), 1000 units
Q5106	Injection, epoetin alfa, biosimilar, (Retacrit) (for non-ESRD use), 1000 units
J0888	Injection, epoetin beta, 1 microgram, (for non-ESRD use)
No Prior Authorization Required	
J0882	Injection, darbepoetin alfa, 1 microgram (for ESRD on dialysis)
Q4081	Injection, epoetin alfa, 100 units (for ESRD on dialysis)
Q5105	Injection, epoetin alfa, biosimilar, (Retacrit) (for ESRD on dialysis), 100 units
J0887	Injection, epoetin beta, 1 microgram, (for ESRD on dialysis)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU020.0224	**NEUROMUSCULAR DRUGS** **EXON-SKIPPING THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY** See Table 1 for Medications
Effective Date: 4/1/2024	**Review/Revised Date**: 11/16, 06/17, 07/18, 06/19, 02/20, 07/20, 11/20 05/21, 07/21, 06/22, 01/24 (JCN)
Original Effective Date: 03/17	**P&T Committee Meeting Date**: 12/16, 08/17, 08/18, 08/19, 04/20, 08/20, 12/20, 06/21, 08/21, 08/22, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY:

Exon-skipping therapies for Duchene muscular dystrophy are not considered medically necessary and will not be covered due to the lack of clinical evidence of improved outcomes and safety.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Eteplirsen (Exondys 51®) was approved by the Food and Drug Administration (FDA) 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. Product labeling notes, "This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials." Golodirsen (Vyondys® 53) was the second FDA approved exon-skipping therapy for Duchene Muscular Dystrophy and is for patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Then viltolarsen (Viltepso®) and casimersen (Amondys® 45) were also approved. Like eteplirsen, these three therapies were approved under accelerated approval which were based on small trials that only showed a small increase in dystrophin levels and clinical benefit has not been established.

FDA APPROVED INDICATIONS:

Eteplirsen (Exondys 51®):
Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with Exondys 51®. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Golodirsen (Vyondys 53®):
Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials

Viltolarsen (Viltepso®):
Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILTEPSO. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Casimersen (Amondys 45®):

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU020	NEUROMUSCULAR DRUGS EXON-SKIPPING THERAPIES FOR DUCHENNE MUSCULAR DYSTROPHY See Table 1 for Medications

Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

POSITION STATEMENT:
Muscular dystrophies are genetic disorders causing weakness, which may lead to respiratory failure or cardiomyopathy. Duchenne muscular dystrophy (DMD) is a type of muscular dystrophy that affects almost exclusively males, with symptom onset usually between ages 2 and 3 with diagnosis usually by the age of five. DMD is characterized by progressive muscle weakness and atrophy. Lower extremities are affected first and the ability to walk is often lost by the age of 12 or 13. Improved respiratory and cardiac care have increased life expectancy into the fourth decade of life.

DMD results from mutation in the DMD (also known as dystrophin) gene leading to deficiency in the protein dystrophin. Dystrophin is located primarily in the skeletal and cardiac muscles. It helps strengthen muscle fibers and protect them from injury during contraction and relation. The DMD (dystrophin) gene is one of the largest known human genes.

There is no curative treatment for DMD. Current treatment includes supportive care and medications such as corticosteroids and exon-skipping therapies.

Corticosteroids, including prednisone and deflazacort (Emflaza®) are a main stay of treatment for patients with DMD. The exact mechanism is unknown, but it is likely due to anti-inflammatory and immunomodulatory effects. Corticosteroids have shown to slow the decline in muscle strength and function in patients with DMD. Although the benefits of glucocorticoid therapy are well established, uncertainty remains about which glucocorticoids are best and at what doses.

Exon-skipping therapies target dystrophin pre-messenger ribonucleic acid (mRNA) and induce skipping of mutated exons of the DMD gene that disrupt downstream protein synthesis and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin that may be beneficial in slowing progression of the disease, though clinical correlation has yet to be established.

- Clinical trials assessing the use of eteplirsen, viltolarsen, casimersen and golodirsen are limited by small sample sizes and a lack of clinical outcome assessments.
- One trial including a total of 12 patients suggested that use of the FDA approved dose of eteplirsen by 4 patients lead to an increase in dystrophin positive fibers after 24 weeks of treatment. An improvement in six-minute walk test (6MWT) was not shown. Two of the 4 patients treated with the FDA approved dose of eteplirsen lost their ability to ambulate early in the study.
- A longitudinal review including 12 patients treated with the FDA approved dose of eteplirsen, as well as a higher dose, proposed a benefit in 6MWT results and maintenance of ambulation, compared to a historical control. This was not a randomized, placebo-controlled trial.
- A 48-week trial suggested a minimal increase in muscle dystrophin with eteplirsen. Results were available for 12 patients and dystrophin levels increased from 0.16% ± 0.12% of the dystrophin level in a healthy subject at baseline to 0.44% ± 0.43% the level of a healthy subject, after 48 weeks, with a median increase of 0.1%. It is unclear of the magnitude of change confers a clinically meaningful outcome.
- The approval of golodirsen was based on a two part study, Part 1 was a double-blind, placebo-controlled, dose-titration study in 12 DMD patients. Part 2 was a 168-week, open-label study assessing the efficacy and safety of golodirsen in the 12 patients enrolled in Part 1, plus 13 additional treatment-naïve patients. Mean dystrophin levels increased from 0.10% of normal at baseline to 1.02% of normal by week 48, with a mean change in dystrophin of 0.92% of normal levels ($p < 0.001$); the median change from baseline was 0.88%. This trial is ongoing and there are plans to measure 6MWT at week 144 so data on functional improvement is not yet available yet.
- A small phase 2 trial open label trial showed an increase in dystrophin expression to an average of 5.9% of normal after 24 weeks of treatment with viltolarsen. This trial did include functional outcome measures and showed some benefit compared to historical controls. However, these functional outcome measures can be effort-dependent and since this was not a large, randomized, placebo-controlled trials this evidence is not yet compelling that there is a meaningful clinical benefit with therapy.
- There is no clear threshold for the amount of dystrophin increase that is needed to produce clinical benefit. Previous research has suggested dystrophin levels of at least 20-29% of normal are needed to avoid muscular dystrophy, and levels of at least 10% of normal can produce a more mild form of dystrophy.
- Side effects of eteplirsen include: balance disorder, vomiting, contact dermatitis, and hypersensitivity reactions. Post-marketing reporting with eteplirsen has

identified 11 cases of serious device related infections out of 469 patients exposed to therapy
    - Side effects of golodirsen include: headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea. Warning and precautions include hypersensitivity reactions and renal toxicity.
- Confirmatory, randomized placebo-controlled trials for exon skipping therapies have not been completed.
- A 2019 Institute for Clinical and Economic Review (ICER) evidence report for deflazacort, eteplirsen, and golodirsen was completed in July 2019. The review has the following conclusion for eteplirsen and golodirsen
    - "Data on the exon-skipping drugs is extremely limited and randomized trial benefits are limited to the surrogate outcome of dystrophin levels. The small increases in dystrophin levels seen in the RCTs are of uncertain clinical significance. Observational studies comparing outcomes with historical controls have suggested potential functional benefits with eteplirsen, but these data may be confounded and effort dependent. Based on the current evidence, there are no particularly concerning safety issues with either drug but given the small numbers of patients and limited follow-up, harms could be missed. We considered the data for eteplirsen and golodirsen to be insufficient ("I")."
    - "No price can be suggested as a fair value-based price for eteplirsen or golodirsen because no persuasive evidence yet exists to demonstrate the clinical effectiveness of either drug"
- There is insufficient evidence that these drugs are clinically effective in DMD and are therefore not considered medically necessary for coverage.

REFERENCE/RESOURCES:

1. Relevant package inserts.
2. Facts about muscular dystrophy. Center for Disease Control and Prevention. Available at: http://www.cdc.gov/ncbddd/musculardystrophy/facts.html. Accessed November 3, 2016.
3. FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm. Accessed October 18, 2016.
4. Aartsma-Rus A, Fokkema I, Verschuuren J, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat*. 2009;30:293–299.
5. Mendell JR, Rodino-Klapac LR, Sahenk Z. Eteplirsen for the treatment of

Duchenne muscular dystrophy. *Ann Neurol*. 2013;74:637-47.
6. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016:79(2)257-71.
7. Vyondys package insert. Cambridge, MA: Sarepta Therapeutics, Inc.; 2019, Dec.
8. Golodirsen In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed February 3, 2020
9. Golodiresen In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed January 31, 2020
10. ICER: Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value. Evidence Report. July 11, 2019. https://icer-review.org/wp-content/uploads/2018/12/ICER_DMD_Evidence-Report_071619.pdf. Accessed: February 3, 2020.
11. Center for Drug Evaluation and Research. Application Number: 211970Orig1s000. August 19, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000MedR.pdf. Accessed: February 3, 2020.
12. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9(1):77-
13. Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial [published correction appears in doi: 10.1001/jamaneurol.2020.2025]. JAMA Neurol. 2020;77(8):982-991.
14. Viltolarsen In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed October 23, 2020
15. Viltolarsen In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed October 23, 2020
16. Casimersen In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 9, 2021
17. Casimersen In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed April 9, 2021
18. National Library of Medicine (U.S.). (July 2015 -). Study of SRP-4045 and SRP-4053 in DMD Patients (ESSENCE). Identifier NCT02500381. https://clinicaltrials.gov/ct2/show/NCT02500381

Table 1

Brand Name	Generic Name
Exondys 51	eteplirsen vial
Viltepso	viltolarsen vial
Vyondys-53	golodirsen vial
Amondys-45	casimersen vial

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH044.1023	**MISCELLANEOUS PRODUCTS** **FcRn ANTAGONISTS** See Table 1 for medications covered by policy
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/22, 08/23 (MTW) P&T Committee Meeting Date: 04/22, 10/22, 10/23 Original Effective Date: 06/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy (new starts)** for Generalized Myasthenia Gravis (gMG), all the following must be met (1-5):

1. Anti-acetylcholine receptor (anti-AChR) antibody positive OR anti-muscle-specific tyrosine kinase (MuSK) antibody positive (Rystiggo® only)
2. One of the following:
    a. For Vyvgart®:
        i. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
        ii. Myasthenia Gravis - Activities of Daily Living (MG-ADL) total score of five or greater
    b. For Rystiggo®:
        i. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IVa
        ii. Myasthenia Gravis - Activities of Daily Living (MG-ADL) total score of three or greater (with 3 or greater points from non-ocular symptoms)

3. Failure with treatment of one of the following over the course of at least 12 months, unless intolerance or contraindication to all therapies:
    a. At least TWO immunosuppressive agents (such as azathioprine, methotrexate, cyclosporine, mycophenolate, corticosteroids, tacrolimus, cyclophosphamide, or rituximab)
    OR
4. ONE immunosuppressive therapy and required at least four infusions/year of either intravenous immunoglobulin (IVIG), or plasmapheresis/plasma exchange (PLEX) Dose and frequency are in accordance with FDA-approved labeling

For patients established on therapy (within the previous year) for Generalized Myasthenia Gravis (gMG), all the following must be met (1-2):
1. Documentation of improvement in MG-ADL by at least two points from baseline
2. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist or rheumatologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Efgartigimod alfa (Vyvgart®) is approved for the treatment of generalized myasthenia gravis. It is a human immunoglobulin G1 (IgG1) antibody fragment that binds the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG and abnormal AChR antibodies.

Rozanolixizumab-noli (Rystiggo®) is a humanized IgG4 monoclonal antibody that binds to the neonatal Fc receptor (FcRn), resulting in the reduction of circulating IgG.

FDA APPROVED INDICATIONS:
Efgartigimod alfa (Vyvgart®) is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Rozanolixizumab-noli (Rystiggo®) s indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive.

POSITION STATEMENT:
- Generalized Myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission. The incidence ranges from 14 to 20 per 100,000 population[15], and it is estimated to affect over 700,000 people worldwide. It is characterized by muscle weakness including ocular motor disturbances, oropharyngeal, respiratory, and limb muscle weakness. Symptoms can fluctuate and can become progressively severe. This disorder occurs when proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors and/or receptor-associated proteins) are attacked by antibody-mediated T-cells. The diagnosis of myasthenia gravis can be established by clinical and serologic testing. For most patients with a suspected diagnosis of MG, the diagnosis may be confirmed through the presence of autoantibodies against either the acetylcholine receptor (AChR) or another muscle receptor-associated protein, such as muscle-specific tyrosine kinase (MuSK) or low-density lipoprotein receptor-related protein 4 (LRP4). It is estimated that approximately 85% of patients diagnosed with gMG have AChR antibodies, 8% have MuSK antibodies, 1% have LRP4 antibodies, and 6% are seronegative and diagnosis is confirmed using electrodiagnostic testing that shows evidence of impaired signal transmission at the neuromuscular junction.
- The myasthenia gravis activities of daily living (MG-ADL) is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. A 2-point improvement in the MG-ADL indicates clinical improvement.

- The Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) developed the MGFA Clinical Classification, which divides MG into five main classes. This classification system is used to evaluate the severity of disease and is commonly used in clinical trial inclusion criteria.
- There is no cure for gMG, but rather treatment aims to control symptoms. Per the American Academy of Neurology 2016 guidelines, the following treatments are recommended for symptomatic and immunosuppressive (IS) treatment of MG:
    - Pyridostigmine should be part of the initial treatment in most patients with MG.
    - Corticosteroids or immunosuppressant (IS) therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. A nonsteroidal IS agent should be used alone when corticosteroids are contraindicated or refused.
    - Nonsteroidal IS agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. These therapies can often take several months to show a benefit, and bridging therapies are often required.
    - Patients with refractory MG should be referred to a physician or a center with expertise in management of MG. In addition to the previously mentioned IS agents, the following therapies may also be used in refractory MG: IVIG, PLEX, cyclophosphamide, rituximab
    - In non-thymomatous MG, thymectomy is performed as an option to potentially avoid or minimize the dose or duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy or have intolerable side-effects from that therapy. Thymectomy should be strongly considered in patients with AChR-Ab+ generalized MG if they fail to respond to an initial adequate trial of immunotherapy or have intolerable side effects.
- In a 2021 update to The American Academy 2016 guidelines, Soliris® (eculizumab) was added as a treatment option to consider for severe, refractory, AChR-Ab+ generalized MG after trials of other immunotherapies have been unsuccessful in meeting treatment goals.
- Vyvgart® (efgartigimod alfa) and Ultomiris® (ravulizumab) are both indicated for the treatment of refractory generalized myasthenia gravis in adults who are anti acetylcholine receptor antibody positive (AChR+). These therapies are new and not listed in the most recent guidelines but are typically considered in patients who fail or are unable to tolerate corticosteroids or immunosuppressants; they may also be used as a bridge therapy to slower-acting agents.
- Patients with anti-MuSK Ab+ gMG typically have a poor response to cholinesterase inhibitors as initial therapy. These patients often respond well to

steroids and frequently remain steroid-dependent despite use of nonsteroidal immunosuppressive drugs. Patients who are anti-MuSK Ab+ may respond well to rituximab based on observational data.

- Approval of Vyvgart® was based on a phase 3, randomized, double-blind, placebo-controlled trial (NCT036695889, ADAPT trial)
    - The efficacy of efgartigimod was measured using the Myasthenia Gravis-Specific Activities of Daily Living scale (MG-ADL) which assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG.
    - Primary endpoint: Comparison of the percentage of MG-ADL responders during the first treatment cycle between treatment groups in the AChR-Ab positive population.
    - Inclusion criteria: Age greater than 18 years, all serotypes, regardless of Ab status and including MuSK, LRP4, and AChR-Ab- in addition to AChR-Ab+, MGFA Class II-IV gMG, MG-ADL score ≥5, receiving a stable dose of ≥1 of the following gMG treatments prior to randomization: acetylcholinesterase inhibitors (no dose change for 2 weeks prior to screening), steroids (at least 3 months of treatment, no dose change for one month) or NSIST (at least 6 months of treatment, no dose change for three months)
    - Exclusion criteria: MGFA Class I and V patients
    - Moderate quality of evidence that efgartigimod results in a statistically significant difference in the MG-ADL (Myasthenia Gravis-Specific Activities of Daily Living) responder rate during the first treatment cycle in patients with gMG compared to placebo
    - Although AChR antibody–negative patients were included in the ADAPT trial, they were not included in the study's final analysis. The FDA-approved labeling of Vyvgart® excludes use in the AChR antibody–negative population. In the ADAPT trial, 68% of acetylcholine receptor antibody-negative efgartigimod-treated patients had a response, similar to that in acetylcholine receptor antibody-positive patients, but there was an unexpectedly high response rate in the placebo group. A post-hoc analysis of acetylcholine receptor antibody-negative patients who were both MG-ADL and QMG responders in cycle 1 showed a treatment effect, suggesting efgartigimod might be effective in this patient population.
- Safety:
    - Warnings and Precautions: Increased risk of infections, hypersensitivity reactions
    - The most common adverse reactions were respiratory tract infection, headache, and urinary tract infection
- Dosing:

- The recommended dosage is 10 mg/kg administered as an intravenous infusion over one hour once weekly for four weeks. In patients weighing 120 kg or more, the recommended dose is 1200 mg (three vials) 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.
- Vyvgart® should be administered via intravenous infusion by a healthcare professional.

Cost Effectiveness[8]:
Given the information available regarding short-term benefits, with uncertainties about dosing, long-term benefits, and long-term safety, ICER concluded there is "moderate certainty of a comparable, small, or substantial net health benefit of efgartigimod added to conventional therapy with high certainty of at least comparable net health benefit (C++) in adults with gMG positive for anti-AChR antibodies". With sparse and uncertain clinical and statistical significance of the evidence of efgartigimod in adults with gMG negative for anti-AChR antibodies, ICER concluded that the evidence was insufficient to determine the net health benefit of adding efgartigimod to conventional therapy versus conventional therapy alone in this population. In addition, there is insufficient evidence to determine the net health benefits of rituximab and IVIG from placebo, eculizumab, and efgartigimod.

Icer evaluated the cost effectiveness of efgartigimod added to conventional therapy versus conventional therapy alone in the patients with gMG, including those with or without anti-AChR-antibodies. Using a placeholder price of $418,400, the incremental cost per QALY and incremental cost per evLYG were estimated to be $2,076,000. From the cost-effectiveness base case, ICER estimated the health benefit price benchmark (HBPB) for efgartigimod. The HBPB range was estimated to be $18,300 to $28,400 (discounts not presented due to placeholder price).

Annual Health Benefit Price Benchmarks for Efgartigimod

	Annual FSS	Annual Price at $100,000 Threshold	Annual Price at $150,000 Threshold	Discount from FSS to Reach Threshold Prices
QALYs Gained	NA	$18,300	$28,400	NA
evLYG	NA	$18,300	$28,400	NA

evLYG: equal value life year gained, QALY: quality-adjusted life year, FSS: Federal Supply Schedule, NA: not applicable
*There were no differences in survival. Cost per evLYG is equal to the cost per QALY gained.

**Efgartigimod evaluated using an annual placeholder price of $418,400

Benefits not included in the economic model include potential to improve childbearing age career opportunities for women who are diagnosed early in their lives. MG is serious and lifelong with life-threatening manifestations, and most patients do not achieve treatment goals with conventional therapy. Efgartigimod improves function and quality of life for patients with gMG, however has an incremental cost-effectiveness ration well above typical willingness-to-pay-thresholds.

The approval for Rystiggo was based on one randomized, double-blind, placebo-controlled, parallel-group, two-stage adaptive, phase 3 clinical trial (*MycarinG [NCT03971422, PubMed ID #37059507])*

- Study Duration: 4-week screening period and 6-week treatment period, followed by 8 weeks of observation.
- Patient population: Patients (N=200) aged ≥18 years with a diagnosis of gMG, MGFA class II–IVa, presence of AChR or MuSK autoantibodies, MG-ADL ≥ 3 (for non-ocular symptoms), on a stable dose of MG therapy prior to screening that included AChE inhibitors (stable dose not required), oral corticosteroids (stable for 4 weeks before baseline), azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and tacrolimus (all received for the previous 6 months and on a stable dose 2 months before baseline), in combination or monotherapy
    - Key exclusions: severe oropharyngeal or respiratory weakness, clinically relevant active infection, recent serious infection
    - Prohibited concomitant medications: intravenous immunoglobulin or plasma exchange (other than when used as rescue therapy), biological agents (including rituximab and eculizumab), cyclophosphamide, pimecrolimus, immunoadsorption, and vinca alkaloids
    - Baseline demographics: median MG-ADL total score was 8 and median quantitative myasthenia gravis (QMG) total score was 15. 89.5% were positive for AChR antibodies; 10.5% were positive for anti-MuSK antibodies. At baseline, more than 83% of patients received AChE inhibitors, more than 56% received steroids, and 50% received NSISTs at stable doses
- Intervention: Patients randomly assigned (1:1:1) to rozanolixizumab 7 mg/kg, rozanolixizumab 10 mg/kg, or placebo, once a week x6 weeks. Randomization was stratified by presence of AChR or MuSK autoantibodies.
- Primary endpoint: change from baseline to day 43 in MG-ADL
    - Key secondary endpoints: change from baseline to day 43 in QMG and MG-ADL response (based on the established clinically meaningful improvement on an individual patient level of ≥2 points)

- Efficacy:

Efficacy Endpoints	Rozanolixizumab 7 mg/kg n = 66	Rozanolixizumab 10 mg/kg n = 67	Placebo n = 67
MG-ADL Total Score			
Least-squares (LS) Mean (Standard of Error [SE])	−3.37 (0.49)	-3.4 (0.49)	-0.78 (0.49)
Difference from placebo (95% CI)	-2.59 (-4.09, -1.25)	-2.62 (-3.99, -1.16)	-
P-value	<0.001	<0.001	-
QMG Total Score			
LS Mean (SE)	−5.40 (0.7)	−6.67 (0.7)	−1.92 (0.7)
Difference from placebo (95% CI)	−3.48 (−5.61, −1.58)	−4.76 (−6.82, −2.86)	-
P-value	<0.001	<0.001	-
MG-ADL responders			
Measure*	46/64 (72%)	43/62 (69%	20/64 (31%)

*Observed values; this outcome was not included in the hierarchical testing procedure

  - Reductions from baseline to day 43 in MG-ADL scores were observed in patients with AChR autoantibody-positive gMG (rozanolixizumab 7 mg/kg least-squares mean –3.03 [SE 0.89]; rozanolixizumab 10 mg/kg –3.36 [0.87]; placebo –1.10 [0.87]; least-squares mean difference from placebo −1.94 [97.5% CI −3.06 to −0.81] and −2.26 [−3.39 to −1.13] in the rozanolixizumab 7 mg/kg and 10 mg/kg groups, respectively). For patients with MuSK autoantibody-positive gMG, least-squares mean reductions were –7.28 [SE 1.94] in the rozanolixizumab 7 mg/kg group, –4.16 [1.78] in the rozanolixizumab 10 mg/kg group, and 2.28 [1.95] in the placebo group (least-squares mean difference from placebo for rozanolixizumab 7 mg/kg −9.56 [97.5% CI −15.25 to −3.87]; −6.45 [−11.03 to –1.86] for the rozanolixizumab 10 mg/kg group).
  - Both rozanolixizumab groups showed statistically significant improvements compared with placebo for change from baseline to day 43 in MGC scores, Myasthenia Gravis Symptoms PRO scales were also significantly improved.
  - Improvements from baseline in MG-ADL, MGC, QMG, and Myasthenia Gravis Symptoms PRO scores were seen as early as day 8 and throughout the treatment period, before returning towards baseline levels by day 99
- Safety:

- Side effects experienced by ≥10% of patients in treatment group (n = 133): headache (44%), infections (23%), diarrhea (20%), pyrexia (17%), hypersensitivity reactions (11%), and nausea (10%).
- Five (8%) patients in the rozanolixizumab 7 mg/kg group, seven (10%) in the rozanolixizumab 10 mg/kg group, and six (9%) in the placebo group had a serious treatment-emergent adverse event (TEAE); no deaths occurred.

REFERENCE/RESOURCES:

1. Vyvgart® package insert. Boston, MA: Argenx US, Inc; Feb 2022.
2. Vyvgart® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed February 17, 2022.
3. Vyvgart® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed February 17, 2022.
4. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis. *Neurology*. 2021; 96:114-122.
5. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. 2016 Jul 26;87(4):419-25. doi: 10.1212/WNL.0000000000002790.
6. Howard JF Jr, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial [published correction appears in *Lancet Neurol*. 2021 Aug;20(8):e5]. *Lancet Neurol*. 2021;20(7):526–536. doi:10.1016/S1474-4422(21)00159-9.
7. Tice JA, Touchette DR, Nikitin D, Campbell JD, Lien P-W, Moradi A, Rind DM, Pearson SD, Agboola F. Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value; Revised Evidence Report. Institute for Clinical and Economic Review, September 10, 2021. https://icer.org/assessment/myasthenia-gravis/#timeline
8. Tice JA, Touchette DR, Nikitin D, Campbell JD, Lien P-W, Moradi A, Rind DM, Pearson SD, Agboola F. Eculizumab and Efgartigimod for the Treatment of Myasthenia Gravis: Effectiveness and Value; Final Report. Institute for Clinical and Economic Review, October 20, 2021. https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Final-Report_102021-1.pdf

9. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 2000;55(1):16-23.
10. Rystiggo® Package insert. UCB, Inc. Smyrna, GA. June 2023.
11. Rystiggo® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed August 24, 2023
12. Rystiggo® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed August 24, 2023
13. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis. Neurology. 2021; 96:114-122.
14. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016 Jul 26;87(4):419-25. doi: 10.1212/WNL.0000000000002790.
15. Howard, J. Clinical Overview of MG, Myasthenia Gravis Foundation of America, June 2015, https://myasthenia.org/Professionals/Clinical-Overview-of-MG.
16. Bril V, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. Lancet Neurol. 2023;22(5):383–394. Accessed August 23, 2023. doi:10.1016/S1474-4422(23)00077-7

Myasthenia Gravis Foundation of America (MGFA) clinical classification of MG[9]	
Class (I-V)	**Clinical features**
Class I	Any ocular muscle weakness. May have weak eye closure. All other muscle strength is normal.
Class II	Mild weakness affecting non-ocular muscles May also have any ocular weakness
IIa	Predominantly affecting limb or axial muscles or both May also have oropharyngeal muscle weakness (less than limb/axial)
	vs
IIb	Predominantly affecting oropharyngeal or respiratory muscles or both May also have limb or axial or both muscle involvement (less or equal to oropharyngeal/respiratory)
Class III	Moderate weakness affecting non-ocular muscles May also have any ocular weakness
IIIa	Predominantly affecting limb or axial muscles or both May also have oropharyngeal muscle weakness (less than limb/axial)
	vs
IIIb	Predominantly affecting oropharyngeal or respiratory muscles or both May also have limb or axial or both muscle involvement (less or equal to oropharyngeal/respiratory)
Class IV	Severe weakness affecting non-ocular muscles May also have any ocular weakness
IVa	Predominantly affecting limb or axial muscles or both May also have oropharyngeal muscle weakness (less than limb/axial)
	vs
IVb*	Predominantly affecting oropharyngeal or respiratory muscles or both May also have limb or axial or both muscle involvement (less or equal to oropharyngeal/respiratory)
Class V	Defined by intubation with or without mechanical ventilation (except when this is employed during routine post-op management)

Note: use of a feeding tube without intubation places a patient in class IVb

Table 1

Brand Name	Generic Name	HCPCS Code
Vyvgart	efgartigimod alfa	J9332
Rystiggo	rozanolixizumab-noli	J3590 (dump code)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCGAS030.1223	**GASTROINTESTINAL AGENTS** **FECAL MICROBIOTA AGENTS** See Appendix 1 for medications covered by policy
Effective Date: 2/1/2024	**Review/Revised Date**: 07/23, 11/23 (MTW)
Original Effective Date: 06/23	**P&T Committee Meeting Date**: 04/23, 08/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B – Rebyota® only
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Authorization for the prevention of recurrence of *Clostridioides difficile* infection (CDI) requires all the following criteria be met:
1. Confirmed diagnosis of recurrent CDI, defined as two or more recurrences after a primary episode (greater than or equal to three total CDI episodes) within 12 months
2. Positive stool test for *C. difficile* within 30 days before prior authorization request
3. Member has completed, or will have completed, an appropriate antibiotic treatment regimen for recurrent CDI prior to administration as outlined in the package label (see Appendix 1)
4. Current episode of CDI must be controlled (less than three unformed/loose stools/day for two consecutive days)

EXCLUSION CRITERIA:
Treatment of CDI

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCGAS030	GASTROINTESTINAL AGENTS FECAL MICROBIOTA AGENTS See Appendix 1 for medications covered by policy

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an infectious disease specialist or gastroenterology specialist

COVERAGE DURATION:
Authorization will be approved for one treatment course.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Rebyota® is the first and only FDA-approved microbiota-based live biotherapeutic to prevent recurrence of *Clostridioides difficile* infection starting at first recurrence. A single dose is administered 24 to 72 hours after the last dose of antibiotics for *Clostridioides difficile* (CDI) by a healthcare professional.

FDA APPROVED INDICATIONS:
For the prevention of recurrence of *Clostridioides difficile* (CDI) in individuals 18 years of age and older following antibiotic treatment for recurrent CDI.

Limitation of Use: Not indicated for treatment of CDI.

POSITION STATEMENT:
- Approximately 500,000 patients in the United States experience CDI each year. About one in six people who get *C. diff* will get it again in the subsequent two to eight weeks.[8]
- Recurrent CDI is defined as an episode of symptom onset and positive assay result following an episode with positive assay result in the previous 2–8 weeks.[4]

- For those with repeat infections, fecal microbiota transplants have shown positive results.[4]
- Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) Guidelines[4]
    - In patients with recurrent CDI episodes, fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin is recommended (conditional recommendation, low certainty evidence).
    - Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.
    - For patients with a recurrent CDI episode within the last six months, bezlotoxumab as a co-intervention along with standard-of-care (SOC) antibiotics is recommended (conditional recommendation, very low certainty of evidence).
- American College of Gastroenterology (ACG) Guidelines[5]
    - Recommend against probiotics for the prevention of CDI recurrence (secondary prevention) (strong recommendation, very low quality of evidence).
    - Recommend patients experiencing their second or further recurrence of CDI be treated with fecal microbiota transplantation (FMT) to prevent further recurrences (strong recommendation, moderate quality of evidence).
    - Suggest repeat FMT for patients experiencing a recurrence of CDI within eight weeks of an initial FMT (conditional recommendation, very low quality of evidence).
    - For patients with recurrent CDI who are not candidates for FMT, who relapsed after FMT, or who require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences (conditional recommendation, very low quality of evidence).
    - Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence (conditional recommendation, low quality of evidence).
    - Suggest bezlotoxumab (BEZ) be considered for prevention of CDI recurrence in patients who are at high risk of recurrence (conditional recommendation, moderate quality of evidence).
- Fecal microbiota transplantation[9]
    - Prior to approval of fecal microbiota, live-jslm, no fecal microbiota transplant (FMT) product has been FDA-approved as safe and effective

for prevention of recurrent CDI. However, FMT has been recommended by various infectious diseases and gastroenterology practice guidelines and used widely as an unapproved product for this indication.
  - FMT is available as an unapproved therapy for recurrent CDI under FDA's investigational new drug (IND) enforcement discretion policy since July 2013.
  - FMT products are manufactured by collecting a stool sample from a donor whom has passed screening for potential health risks, the stool sample is then processed by mixing in a buffer to help bacteria survive being frozen, then stored frozen till use.
  - Concerns with currently available FMT products include product safety, integrity and accessibility.

Rebyota®:[6, 7]

- Efficacy was established in a randomized, double-blind, placebo-controlled, phase 3 study (PUNCH CD3), which formally integrated treatment success rates, utilizing a Bayesian analysis, from a placebo-controlled phase 2 study (PUNCH CD2). This Bayesian analysis provided the primary evidence of effectiveness for fecal microbiota, live-jslm.
  - Key inclusion criteria: Adults (aged ≥ 18 years) with documentation of recurrent CDI (defined as one or more recurrences after a primary episode in PUNCH CD3 or at least two recurrences after a primary episode in PUNCH CD2) who had completed standard-of-care antibiotic therapy or had two or more episodes of severe CDI resulting in hospitalization within the past year. Participants were required to have a positive stool test for the presence of C. difficile. Participants must have been taking or just been prescribed antibiotics to control recurrent CDI symptoms.
  - Key exclusion criteria: Known history of refractory CDI, inflammatory bowel disease, irritable bowel syndrome, chronic diarrhea, celiac disease, colostomy, active colitis, continued diarrhea despite antibiotic therapy, required antibiotic therapy for another condition, or had a previous FMT.
  - Primary endpoint: Treatment success was defined as the absence of CDI diarrhea within eight weeks of blinded treatment. CDI diarrhea was defined as the passage of ≥ 3 unformed/loose stools in ≤ 24 hours for at least two consecutive days and a positive stool test for the presence of *C. difficile* toxin at the time of the diarrhea.
  - Results:

Treatment Success at eight weeks Post-Treatment

Parameter	Fecal Microbiota Mean (95% CrI)	Placebo Mean (95% CrI)	Treatment Effect (Fecal microbiota – Placebo) Mean (95% CrI)
Model-Estimated Treatment Success (%)	70.6 (64.1, 76.8)	57.5 (48.1, 67.1)	13.1 (2.3, 24.0)

Posterior Probability of Superiority	-	-	0.991†

CrI=credible interval
† Pre-defined threshold was 0.975

- PUNCH CD3 evaluated sustained clinical response. The difference in sustained clinical response rate (9.1%; 95% CI: -3.6%, 21.7%) was not statistically significant between the fecal microbiota, live-jslm (65.5%) and the placebo groups (56.5%).
- Safety:
  - Adverse reactions in ≥3% of fecal microbiota, live-jslm recipients in PUNCH CD3:
    - Abdominal pain: 16 (8.9%)
    - Diarrhea: 13 (7.2%)
    - Abdominal distension: 7 (3.9%)
    - Flatulence: 6 (3.3%)
    - Nausea 6 (3.3%)

Vowst®:[13, 14]

- Efficacy was established in a randomized, double-blind, placebo-controlled, phase 3 study (ECOSPOR III). Moderate quality of evidence that fecal microbiota spores may successfully prevent the recurrence of CDI.
  - Key inclusion criteria: 18 years and older, history of three or more episodes of CDI within 12 months, positive *C.difficile* toxin test, resolution of symptoms (defined as less than three uniformed stools in 24 hours for two or more consecutive days) while receiving 10 to 21 days of standard-of-care antibiotic therapy (vancomycin or fidaxomicin)
  - Key exclusion criteria: Known or suspected toxic megacolon and/or known small bowel ileus, history of irritable bowel syndrome, history of active inflammatory bowel disease with diarrhea believed to be caused by active inflammatory bowel disease, history of fecal microbiota transplantation
  - Primary endpoint: CDI recurrence through eight weeks after completion of treatment. Participants were assessed for recurrence, which was defined as ≥3 unformed stools per day for two consecutive days with continued diarrhea until antibacterial treatment was initiated, a positive C. difficile test on a stool sample determined by a toxin assay, and assessment by the Investigator that the clinical condition of the participant warranted antibacterial treatment.
  - Results:

	Treatment Group (n=89) n (%)	Placebo Group (n=93) n (%)	RR (95% CI)[a]	ARR	NNT
CDI recurrence through 8 weeks	11 (12.4)	37 (39.8)	0.32 (0.18-0.58; P <0.001)	27%	4
CDI recurrence through 12 weeks	16 (18.0)	43 (46.2)	0.40 (0.24-0.65; P <0.001)	28%	4
CDI recurrence through 24 weeks	19 (21.3)	44 (47.3)	0.46 (0.30-0.73; P <0.001)	26%	4

RR = Relative Risk; ARR = Absolute Risk Reduction; NNT = Number Needed to Treat
[a]Study treatment group met the pre-specified success criterion of the upper bound of the two-sided 95% confidence interval of the CDI relative risk lower than 0.83

- By week eight, 48 recurrences occurred in the overall trial population. Of these, a total of 36 (75%) occurred within two weeks and 41 (85%) occurred within four weeks after administration of fecal microbiota spores, live-brpk or placebo.

- Safety:
  - No serious adverse effects were observed
  - Common adverse reactions were abdominal distension (54%), fatigue (59%), constipation (31%), chills (23%), and diarrhea (24%)
  - Three deaths occurred in the treatment group, none of which were deemed by the investigators, who were unaware of the trial-group assignments, to be drug-related

REFERENCE/RESOURCES:

1. Rebyota® package Insert. Roseville, MN: Ferring Pharmaceuticals; January 2023.
2. Rebyota® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed February 23, 2023.
3. Rebyota® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.

4. Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults. Clinical Infectious Diseases. 2021 Sept; 73(5): e1029–e1044.
5. Kelly, CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis and Treatment of *Clostridioides difficile* Infections. The American Journal of Gastroenterology. 2021 Jun; 116(6):1124-1147.
6. Dubberke ER, Lee CH, Orenstein R, et al. Results From a Randomized, Placebo-Controlled Clinical Trial of a RBX2660-A Microbiota-Based Drug for the Prevention of Recurrent Clostridium difficile Infection. Clin Infect Dis. 2018 Sep 28;67(8):1198-1204.
7. Khanna S, Assi M, Lee C, Yoho D, et al. Efficacy and Safety of RBX2660 in PUNCH CD3, a Phase III, Randomized, Double-Blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent Clostridioides difficile Infection. Drugs. 2022 Oct;82(15):1527-1538. doi: 10.1007/s40265-022-01797-x. Epub 2022 Oct 26. Erratum in: Drugs. 2022 Nov 7.
8. Centers for Disease Control and Prevention. What is *C.diff*? September 2022. Available at: www.fda.gov/oc/oha/useofinv.html Accessed February 24, 2023.
9. Food and Drug Administration. Fecal Microbiota, Live. BLA Clinical Review Memorandum. 2022. https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota Accessed February 27, 2023.
10. Vowst® package Insert. Cambride, MA: Seres Therapeutics, Inc.; April 2023.
11. Vowst® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed June 12, 2023.
12. Vowst® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed June 12, 2023.
13. Feuerstadt P, et al. SER-109, an oral microbiome therapy for recurrent Clostridioides difficile infection. N Engl J Med. 2022;386(3):220–229. doi:10.1056/NEJMoa2106516.
14. Sims MD, Khanna S, Feuerstadt P, et al. Safety and Tolerability of SER-109 as an Investigational Microbiome Therapeutic in Adults With Recurrent Clostridioides difficile Infection: A Phase 3, Open-Label, Single-Arm Trial. *JAMA Netw Open.* 2023;6(2):e2255758

Appendix 1. Dosage and Administration[1]

Drug	Dose and Administration
Rebyota®	Administer a single dose (150 mL) rectally 24 to 72 hours after the last dose of antibiotics for CDI.
Vowst®	Four capsules taken orally once daily for three consecutive days. Complete antibacterial treatment for recurrent CDI two to four days before initiating treatment with Vowst®.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND081.0623	**ENDOCRINE & METABOLIC DRUGS** **FERTILITY AND RELATED MEDICATIONS** (See Table 1 for medications)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: P&T Committee Meeting Date: 06/23 Original Effective Date: 06/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications, Some Medically-Accepted Indications

REQUIRED MEDICAL INFORMATION:

1. For initiation of therapy (new starts) for **fertility preservation and treatment of infertility**, preferred gonadotropins and Lupron® may be covered.
    a. Non-preferred therapies may be covered subject to the following criteria:
        i. For Gonal-F®: documented inadequate response, intolerance, or contraindication to Follistim AQ®
        ii. For Ovidrel®: documented inadequate response, intolerance, or contraindication to Novarel®, Pregnyl®, or generic chorionic gonadotropin
        iii. For Cetrotide®: documented inadequate response, intolerance, or contraindication to Ganirelix®

2. Patients established on therapy within the previous year will have continued coverage

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND081	ENDOCRINE & METABOLIC DRUGS FERTILITY AND RELATED MEDICATIONS (See Table 1 for medications)

EXCLUSION CRITERIA:

1. Hypogonadism, unrelated to infertility
2. Cryptorchidism

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved for one year

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
This policy refers to medications used to promote the ability to conceive and produce viable offspring. Human menopausal gonadotropin or hMG (Menopur®) is a medication often used for women who don't ovulate because of problems with their pituitary gland—hMG acts directly on the ovaries to stimulate development of mature eggs. Follicle-stimulating hormone or FSH (Gonal-F®; Follistim®) is a medication that works much like hMG. It stimulates development of mature eggs within the ovaries. Gonadotropin-releasing hormone (GnRH) analogs and GnRH antagonists (e.g., ganirelix) are medications that act on the pituitary gland to prevent a woman from ovulating. They are used during in vitro fertilization (IVF) cycles, or to help prepare a woman's uterus for an embryo transfer.

Chorionic gonadotropins, hCG, (Pregnyl®, Novarel®, Ovidrel®) stimulate the production of androgens.

Table 1. Therapies used in fertility treatments

Drug Product	Preparation
Preferred Products	
Follistim AQ® (follitropin β)	FSH
Generic chorionic gonadotropin	hCG
Pregnyl® (chorionic gonadotropin)	hCG
Novarel® (chorionic gonadotropin)	hCG
Ganirelix® (ganirelix acetate)	GnRH antagonist
Menopur® (menotropins)	FSH/LH
Non-Preferred Products	
Gonal F® (follitropin α/β)	FSH
Ovidrel® (choriogonadotropin α)	hCG
Cetrotide® (cetrorelix acetate)	GnRH antagonist
Other therapies	
Lupron® (leuprolide)	GnRH analog

POSITION STATEMENT:
Reasonable and necessary tests and treatments for infertility when fertility would be expected are covered. Refer to the Medicare Benefit Policy Manual, Chapter 15, §20.1 – Physician Expense for Surgery, Childbirth, and Treatment for Infertility. (Accessed May 22, 2023).[9]

The use of leuprolide acetate (Lupron®) may be covered for members with a contracted benefit. GnRH analogs are used with hormone injections to stimulate ovaries and prevent spontaneous release of eggs prior to planned surgical retrieval.

Fertility declines in women with increasing age, with age being a strong predictor of the potential for successful reproduction. Ovulatory dysfunction accounts for about 40% of infertility in women. According to the American Society for Reproductive Medicine (ASRM), “the most common causes of ovulatory dysfunction include polycystic ovary syndrome (PCOS), obesity, perimenopause, weight gain or loss, strenuous or excessive exercise, thyroid dysfunction, and hyperprolactinemia.”[1]

Patients that are found to have oligomenorrhea (infrequent menstrual cycles) or anovulation (lack of ovulation) should undergo a complete workup to determine the cause. Treatment of various causes are outlined below.

Patients with **Hypogonadotropic Hypogonadism**, also known as Hypothalamic Amenorrhea typically present with anovulation and low or low-normal levels of endogenous circulating follicle stimulating hormone (FSH) and luteinizing hormone (LH).[2] Risk factors include low body weight (eating disorders, malabsorption), excessive exercise, and/or emotional stress. Patients may regain ovulatory cycles after achieving a normal body weight, addressing malabsorption issues, reducing strenuous physical activity and stress. These patients are unlikely to respond to oral therapies, such as clomiphene or letrozole.[2]

Patients with **Eugonadotropic Eugonadism** typically present with normal or low FSH levels and increased LH levels. Polycystic Ovarian Syndrome (PCOS) accounts for the majority of cases. PCOS is characterized by excessive androgen levels, irregular menstrual cycles, and polycystic ovaries that can result in anovulation. Patients with a BMI > 30 should be counseled to lose weight, as weight loss alone can restore ovulation, improve response to ovulation induction agents and have a positive impact on pregnancy outcomes. The American College of Obstetricians and Gynecologists (ACOG) and the ASRM support the use of letrozole as first-line for ovulation induction women with PCOS. Clomiphene and metformin may be considered, but do not appear to have the same efficacy as letrozole. Gonadotropins in this population can increase the risk of ovarian hyperstimulation syndrome (OHSS) and multiple-gestation pregnancy.[1-4]

For **male factor infertility**, several contributing factors can lead to infertility, and many may overlap. Endocrine disorders such as hypogonadism (testosterone deficiency), sperm and sperm transport abnormalities, congenital or developmental disorders such as cryptorchidism, or acquired disorders of the testes may all be factors. Treatment may depend on addressing the underlying cause, gonadotropins to induce spermatogenesis or ART procedures.[5]

The American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) guideline for diagnosing and treating infertility in men states that a thorough workup should be completed to determine possible causes of infertility. In infertile men with low serum testosterone, aromatase inhibitors, hCG, selective estrogen receptor modulators (SERMs), or a combination thereof may be considered to increase sperm production. The guidelines recommend against the use of testosterone in this population. For men with idiopathic infertility, a FSH analog may be considered to improve sperm concentration.[6]

The AUA guideline for the evaluation and management of testosterone deficiency go on to say that hCG should only be considered for patients with testosterone deficiency (formerly referred to as hypogonadism) desiring to maintain fertility. Testosterone replacement is the treatment of choice for patients with testosterone deficiency.[8] Therefore, hCG will not be covered for hypogonadism, unless related to infertility management and the member has the associated benefit.

Cryptorchidism [also known as undescended testis (UDT)] is one of the more common genital disorders identified at birth for males. It is typically considered congenital (testes are undescended from birth) or acquired (testes were descended but then move to an undescended position later in life). Congenital cases typically resolve in the first few months of life; if they do not by month six, it is recommended to refer patients to a surgical specialist. Acquired cases can occur 1-7% of boys and typically occurs before eight years of age. If left untreated, cryptorchidism can cause impairment of fertility potential, testicular malignancy, torsion and/or associated inguinal hernia. Human chorionic gonadotropins (hCG) are sometimes used in these patients due to a hypothesis that there is a deficiency in the hypothalamic-pituitary-testicular axis at the end of gestation or shortly after birth. These hCG products stimulate the production of androgens and can lead to descent of the testes; however, this treatment typically only works ~20% of the time, and many patients experience a re-ascent of the testes. The American Urological Association states that “Providers should not use hormonal therapy to induce testicular descent as evidence shows low response rates and lack of evidence for long-term efficacy. (Standard; Evidence Strength: Grade B).” Surgery (orchiopexy) to relocate the testes is typically the first-line treatment and should be completed by 18 months of age for the best outcomes; however, surgery should be performed in all prepubertal boys at the time of diagnosis.[8] Therefore, treatment of cryptorchidism with gonadotropins is not considered medically necessary and will not be covered.

REFERENCE/RESOURCES:

1. American Society for Reproductive Medicine. Fertility evaluation of infertile women: a committee opinion. Available at https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/diagnostic_evaluation_of_the_infertile_female.pdf (Accessed May 12, 2023)
2. American Society for Reproductive Medicine. Use of exogenous gonadotropins for ovulation induction in anovulatory women: a committee opinion. Available at https://www.asrm.org/globalassets/asrm/asrm-

content/news-and-publications/practice-guidelines/for-non-members/use_of_exogenous_gonadotropins_in_anovulatory_women.pdf (Accessed May 12, 2023)

3. American Society for Reproductive Medicine. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Available at https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/recs_from_the_international_evidence-based_guideline_for_pcos.pdf (Accessed May 12, 2023)
4. Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. *Fertility and Sterility*. 2017; 108(3): 426-441. http://dx.doi.org/10.1016/j.fertnstert.2017.06.026
5. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab. 2009;94(3):801-8.
6. American Urological Association/American Society for Reproductive Medicine. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline (2020). Available at https://www.auanet.org/guidelines/guidelines/male-infertility (Accessed May 15, 2023)
7. American Urological Association. Evaluation and Management of Testosterone Deficiency (2018). Available at https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline(Accessed March 15, 2023)
8. American Urological Association. Evaluation and Treatment of Cryptorchidism (2014, reaffirmed 2018). Available at https://www.auanet.org/guidelines/guidelines/cryptorchidism-guideline#x2578 (Accessed May 15, 2023)
9. Medicare Benefit Policy Manual. Chapter15- Covered Medical and Other Health Services. Updated 03/16/23. Available at: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf (Accessed May 22, 2023).

CODING:

Brand	HCPCS code	Details
Menopur®	S0122	injection, menotropins, 75 iu
Gonal-F®	S0126	injection, follitropin alfa, 75 iu
Follistim AQ®	S0128	injection, follitropin beta, 75 iu
Pregnyl®	J0725	Injection, chorionic gonadotropin, per 1000 USP units
Ovidrel®	J0725	injection, chorionic gonadotropin, per 1000 USP units

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH050.1223	**MISCELLANOUS PRODUCTS** **GENE THERAPY FOR HEMOPHILIA** See Table 1 for medications covered by policy
Effective Date: 2/1/2024	**Review/Revised Date**: 08/23, 10/23 (MTW)
Original Effective Date: 04/23	**P&T Committee Meeting Date**: 02/23, 10/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 13	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Gene therapy may be approved when all the following criteria are met:
1. One of the following:
    a. For Hemgenix®: Diagnosis of severe or moderately severe hemophilia B, defined by one of the following: Factor IX level less than 2 IU/dL or less than or equal to 2% of normal, provider attestation, or prior records of moderate to severe hemophilia B
    b. For Roctavian®: Diagnosis of severe hemophilia A, defined by Factor VIII level less than 1 IU/dL or less than or equal to 1% of normal
2. Patient is a biological male
3. One of the following:
    a. Patient is currently on a stable dose of prophylaxis therapy (has been receiving prophylaxis for two months of more) with greater than 150 exposure days of prophylaxis
    b. Current or historical life-threatening hemorrhage
    c. Documentation of repeated, serious spontaneous bleeding episodes

4. Patient is negative for Factor inhibitors, defined by a Factor inhibitor level assay less than 0.6 Bethesda units (BU) per mL. If initial test is positive, documentation of a subsequent negative test within 1-4 weeks will be allowed
5. Roctavian®: Patient is negative for pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
6. Gene therapy will be administered by or in consultation with a Hemophilia Treatment Center (HTC)

EXCLUSION CRITERIA:

- Current or prior presence of factor IX inhibitors (Hemgenix®) or Factor VIII inhibitors (Roctavian®)
- HIV not controlled with antiviral therapy (CD4+ counts equal to 200/µL or by a viral load of greater than 200 copies/mL)
- Active hepatitis B or C infection
- Evidence of advanced liver fibrosis (Fibroscan score of 9 kPA or greater)
- ALT, AST, total bilirubin, alkaline phosphatase, or creatinine greater than two times the upper limit of normal, unless evaluated by hepatology
- Previous treatment with gene therapy for the same indication

AGE RESTRICTIONS:

May be approved for patients aged 18 years and older.

PRESCRIBER RESTRICTIONS:

Must be prescribed by, or in consultation with, a hematologist.

COVERAGE DURATION:

Authorization will be limited to one treatment course per lifetime.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:
Etranacogene dezaparvovec-drlb (Hemgenix®) is an adeno-associated virus serotype 5 (AAV5) based gene therapy designed to deliver a copy of a gene encoding the Padua variant of human coagulation Factor IX (hFIX-Padua). A single intravenous infusion results in cell transduction and increase in circulating Factor IX activity.

- The recommended dose is 2 x 10^{13} genome copies (gc) per kg of body weight, administered as a one-time intravenous infusion.

- Valoctocogene roxaparvovec-rvox (Roctavian®) an adeno-associated virus serotype 5 (AAV5) based gene therapy vector, designed to introduce a functional copy of a transgene encoding the B-domain deleted SQ form of human coagulation factor VIII (hFVIII-SQ). Transcription of this transgene occurs within the liver, using a liver-specific promoter, which results in the expression of hFVIII-SQ. The expressed hFVIII-SQ replaces the missing coagulation factor VIII needed for effective hemostasis.The recommended dose is 6 × 1013 vector genomes (vg) per kg of body weight, administered as a one-time intravenous infusion.

FDA APPROVED INDICATIONS:
Etranacogene dezaparvovec-drlb (Hemgenix®) is indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

Valoctocogene roxaparvovec-rvox (Roctavian®) 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.

POSITION STATEMENT:
Hemophilia B

- Hemophilia B is a recessive X-linked coagulation disorder causing a deficiency of coagulation factor IX (FIX). Occurring primarily in males, the estimated prevalence in the United States is 3.7 cases per 100,000 males, occurring in about 1 per 19,283 male births[8]. Severity is dependent on the level of FIX produced by the patient, with about 44% of patients having severe disease (FIX < 1IU/dL, or <1% of normal). Patients with hemophilia B can experience lifelong spontaneous hemorrhaging into joints, muscles, and soft tissues, which leads to inflammation, pain, and joint damage. Depending on the severity, people with

hemophilia can have substantial disability, and life-threatening bleeding following injuries or surgeries may occur.

- Factor IX concentrate is used in patients with moderate to severe hemophilia B as prophylaxis therapy to prevent bleeds and prevent long-term adverse joint effects. Prophylaxis is done to provide sufficient levels of FIX to prevent spontaneous bleeding and requires regular infusions (up to three times a week). About 1-4% of patients with severe hemophilia B develop an antibody to FIX replacement therapy[10], called an inhibitor.

Clinical Trials:

HOPE-B (NCT03569891)

- Phase 3 prospective, open-label, single-dose, single-arm, multinational study
- Study Duration: 6-month lead-in period until treatment, followed by monthly follow-up until month 12. On-going follow-up period of 5 years
- Patient population: Adult males (N=54) 19 to 75 years old with moderate to severe hemophilia B (FIX levels of ≤2% of normal) that had received continuous prophylaxis for ≥2 months and had >150 previous exposure days of treatment with Factor IX protein.
    - Key exclusions: FIX inhibitors, active hepatitis B/C infection, uncontrolled HIV infection, evidence of advanced liver fibrosis, and previous gene therapy 60 days prior to trial
    - Baseline demographics: mean age: 41.5 years (range, 19-75 years), 100% male, severity of disease: FIX level <1%: 44 (81.5%), FIX level of 1%–2%: 10 (18.5%), prescreening FIX treatment: extended half-life 31 (57.4%), standard half-life: 23 (42.6%), detectable anti-AAV5 NAbs at baseline: 21 (38.8%), participants with zero bleeds during lead-in period: 14 (25.9%)
- Intervention: All 54 patients received a single intravenous dose of 2×10^{13} gc/kg body weight of etranacogene
- Primary endpoint: a non-inferiority test of annualized bleeding rate (ABR) during months 7 to 18 after etranacogene treatment compared with the ABR during the lead-in period, which consisted of at least six months of receiving standard of care routine Factor IX prophylaxis
    - Key secondary endpoints: FIX activity measured by one-stage assay at six, 12 and 18 months after dosing, FIX consumption
- Efficacy: The estimated mean ABR during Months 7 to 18 after treatment was 1.9 bleeds per year [95% CI: 1.0, 3.4], compared with an estimated mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment / lead-in) was 0.46 [95% CI: 0.26, 0.81], demonstrating non-inferiority of ABR during Months 7 to 18 compared to the lead-in period.

Total bleeding events and ABRs (Full Analysis Set: N = 54)

	Lead-in Period	Months 7 to 18 after treatment
All bleeds	136	96
Follow-up time (Person-Year)	33	52
Mean adjusted ABR (95% CI)	4.1 (3.2, 5.4)	1.9 (1.0, 3.4)
Subjects with bleeds	40 (74%)	20 (37%)
Subjects with zero bleeds	14 (26%)	34 (63%)
Observed spontaneous bleed count (proportion of total bleeds)	50 (37%)	14 (26%)
Observed joint bleed count (proportion of total bleeds)	77 (57%)	19 (35%)

- Secondary endpoints:
  - Mean (SD; min, max) FIX activity was 39.0 IU/dL (±18.7; 8.2, 97.1) at six months and 36.9 IU/dL (±21.4; 4.5, 122.9) at 18 months
  - An overall 97% reduction in FIX consumption from lead-in to seven to 18 months post-treatment, mean (SD) difference in FIX consumption was –248,825 (21,102) IU/year/participant (P<0.0001)
  - 52 out of 54 (96.3%) of participants were able to stop prophylactic FIX infusions. None of the 52 participants returned to prophylaxis during study period

- Safety:

Adverse reactions following treatment with etranacogene dezaparvovec-drlb

Adverse Reactions ≥5%	Subjects (%) (N = 54)
Alanine aminotransferase increased	24 (42%)
Headache	10 (18%)
Blood creatine kinase increased	24 (42%)
Flu-like symptoms	8 (14%)
Infusion-related reactions	19 (33%)
Fatigue	7 (12%)

Aspartate aminotransferase increased	24 (42%)
Nausea	4 (7%)
Malaise	7 (12%)

AMT-061-01 (*NCT03489291)*

- Phase 2b, open-label, single-dose, single-arm, multicenter, dose-confirmation/safety trial
- Study Duration: 52 weeks with long-term follow-up assessments over 4 years
- Patient population: Adult males (N=3) with moderate to severe hemophilia B (FIX activity ≤2% of normal) receiving either prophylactic FIX, or on-demand FIX with ≥4 bleeds/year or chronic hemophilic arthropathy (defined as pain, joint destruction, and loss of range of motion in ≥1 joint as assessed by individual investigators).
    - Key exclusions: FIX inhibitors, active hepatitis B/C infection, uncontrolled HIV infection, select laboratory values greater than 2 time the upper limit of normal, thrombocytopenia
    - Baseline demographics: mean age: 46.5 years (range, 43-50 years), 100% male, severity of disease: FIX level <1%: 2 (66%), FIX level of 1%: 1 (33%), prescreening FIX treatment: extended half-life 3 (100%), detectable anti-AAV5 NAbs at baseline: 3 (100%)
- Intervention: All 3 participants were administered a single, 500-mL IV infusion of 2×10^{13} gc/kg infused over 1 hour
- Primary endpoint: To confirm whether a single dose of 2×10^{13} gc/kg of etranacogene dezaparvovec would result in FIX activity levels ≥5% at 6 weeks after dosing. Key secondary endpoints: FIX activity at other time points, bleeding rates, and the use of FIX replacement therapy
- Efficacy:

	FIX activity (% of normal)			
	Prior to treatment	**Week 6**	**Week 12**	**Week 26**
Participant 1	1	37.8	37.9	51.0
Participant 2	<1	23.9	24.9	33.2
Participant 3	<1	30.0	51.1	57.0

    - In the year prior to treatment with etranacogene dezaparvovec, all three participants received prophylactic FIX replacement plus additional doses of FIX for treatment of bleeding events (participants 1, 2, and 3 experienced 3, 1, and 5 bleeds requiring FIX treatment, participant 3 also reported a suspected bleed during the screening period). There were no

reported bleeds and no requirement for FIX replacement up to 26 weeks post treatment with etranacogene dezaparvovec. As part of the study protocol, participant 1 received two doses of short-acting FIX (on the day of dosing and day three posttreatment), and the other two participants each received 1 dose of short-acting FIX on the day of dosing.

- Safety: Two adverse events determined to be possibly related to treatment with etranacogene dezaparvovec occurred: Participant 1 reported a headache on the day of dosing, and had a mild elevation in C-reactive protein level on day 14 posttreatment (7.4 mg/L; reference range 0-3 mg/L) that resolved without intervention.

Hemophilia A

- Hemophilia A is an X-linked recessive inherited disorder leading to deficiencies of one of the proteins necessary for normal blood clothing, factor VIII (FVIII). Affecting predominately males, the estimated number of males living with hemophilia (A or B) in the United States is between 30,000-33,000[14] with approximately 76% of them having hemophilia A. About 60% of these individuals have the severe form of the disorder[15], which is defined as less than 1% of baseline clotting factor activity. Individuals with hemophilia (particularly those with severe disease) are at risk for life-threatening bleeding, including intracranial bleeding. Individuals often have bleeding following an injury, however, may also have frequent spontaneous bleeding episodes, most commonly into the joints (hemarthrosis) or muscles. Joint and muscle bleeds occur most frequently and can lead to substantial disability.
- Prophylaxis with plasma-derived or recombinant standard half-life factor, extended half-life factor, or non-factor replacement emicizumab (Hemlibra®) to prevent bleeding is the current standard of care of patients with severe hemophilia to prevent musculoskeletal complications from recurrent joint and muscle bleeds[16,17]. This is typically started early in life before the age of 3. Patients who develop inhibitors may eradicate inhibitors through immune tolerance induction (ITI) therapy. Patients who do not respond to enhanced factor dosages or ITI may use bypassing agents or emicizumab. All available prophylaxis products can effectively prevent bleeding; however, each can have different patient responses, safety profiles (inhibitor development risks), costs, and product characteristics (half-life, effects on monitoring). The choice of prophylaxis product is made as a team evaluating the patient's specifics circumstances and needs. The goal of prophylaxis is to prevent bleeding at all times.

Clinical Trials:
GENEr8-1 (NCT03370913)

- Phase 3 prospective, open-label, single-dose, single-arm

- Duration: median follow-up 60.2 weeks (range, 51.1 to 150.4)
- Inclusion criteria: Males ≥18 years with severe hemophilia A (FVIII activity level ≤1 IU/dL) receiving FVIII prophylaxis ≥1 year before enrollment, and treated/exposed to FVIII concentrates/ cryoprecipitate for ≥150 exposure days
    - ITT: 134 (all receiving gene therapy)
    - The modified intention-to-treat (mITT) population: 132 (ITT & HIV negative)
    - Rollover: 112 (mITT & ≥6 months bleeding & FVIII usage data)
- Key exclusions: anti-AAV5 antibodies, chronic/active hepatitis B/C, HIV, current/prior FVIII inhibitor, significant liver dysfunction/fibrosis, cirrhosis, liver function test abnormalities
- Baseline demographics: 61.9% were receiving prophylaxis with standard half-life products, 27.6% with extended half-life products, and 17.9% plasma-derived products. No participants were receiving Hemlibra.
- Intervention: All participants received valoctocogene roxaparvovec at a dose of 6×10^{13} vector genomes (vg) per kilogram of body weight through peripheral vein infusion. Glucocorticoids or other immunosuppressant (IS) were administered in response to ALT elevations. FVIII prophylaxis continued through 4 weeks after infusion; then as needed
- Primary endpoint: change from baseline in FVIII activity at 49-52 weeks after infusion. Baseline FVIII activity level imputed as 1 IU/dL (no FVIII washout period was required)
- Efficacy: In the mITT population (132 participants) the mean and median changes from baseline were 41.9 IU/dL (95% confidence interval [CI], 34.1 to 49.7; P<0.001) and 22.9 IU/dL (interquartile range, 10.9 to 61.3). At weeks 49-52, median FVIII activity level was ≥ 40 IU/dL (i.e., nonhemophilic) in 50 participants (37.9%), > 5 and < 40 IU/dL (mild hemophilia) in 66 participants (50.0%), and < 5 IU/dL in 16 participants (12.1%); 12 participants (9.1%) had a median FVIII activity level of < 3 IU/dL
- Safety: The most common adverse reactions (ARs) (≥5%) were nausea (31%), fatigue (16%), headache (7%), infusion-related reactions (7%), vomiting (6%), and abdominal pain (6%). The most common laboratory abnormalities (≥10%): elevated alanine transaminase (ALT) (81%), aspartate aminotransferase (AST) (69%), lactate dehydrogenase (LDH) (57%), creatine phosphokinase (CPK) (45%), FVIII activity levels (28%), gamma-glutamyl transferase (GGT) (18%), and bilirubin (13%) greater than the upper limit of normal (ULN). There were 6 serious ARs related to treatment: ALT elevation, presyncope, maculopapular rash, anaphylaxis, and hypersensitivity reaction.
    - 92/112 patients (82%) required corticosteroids for ≥1 episodes of ALT elevation, 39/112 (35%) required alternate IS.

GENEr8-1 (NCT03370913): Primary analysis of the change in the annualized treated bleeding rate at 2 or more years after gene transfer, an extension trial of GENEr8-1

- Duration: follow-up period of 104 weeks after gene transfer
- Primary endpoint: (amended in response to FDA feedback) change in annualized treated bleeding rate in the rollover population, tested for noninferiority (margin, 3.5 episodes per year; estimated from pivotal studies of factor VIII replacement products), as compared with baseline. The efficacy evaluation period (EEP) started from study day 33 (week 5), or the end of FVIII prophylaxis including a washout period after gene therapy, whichever was later, and ended when a patient completed the study
    - Secondary endpoints: change from baseline to week 104 in FVIII activity in the mITT population and change from baseline in annualized number of bleeding events at week 104 compared to baseline
- Efficacy: Among the rollover participants (N=112), the mean change in annualized treated bleeding rate was -4.1 bleeding events (95% CI, -5.3 to -2.9) per year (-84.5%, P<0.001). This change exceeded the noninferiority margin of 3.5.
    - Annualized occurrence of all bleeding events (ABR) during post prophylaxis period: In the published clinical trial the ABR changed from baseline in the rollover population by a mean of −4.1 (95% CI, −5.4 to −2.8) bleeding events per year (–77.0%, P<0.001). In the FDA approval letter, the mean imputed EEP ABR was 2.6 bleeds/year, compared to a mean observed baseline ABR of 5.4 bleeds/year, with a mean difference in ABR of -2.8 bleeds/year (95% confidence interval (CI): -4.3, -1.2). Of note, BioMarin did not input ABR when patients used prophylaxis treatment during the EEP. In the package insert, the FDA input an ABR of 35 for the periods when patients were on prophylaxis. This resulted in a calculated mean ABR reduction of 52%, as opposed to 77% in the published clinical trial.
    - FVIII activity increased from baseline (imputed at 1 IU per deciliter) to week 104 by a mean of 22.0 IU/dL (95% CI, 16.4 to 27.7; P<0.001) as measured with a chromogenic substrate assay (CSA) in the mITT population and by 35.1 IU/dL (95% CI, 26.9 to 43.2) as measured with a one-stage assay. Data for two participants who did not complete week 104 were imputed as 0 IU/dL.
    - The mean annualized FVIII concentrate consumption at baseline was 3961.2 ± 1751.5 IU/kg/year, compared to after treatment: 69.9 IU/kg/year. The change in mean was -3891.3 (95% CI, -4221.0 to -3561.5) (98.2% reduction; P<0.001).
    - 10/112 subjects returned to routine prophylaxis as of 3-year data cutoff. Per FDA analysis, a total of 22 subjects [20% (including 10 subjects who

had returned to prophylaxis)] identified as having not ever having benefitted from valoctocogene (n=5), or for whom benefit was lost (n=17) over a median time of 2.3 (range: 1.0 to 3.3) years as of 3-year data cutoff. In the directly enrolled population of 22 subjects, 1 subject did not respond (5%) and 6 subjects (27%) lost response to valoctocogene over a median time of 3.6 (range: 1.2 to 4.3) years as of the 3-year data cutoff.

- Safety: The most common nonlaboratory adverse reactions (incidence ≥5%) included infusion-related reactions (including hypersensitivity reactions and anaphylaxis), nausea, headache, fatigue, vomiting, diarrhea, and abdominal pain. The most common laboratory adverse events (incidence ≥10%) were elevations > upper limit of normal (ULN) in ALT, aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactate dehydrogenase, gamma glutamyl transferase (GGT), bilirubin, and FVIII activity level. 5 subjects had 6 serious adverse events (SAEs) attributed to treatment: anaphylaxis, Grade 3 ALT elevation, and symptoms of hypersensitivity reaction. 97 subjects (87%; 97/112) in the rollover population received IS for ALT elevation. 92 (82%; 92/112) subjects received corticosteroids (prednisone or prednisolone), while 39 subjects (35%) received alternate IS that included tacrolimus and mycophenolate. The median (range) duration of overall IS, corticosteroid, and alternate IS use was 39.6 (3.4, 131), 35 (3.1, 120), and 26 (6, 118) weeks respectively. 20 subjects received > a year of IS therapy.

Cost-effectiveness studies**:**

Institute for Clinical and Economic Review (ICER): Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value[7]

Hemgenix®:

- Compared to factor IX prophylaxis, ICER concludes that there is moderate certainty of a small or substantial net health benefit, and high certainty of at least a small net health benefit (B+)
- At a price of $3,500.000, etranacogene dezaparvovec transitions from being not cost effect at $150,000 per QALY to a dominant treatment at 7.5 years
- The Health Benefit Price Benchmark (HBPB) is $2.93 to $2.96 million
- Due to the high costs of factor prophylaxis, all patients could be treated with etranacogene dezaparvovec without crossing the annual budget impact threshold

Roctavian®:

- Low certainty about the net health benefit (I) for valoctocogene compared with emicizumab. Moderate certainty of a comparable, small, or substantial health benefit with high certainty of at least a comparable net health benefit (C++) for valoctocogene compared with factor VIII prophylaxis
- The Health Benefit Price Benchmark (HBPB) is $1.96 million

- Valoctocogene transitions from not being cost effective at $150,000 per QALY to being a dominant treatment in year 4 (cycle 8) at a placeholder price of $2,500,000.

REFERENCE/RESOURCES:

1. Hemgenix® Package insert. King of Prussia, PA: CSL Behring LLC; 2022 Nov.
2. Hemgenix® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed December 21, 2022
3. Hemgenix® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed December 20, 2022
4. Miesbach W, et al; HOPE-B Investigators. Final analysis from the pivotal Phase 3 HOPE-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe haemophilia B. Paper presented at: 15th Congress for the European Association for Haemophilia and Allied Disorders; February 2–4, 2022. Accessed December 20, 2022.
5. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158. https://doi.org/10.1111/hae.14046
6. National Hemophilia Foundation. MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors. Accessed December 29, 2022.
7. The Institute for Clinical and Economic Review. Gene Therapy for Hemophilia B and An Update on Gene Therapy for Hemophilia A: Effectiveness and Value, Final Evidence Report. December 22, 2022.
8. Centers for Disease Control and Prevention. A New Study of Hemophilia Occurrence Finds Many More Cases in the United States. Accessed December 8, 2022.
9. Wolfgang M, Karina M, Michiel C, et al; Gene therapy with adeno-associated virus vector 5–human factor IX in adults with hemophilia B. Blood 2018; 131 (9): 1022–1031. doi: https://doi.org/10.1182/blood-2017-09-804419
10. National Hemophilia Foundation. What is an inhibitor? Accessed December 12, 2022.
11. Noone D, et al. Prophylactic treatment in people with severe hemophilia B in the US: an analysis of real-world healthcare system costs and clinical outcomes. Blood. 2019;134(suppl 1):2118. doi:10.1182/blood-2019-126576
12. Annette VD, Adam G, Giancarlo C, et al; Etranacogene dezaparvovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in

hemophilia B. Blood Adv 2019; 3 (21): 3241–3247. doi: https://doi.org/10.1182/bloodadvances.2019000811
13. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: Communication from the SSC of the ISTH. Journal of Thrombosis and Haemostasis, 2014; 12(11):1935-9.
14. Centers for Disease Control and Prevention (CDC). A new study of hemophilia occurrence finds many more cases in the United States. Accessed August 24, 2023. https://www.cdc.gov/ncbddd/hemophilia/features/keyfinding-hemophilia-occurrence-US.html
15. National Hemophilia Foundation. Hemophilia A. Accessed August 24, 2023. https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a
16. Srivastava, A, Santagostino, E, Dougall, A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158. https://doi.org/10.1111/hae.14046
17. "MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors: NBDF." MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors, National Bleeding Disorders Foundation, 27 Apr. 2022, www.hemophilia.org/healthcare-professionals/guidelines-on-care/masac-documents/masac-document-267-masac-recommendation-concerning-prophylaxis-for-hemophilia-a-and-b-with-and-without-inhibitors.
18. Ozelo MC, et al. Valoctocogene roxaparvovec gene therapy for hemophilia A. N Engl J Med. 2022;386(11):1013-1025. doi:10.1056/NEJMoa2113708
19. Mahlagu J, Kaczmarek R, Drygalski A, et al. Two-Year Outcomes of Valoctocogene Roxaparvovec Therapy for Hemophilia A. N Engl J Med. 2023; 388:694-705. DOI: 10.1056/NEJMoa2211075
20. Roctavian® package insert. Novato, CA; BioMarin Pharmaceutical Inc.; 2023 June.
21. Roctavian® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed August 30, 2023
22. Roctavian® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed August 30, 2023

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH050	MISCELLANOUS PRODUCTS GENE THERAPY FOR HEMOPHILIA See Table 1 for medications covered by policy

Table 1

Brand Name	Generic Name	HCPCS Code
Hemgenix®	etranacogene dezaparvovec-drlb	J1411
Roctavian®	valoctocogene roxaparvovec-rvox suspension	J3590 (dump code)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM022.1223	**HEMATOLOGICAL AGENTS** **GIVLAARI®** (givosiran sodium vial)
Effective Date: 2/1/2024	**Review/Revised Date**: 04/20, 11/20, 10/21, 10/22, 10/23 (JCN)
Original Effective Date: 06/20	**P&T Committee Meeting Date**: 04/20, 12/20, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:

1. Confirmed diagnosis of acute hepatic porphyria [acute intermittent porphyria, hereditary coproporphyrin, variegate porphyria, aminolevulinic acid (ALA) dehydratase deficient porphyria]
   AND
2. One of the following:
   a. Active disease defined as two documented porphyria attacks within the past six months which required either hospitalization, urgent care visit, or intravenous hemin administration, or
   b. Patient is currently receiving treatment with prophylactic hemin to prevent porphyria attacks
3. Documentation that patient will not receive concomitant prophylactic hemin treatment while on therapy with givosiran therapy
4. Documentation that patient's dosing is in accordance with FDA labeling (patient's current weight must be included in documentation) and is subject to audit

Reauthorization requires documentation of one of the following:

1. Reduction in the number or severity of porphyria attacks
2. Reduction in number of hospitalizations due to acute porphyria attacks
3. Decreased hemin administration from baseline

EXCLUSION CRITERIA:
Use post liver transplant

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hepatologist, gastroenterologist, or hematologist

COVERAGE DURATION:
Initial authorization will be approved for six months.
Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Givosiran is the first GaINAc-conjugate RNA therapeutic approved in adults with acute hepatic porphyria (AHP). Givosiran causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP. Givosiran requires administration by a medical professional.

FDA APPROVED INDICATIONS:
Treatment of adults with acute hepatic porphyria (AHP)

POSITION STATEMENT:
Background:
Acute hepatic porphyria (AHP) is a family of rare, genetic diseases caused by a deficiency in one of the enzymes in heme biosynthesis in the liver. Acute intermittent porphyria (AIP) is the most common AHP that presents with a mutation in hydroxymethylbilane synthase (HMBS). AHP occurs when the induction of ALAS1 leads to accumulation of neurotoxic heme intermediates of ALA/PBG. ALA is believed to be the primary neurotoxic intermediate that causes the disease manifestations.

AHP is characterized by debilitating, potentially life-threatening neurovisceral attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life. Disability and social isolation is common in patients with AHP. Long-term complications can include chronic neuropathic pain, hypertension, chronic kidney disease, and liver disease.

The goal of therapy for an acute attack of AIP (and any other acute neurovisceral porphyria, AHPs) is to stop the attack as quickly as possible. Hospitalization is usually required for acute attacks since it facilitates treatment of severe symptoms, allows monitoring (respiration, electrolytes, nutritional status); and provides access to intravenous (IV) hemin administration (only approved drug available for treatment of AHP). Although there are no high-quality data from large randomized trials available to support efficacy of hemin (and other acute porphyria therapies), many case series and reports have found hemin effective in speeding recovery from acute attacks, with a low risk of adverse events.

Guideline:
The Emergency Room Guidelines for Acute Porphyrias, released before the approval of givosiran, state that treatment should start promptly after a diagnosis of porphyria is made. It states that most acute attacks should be treated with hemin and that other pharmacotherapies for prevention of porphyria attacks are not approved. Another option mentioned by the guidelines for porphyria attacks include liver transplantation for refractory cases.

Efficacy:
There is low quality evidence that givosiran compared to placebo showed a reduction in the annualized rate of composite porphyria attacks in patients (N=94) with acute intermittent porphyria (AIP) over a 6-month treatment period based on

one phase 3 trial (ENVISION). This trial included patients aged at least 12 years with acute hepatic porphyria, an elevated level of urinary delta-aminolevulinic acid (ALA) or porphobilinogen (PBG), and either a confirmed pathogenic mutation associated with acute hepatic porphyria or biochemical and clinical criteria consistent with a diagnosis of acute hepatic porphyria. Patient has to have a documentation of 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. Some patient exclusions were patients who had abnormal liver function, abnormal INR, renal dysfunction, and patients who had scheduled surgery.

AHP patients on givosiran experienced a 74% reduction in mean annualized rate of composite attack rate in AIP patients compared to placebo [3.2 (95% CI 2.25 to 4.59) for givosiran and 12.5 (95% CI 9.35 to16.76) for placebo, p<0.001]. As a secondary endpoint, givosiran also reduced the annualized days on hemin in AIP to 6.77 days compared to placebo at 29.71 days (p<0.001). In summary, the ENVISION trial was a large population for an ultra-rare disease and had low attrition with 93 out of 94 patients continuing in the optional open label extension trial. Some limitations of the study include very non-white patients, the majority of patients had AIP with mutation in the HMBS gene for AHP type (placebo = 94%, givosiran = 95%), low number of median patients (N=~4) had porphyria attacks in the past 6 months, and ~40% of patients had prior hemin prophylaxis therapy.

Summary of Safety:

- Warning and precautions include: anaphylactic reaction, hepatic toxicity, renal toxicity, injection site reaction, and blood homocysteine increased
- Adverse events were reported in 43/48 (89.6%) of givosiran patients and in 37/46 (80.4%) of placebo patients in the ENVISION clinical trial
    - The most common adverse reactions (equal or over 20% of patients) included nausea (27%) and injection site reactions (25%)
- Other adverse reactions (equal or over 5%) included rash, serum creatinine increase, transaminase elevations, and fatigue

REFERENCE/RESOURCES:

1. Givlaari prescribing information. Alnylam Pharmaceuticals, Inc. 2023 February.
2. Panhematin prescribing information. Recordati Rare Diseases Inc. November 2017.
3. Givlaari In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed October 31, 2022.

4. Givlaari In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed November 5, 2023.
5. Pimstone NR, Anderson, KE., and Freilich B. Emergency room guidelines for acute porphyrias. American Porphyria Foundation. Available from: https://porphyriafoundation.org/for-healthcare-professionals/emergency-room-guidelines-for-acute-porphyrias/ . Accessed on October 31, 2022.
6. Balwani M, Sardh E, Ventura P et al. Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. *N Engl J Med.* 2020; 382:2289-2301.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC057B.0224	**ANTINEOPLASTIC AGENTS** **GONADOTROPIN RELEASING HORMONE AGONISTS** See Table 1 for medications
Effective Date: 4/1/2024	**Review/Revised Date**: 08/97, 03/98, 08/98, 01/99, 03/00, 05/02, 12/02, 12/03, 12/04, 02/06, 06/07, 12/08, 12/09, 04/10, 06/11, 08/11, 02/12, 02/13, 02/14, 02/15, 04/15, 06/15, 01/16, 01/17,12/17 , 09/18, 01/19, 03/19 , 05/19, 12/19, 08/20, 01/21, 05/21, 07/21, 01/22, 06/22, 12/22, 06/23, 12/23 (MTW)
Original Effective Date: 10/97	**P&T Committee Meeting Date**: 01/99, 03/00, 12/02, 12/03, 12/04, 02/06, 06/07, 12/08, 12/09, 04/10, 08/11, 02/12, 02/13, 02/14, 06/14, 02/15, 04/15, 06/15, 02/16, 02/17, 12/17, 02/18, 09/18, 10/18, 02/19, 04/19, 06/19, 02/20, 08/20, 02/21, 06/21, 08/21, 02/22, 06/22, 02/23, 06/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit. Medically necessary off-label uses may be approved according to the clinical criteria outlined in the policy.

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy** with the requested agent (new starts), must meet the indication-specific criteria outlined below:

1. **For oncological indications,** gonadotropin releasing hormone agonists may be covered if the following criteria are met:
    a. Use is for an FDA approved indication or indication supported by National Comprehensive Cancer Network guidelines with recommendation 2A or higher
2. **For uterine leiomyomata (fibroids),** leuprolide acetate may be covered if one of the following criteria (a or b) are met:
    a. Request is for use prior to surgery to improve anemia caused by fibroids and the following criteria (i and ii) are met:
        i. Documented trial, failure, intolerance, or contraindication to at least 30 days of therapy with iron supplementation alone
        ii. Documentation that leuprolide acetate will be used in combination with iron supplementation

   b. Request is for use prior to surgery to reduce the size of fibroids and the following criteria are met:
      i. Documentation that surgical removal of fibroids is planned within four months
3. **For endometriosis**, leuprolide acetate or goserelin acetate may be covered if the following criteria are met:
   a. Chart notes or provider attestation that other causes of gynecologic pain have been ruled out (such as irritable bowel syndrome, interstitial cystitis, urinary tract disorders)
   b. Documentation that patient has failed a three-month trial of hormonal contraceptives unless they are not tolerated, or contraindicated
4. **For endometrial thinning/dysfunctional uterine bleeding,** goserelin acetate may be covered if the following criteria are met:
   a. Documentation for use prior to endometrial ablation
5. **For central precocious puberty,** gonadotropin releasing hormone agonists may be covered if one of the following criteria (a or b) are met:
   a. Request is for a one-time dose for diagnostic purposes
   b. All the following criteria:
      i. Documentation of a history of early onset of secondary sexual characteristics (age eight years and under for females or nine years and under for males)
      ii. Confirmation of diagnosis by one of the following:
         - Pubertal response to a GnRH or GnRH analog (such as leuprolide) stimulation test [for example stimulated peak luteinizing hormone (LH) of approximately 4.0 to 6.0 IU/L and/or elevated ratio of LH/follicle-stimulating hormone at 0.66 or greater (reference range may vary depending on assay)]
         - Pubertal level of basal LH levels (0.2 IU/L or greater)
         - Bone age advanced one year beyond the chronological age
6. **For gender-affirming services,** gonadotropin releasing hormone agonists may be covered if the following criteria (a and b) are met:
   a. Prescribed by or in consultation with an endocrinologist
   b. Chart notes or provider attestation that puberty has progressed to a minimum of Tanner Stage 2

For patients **established on the requested therapy** (within the previous year), must meet indication-specific criteria below :

1. **For oncological indications:**
   a. Documentation of successful clinical response to therapy
2. **For uterine leiomyomata (fibroids):**

   a. Documentation that the patient has not received more than three months of therapy for current course of treatment. Initial criteria must be met for a new course of treatment.
3. **For endometriosis:**
   a. For leuprolide acetate:
      i. Documentation that it will be used in combination with "add-back" progesterone therapy (such as norethindrone) to help prevent bone mineral density loss
      ii. Documentation that the patient has not received more than 12 months of therapy
   b. For goserelin acetate: Documentation that the patient has not received more than six months of therapy
4. **For endometrial thinning/dysfunctional uterine bleeding:**
   a. Documentation that the patient has not had more than two months of therapy for current course of treatment. Initial criteria must be met for a new course of treatment.
5. **For central precocious puberty:**
   a. Documentation of clinical response to treatment such as pubertal slowing or decline, height velocity, bone age, LH, or estradiol and testosterone level, and
   b. Documentation that hormonal and clinical parameters are being monitored periodically during treatment to ensure adequate hormone suppression
6. **For gender-affirming services:**
   a. Documentation of successful clinical response to therapy

EXCLUSION CRITERIA:
Treatment of male infertility

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
- **Oncological Indications:** Authorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.
- **Uterine leiomyomata (fibroids):** Initial authorization will be approved for three months. No reauthorization.
- **Endometriosis:** For Lupron®- authorization/reauthorization will be approved for up to six months (total of 12 months). For Synarel®/Zoladex® - initial authorization for up to six months and no reauthorization.

- **Endometrial thinning/dysfunctional uterine bleeding:** Initial authorization will be approved for two months. No reauthorization.
- **Central precocious puberty:** Authorization/reauthorization will be approved for one year
- **Gender-affirming services:** Authorization/reauthorization will be approved for one year

---

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Leuprolide acetate, an LH-RH agonist, is a synthetic analog of naturally occurring gonadotropin-releasing hormone (GnRH). GnRH regulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) synthesis and secretion by the pituitary gland. The synthetic leuprolide possesses greater potency than the natural GnRH hormone. With continued leuprolide administration for more than one to three weeks, the pituitary gland downregulates and desensitizes GnRH receptors, reducing FSH and LH secretion. In humans, administration of leuprolide acetate results in an initial increase in circulating levels of FSH and LH, leading to a transient increase in concentrations of gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, leuprolide reduces serum testosterone to castrate levels within two to four weeks after initiation of treatment and requires continuation of therapy as maintenance. Normal pituitary and gonadal function typically return after approximately three months of discontinuation of leuprolide, however testosterone production may not return to baseline in some cases.

Triptorelin, nafarelin, and histrelin are also LH-RH analogs that reversibly inhibit gonadotropin secretion. Initial temporary increase in LH, FSH, testosterone, and estradiol is followed by a sustained reduction in LH and FSH which in turn lowers testicular and ovarian steroidogenesis.

FDA APPROVED INDICATIONS: [1-2]

Camcevi® (leuprolide mesylate)

- Treatment of advanced prostate cancer
  - 42 mg SQ every six months

Eligard® (leuprolide acetate)

- Treatment of advanced prostate cancer
  - 7.5 mg subcutaneously (SC) every month
  - 22.5 mg SC every three months
  - 30 mg SC every four months
  - 45 mg SC every six months

Fensolvi® (leuprolide acetate)

- Central Precocious Puberty (two years and older)
  - 45 mg SC every six months
  - Must be administered by a healthcare professional

Lupron® (leuprolide acetate)

- Treatment of advanced prostate cancer
  - Lupron® Depot 7.5 mg intramuscularly (IM) monthly
  - Lupron® Depot 22.5 mg IM every three months
  - Lupron® Depot 30 mg IM every four months
  - Lupron® Depot 45 mg IM every six months
  - Leuprolide acetate injection 1 mg/0.2 ml SQ daily
- Endometriosis
  - Lupron® Depot 3.75 mg IM monthly (up to six months)
  - Lupron® Depot 11.25 mg IM every three months (up to six months)
- Uterine Leiomyomata (Fibroids)
  - Lupron® Depot 3.75 mg IM monthly (up to three months)
  - Lupron® Depot 11.25 mg IM as a single injection
- Central Precocious Puberty
  - Lupron Depot-Ped® (1-month formulation) IM monthly (weight-based dosing)
    - 25 kg and less: 7.5 mg
    - 25 to 37.5 kg: 11.25 mg
    - 37.5 kg and greater: 15 mg
  - Lupron Depot-Ped® (3-month formulation) IM 11.25 mg or 30 mg every three months

- Lupron Depot-Ped® must be administered by a healthcare professional

Triptodur® (triptorelin)

- Central Precocious Puberty for patients aged two years or older
  - Triptodur® 22.5 mg IM injection every 24 weeks
  - Must only be administered by a healthcare provider

Trelstar® (triptorelin pamoate kit)

- Treatment of advanced prostate cancer
  - Trelstar® 3.75 mg IM injection every four weeks

Supprelin LA® (histrelin acetate implant)

- Central Precocious Puberty
  - Supprelin LA 50 mg implant inserted SQ every 12 months

Zoladex® (goserelin implant)

- Palliative treatment of advanced prostate cancer
  - Zoladex® 3.6 mg SQ every 28 days
  - Zoladex® 10.8 mg SQ every 12 weeks
- Prostate cancer, in combination with flutamide for locally confined stage B2-C disease
  - Zoladex® 3.6 mg SQ followed in 28 days by 10.8 mg, started eight weeks prior to radiotherapy in combination with flutamide
  - Four injections of Zoladex® 3.6 mg at 28-day intervals, two injections prior to and two injections during radiotherapy
- Palliative treatment of advanced breast cancer in pre- and peri-menopausal women
  - Zoladex® 3.6 mg SQ every 28 days for long-term therapy
- Endometriosis
  - Zoladex® 3.6 mg SQ every 28 days for up to six months
- Hypoplasia of endometrium
  - Zoladex® 3.6 mg SQ four weeks prior to endometrial ablation surgery
  - Two Zoladex® 3.6 mg SQ given four weeks apart with endometrial ablation surgery performed within 2-4 weeks of the second injection

Treatment of male infertility is not a covered indication.

POSITION STATEMENT:

Leuprolide is approved, by the Food and Drug Administration (FDA), for several indications including palliative treatment of prostate cancer, uterine fibroids, endometriosis, and central precocious puberty in children. Long term therapy (greater than six months) with leuprolide can reduce bone mineral density. This effect is partially reversible, although bone mineral density may remain below pretreatment values for up to one year after discontinuing leuprolide therapy.

1. **Uterine fibroids or leiomyomata**:

a. Lupron Depot® 3.75 mg IM monthly and 3-Month 11.25 mg as single injection are administered concomitantly with iron therapy to assist in preoperative management of anemia caused by fibroids. Some patients may respond to a one-month trial of iron therapy alone. Leuprolide may be added if the response to iron therapy is not adequate.
b. Treatment with leuprolide can also reduce both uterine and fibroid volume. The recommended duration of therapy with Lupron Depot® for this indication is three months (or a single injection of Lupron Depot®-3 month 11.25 mg). This therapy has only been studied in women 18 years of age and older.
c. Add-back therapy with norethindrone is not indicated for leiomyomas but may be considered to maintain amenorrhea and reduce uterine volume, as well as prevention of vasomotor symptoms.
d. According to a Cochrane review in 2017, there is low quality of evidence to support the use of preoperative GnRH analogs reduced blood loss, operation time, and complication rates during hysterectomy.

2. **Endometriosis**: While there are several agents and procedures used to treat patient symptoms, there is none that results in a cure or long-term management for most patients. The management of endometriosis is dependent on patient specific factors such as type and severity of symptoms, current or future reproductive goals, and patient demographics. First line treatment considerations include non-steroidal anti-inflammatory drugs (NSAIDS), combined oral contraceptives, and progestins. Second line treatment considerations include GnRH agonists, progestin intrauterine devices (IUDs), and aromatase inhibitors. Lupron Depot® 3.75 mg and 3-Month 11.25 mgIM injections, Synarel® nasal solution, and Zoladex® subcutaneous implant are indicated for the management of endometriosis. Concurrent use of progestin, such as norethindrone acetate 5mg, or combined hormone therapy (estrogen and progestin), is also indicated for management of endometriosis as add-back therapy to reduce severity of hypoestrogenic effects of gonadotropin-releasing hormone (GnRH) agonists and to manage pelvic pain. Hypoestrogenic effects include loss of bone density, hot flushes, vaginal dryness, headaches, and mood changes. GnRH agonist monotherapy beyond six months is not recommended due to hypoestrogenic effects, therefore duration of initial treatment or retreatment should be limited to six months. Retreatment with a GnRH agonist (Lupron Depot®) including add-back therapy is recommended. If patients cannot take concomitant norethindrone for retreatment, then retreatment is not recommended. Retreatment with Synarel® and Zoladex® (after initial treatment of six months) is not recommended due to lack of safety data of use beyond six months.
3. **Palliative Treatment of Prostate Cancer**: Leuprolide, goserelin, and triptorelin are treatment options to consider as part of androgen deprivation therapy (ADT)

in prostate cancer. They can be used alone or in combination with antiandrogen therapy. Other options for ADT include LHRH antagonists or orchiectomy. Lupron Depot®, Eligard®, and Zoladex® are approved for use in prostate cancer.

4. **Central Precocious Puberty (CPP)**:
    a. Females less than eight years of age and males less than nine years of age that have an onset of secondary sexual characteristics (e.g., maturation of pubic hair, maturation of breasts in females, maturation of testes and penis in males) should be evaluated for CPP. 3,10,13,15
    b. Children with CPP also have significant advancement of bone age and/or accelerated linear growth for their age.
    c. Prior to initiation of leuprolide, triptorelin, or histrelin therapy, the diagnosis should be confirmed by measuring basal and/or GnRH-analog-stimulated luteinizing hormone (LH) levels.
        i. Typically, prepubertal basal LH level is less than 0.3 IU/L when measured using an ultrasensitive methodology, such as immunochemiluminescence that has a lower limit of detection of 0.1 IU/L.
        ii. For GnRH analog stimulation test, it is suggested that a peak stimulated LH level greater than approximately 4.0 to 6.0 IU/L after GnRH analog administration is indicative of CPP. In contrast, children who are prepubertal will have minimal increase from baseline.
        iii. Due to variable assay and sensitivity limits, precise cutoffs of basal and GnRH analog stimulated LH levels are difficult to establish and results should be interpreted based on specific assay performed.
        iv. A peak stimulated LH:FSH (follicle-stimulating hormone) ratio greater than 0.66 indicates puberty in females. Peak LH:FSH ratio is often used to distinguish progressive CPP (LH:FSH greater than 0.66) from nonprogressive CPP in both males and females.
        v. Measurement of basal or stimulated sex steroids (testosterone and estradiol) can also be helpful in evaluating patient for CPP, although sex steroid levels alone is insufficient to confirm diagnosis of CPP. It is not recommended to utilize random estradiol levels in CPP evaluation since it may be unmeasurable even in advanced puberty stage.
    d. Baseline evaluation should also include height and weight measurements, sex steroid levels, and other diagnostic tests to rule out tumors.
    e. The manufacturer recommends consideration of discontinuation before the age of 11 in females and 12 in males.
5. **Gender Identity Disorder (GID):**

a. GnRH analogs have been shown to be effective in suppressing pubertal hormones.
b. According to the Endocrine Society and World Professional Association for Transgender Health guidelines, adolescents who fulfill eligibility and readiness criteria for gender reassignment should initially undergo treatment to suppress pubertal development. The guideline suggests that clinicians counsel patients regarding options for fertility preservation prior to initiating GnRH treatment.
    i. The suppression of pubertal hormones should begin when girls and boys first exhibit physical changes of puberty (confirmed by pubertal levels of estradiol and testosterone, respectively), but no earlier than Tanner stages 2 to 3.
    ii. Tanner stages, also known as Sexual Maturity Rating (SMR), is a staging system for evaluation of pubertal development in children and adolescents by using description of secondary sexual characteristics which includes pubic hair changes, breast changes in females, and genital changes in males.
c. Off-label dosing for GID, transgender females (male-to-female) according to Endocrine Society guidelines:
    i. Leuprolide acetate (Lupron®, Eligard®) 3.75 mg IM (depot only) or SC once monthly or 11.25 mg IM every three months in combination with other hormonal therapies
    ii. Gosrelin acetate (Zoladex®) 3.8 mg SC every four weeks in combination with estradiol valerate 10 mg IM every 10 days

6. **Endometrial thinning/dysfunctional uterine bleeding:** GnRH agonists, such as Lupron® 3.75 mg IM monthly, can be used for endometrial preparation for hormonal suppression prior to endometrial ablation. Endometrial ablation is a procedure to treat abnormal uterine bleeding and, depending on the ablation technique, it is most effective when performed with relatively thin endometrium which can be achieved with hormonal therapy, including GnRH. Pretreatment should be initiated 30 to 60 days prior to procedure.

REFERENCE/RESOURCES:

1. Relevant package inserts. Accessed on January 3, 2023
2. [Drugs] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.
3. Carel JC, Eugster EA, Rogol A, *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009; 123:e752.

4. Hembree, Wylie C., et al. "Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline." The Journal of Clinical Endocrinology & Metabolism 102.11 (2017): 3869-3903.
5. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. *Cochrane Database Syst Rev*. 2001;(2):CD000547.
6. Klein, Karen, et al. "Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty." *Journal of Pediatric Endocrinology and Metabolism* 29.11 (2016): 1241-1248.
7. Liu H-C, Lai Y-M, Davis O, et al: Improved pregnancy outcome with gonadotropin releasing hormone agonist (GnRH-a) stimulation is due to the improvement in oocyte quantity rather than quality. J Assist Reprod Genet 1992; 9:338-344
8. De la Cruz MSD and Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. *American Family Medicine*. 2017; 95(2):100-107
9. Lethaby A, Puscasiu L, Vollenhoven B. Preoperative medical therapy before surgery for uterine fibroids. *Cochrane Database Syst Rev.* 2017; 11:CD000547. doi: 10.1002/14651858.CD000547.pub2
10. Falcone T, Flyckt R. Clinical Management of Endometriosis. *Obstetrics and Gynecology*. 2018; 131(3):557-571. doi: 10.1097/AOG.0000000000002469
11. Prostate Cancer. NCCN Guideline Version 4.2023. Accessed January 2, 2024
12. Aguirre RS, Eugster EA. Central Precocious Puberty: From genetics to treatment. *Best Practice & Research. Clinical endocrinology & metabolism.* 2018; 32(4):343-354. doi: 10.1016/j.beem.2018.05.008. Epub 2018 May 26
13. Chen M, Eugester EA. Central Precocious Puberty: Update on Diagnosis and Treatment. *Pediatric Drugs.* 2015; 17(4): 273-81.
14. Emmanuel M, Bokor BR. Tanner Stages. [Updated December 18, 2020]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470280/.Accessed January 05, 2023.
15. Siristatidis CS, Gibreel A, Basios G, Maheshwari A, Bhattacharya S. Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction. Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD006919. DOI: 10.1002/14651858.CD006919.pub4.
16. Practice Committee of American Society for Reproductive Medicine. Indications and options for endometrial ablation. *Fertility and Sterility*. 2008 ; 90(5 suppl) : S236-40
17. Coleman E, Radix AE, Bouman WP, et al. Standards of Care for the Health of Transgender and Gender Diverse People (Version 8). International Journal of

Transgender Health. 2022; 23:sup1, S1-S259, DOI: 10.1080/26895269.2022.2100644

18. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Nov 1;102(11):3869-3903. doi: 10.1210/jc.2017-01658. Erratum in: J Clin Endocrinol Metab. 2018 Feb 1;103(2):699. Erratum in: J Clin Endocrinol Metab. 2018 Jul 1;103(7):2758-2759. PMID: 28945902.
19. Lee DM, Chung IH. Morning basal luteinizing hormone, a good screening tool for diagnosing central precocious puberty. *Ann Pediatr Endocrinol Metab*. 2019 Mar;24(1):27-33. doi: 10.6065/apem.2019.24.1.27. Epub 2019 Mar 31. PMID: 30943677; PMCID: PMC6449618.

Table 1. Gonadotropin-Releasing Hormone Agonists

Brand Name	Generic Name	HCPCS Code
Camcevi®	leuprolide mesylate syringe for SC administration	J1952
Eligard®	leuprolide acetate syringe kit for SC administration	J9217
Fensolvi®	leuprolide acetate syringe kit for SC administration	J1951
Lupron Depot® Lupron Depot-Ped®	leuprolide acetate for depot suspension (IM injection)	J1950
Supprelin LA®	histrelin SC implant	J9226
Triptodur®	triptorelin vial for IM injection	J3316
Trelstar®	triptorelin vial for IM injection	J3315
Zoladex®	goserelin SC implant	J9202
IM=intramuscular, SC=subcutaneous		

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM015.1223	**HEMATOLOGICAL AGENTS** **HEMLIBRA ®** (emicizumab-kxwh injectable)
Effective Date: 2/1/2024	**Review/Revised Date**: 01/18, 09/18, 03/19, 11/19, 11/20, 10/21, 11/22, 10/23 (MTW)
Original Effective Date: 04/18	**P&T Committee Meeting Date**: 02/18, 10/18, 04/19, 12/19, 12/20, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:

1. Use is for routine prophylaxis to prevent or reduce the frequency of bleeding episodes

AND

2. Diagnosis of hemophilia A (congenital factor VIII deficiency) and documentation of **ANY** of the following:
    a. Factor VIII inhibitors (defined as at least 5 Bethesda units per milliliter)
    b. Severe hemophilia (defined as pre-treatment factor VIII level less than 1%)
    c. Moderate hemophilia (defined as pre-treatment factor VIII level of 1% to less than 5%) or mild hemophilia (defined as pre-treatment factor VIII level of 5% to less than 40%) with:
        i. One or more spontaneous episodes of bleeding into the central nervous system, large joints (ankles, knees, hips, elbows, shoulders) or other serious, life-threatening bleed

When the above criteria are met, Hemlibra® (emicizumab-kxwh) will be approved for a loading dose of 3 mg/kg once weekly for four weeks, followed by any of the three maintenance dosing regimens below:

- 1.5 mg/kg once weekly
- 3 mg/kg every two weeks
- 6 mg/kg every four weeks

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist.

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Patients with Hemophilia A are prone to bleeding because they have a genetic mutation which causes them to have a factor VIII deficiency. Factor VIII plays a vital role in the clotting cascade for the formation of clots. Emicizumab is a monoclonal antibody that bypasses the need for factor VIII by binding activated factor IX and X (the role normally played by activated VIII in the clotting cascade) to restore function to the coagulation cascade; thereby promoting hemostasis.

FDA APPROVED INDICATION:

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.

POSITION STATEMENT:
Hemophilia is categorized as mild, moderate, or severe. People with mild hemophilia have a factor level greater than 5% but less than 40%. They may have bleeding problems after serious injury, trauma, or surgery and are often not diagnosed until later in life. People with moderate hemophilia have a factor level between 1-5% and may have prolonged bleeding after minor injuries. People with severe hemophilia have a factor level of less than 1% and may experience unprovoked spontaneous bleeds. People with moderate or severe hemophilia are often diagnosed early in life.

National Hemophilia Foundation (NHF) and the Medical and Scientific Advisory Council (MASAC) recommend routine prophylaxis for people with severe hemophilia. This is typically started early in life before the age of 3, and prior to the second joint bleed. Prophylaxis therapy may be considered within the first six months of life to reduce the occurrence of intracranial hemorrhage. It is recommended to individualize prophylaxis by dose and/or frequency, and the goal is to prevent all bleeds at all times. Prophylaxis with plasma-derived or recombinant standard half-life factor, extended half-life factor, or non-factor replacement emicizumab (Hemlibra®) to prevent bleeding is the current standard of care of patients with severe hemophilia to prevent musculoskeletal complications from recurrent joint and muscle bleeds, while allowing patients to lead a physically active lifestyle and achieve the quality of life of an individual without hemophilia. There are no clear guidelines for when to initiate prophylactic therapy in mild-moderate individuals, although prophylactic therapy is often initiated following a spontaneous bleeding episode for mild-moderate hemophilia A.

When using factor replacement, the goal is to keep factor levels greater than 1%. Roughly 30% of patients who are exposed to factor agents develop neutralizing anti-factor VIII antibodies (inhibitors) that render factor replacement ineffective. Patients with a low level of inhibitor (less than five Bethesda units/milliliter) are often given high dose factor agent to overcome the inhibitors. Patients with a high titer of inhibitors (less than or equal to five Bethesda units/milliliter) are offered immune tolerance induction (ITI) or bypassing agents. Bypassing agents circumvent the factor that is blocked by the inhibitor to help the body form a normal clot. Activated prothrombin complex concentrate (aPCC; FEIBA®) and recombinant factor VIIa (NovoSeven®) are commonly used bypassing agents.

ITI therapy requires large amounts on a continual basis over a long period of time (month-years). The intention is to teach the body to accept factor as a normal component of blood and stop the inhibitor from blocking factor in the blood.

All available prophylaxis products can effectively prevent bleeding; however, each can have different patient responses, safety profiles (inhibitor development risks), costs, and product characteristics (half-life, effects on monitoring). The choice of prophylaxis product is made as a team evaluating the patient's specifics circumstances and needs.
A recent weight (within the last six months) is required to ensure the correct dosage and product strength are utilized as emicizumab follows a weight-based dosing regimen.

CODING:

HCPCS Code	Description
J7170	Injection, emicizumab-kxwh, 0.5 mg
C96372	Unclassified drugs or biologicals (when specified as emicizumab)

REFERENCE/RESOURCES:

1. [Hemlibra®] package insert. South San Francisco, CA: Genentech; 2022 June.
2. [Hemlibra®] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed [11/02/2022].
3. [Hemlibra®] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed [11/02/22].
4. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N. Engl J Med 2017; 377:809-818
5. CDC: Hemophilia Inhibitors. Available at: https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html Accessed November 2, 2022.
6. National Hemophilia Foundation. MASAC Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors (Update April 2022). https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/Recommendation-on-the-Use-and-Management-of-Emicizumab-kxwh-Hemlibra-for-Hemophilia-A-with-and-without-Inhibitors (Accessed November 2, 2022)

7. Institute for Clinical and Economic Review (ICER). Roxaparvovec and Emicizumab for Hemophilia A: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, October 16, 2020. Available a t https://icer.org/wp-content/uploads/2020/10/ICER_Hemophilia-A_Final-Report_112020.pdf (Accessed November 2, 2022).
8. Srivastava, A, Santagostino, E, Dougall, A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020: 26(Suppl 6): 1-158.
9. “MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors: NBDF.” MASAC Document 267 - MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors, National Bleeding Disorders Foundation, 27 Apr. 2022.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR043.0623	**CARDIOVASCULAR AGENTS** **HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH) AGENTS** **Evkeeza®** (evinacumab-dgnb vial)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 05/22, 04/23 (JCN) P&T Committee Meeting Date: 06/21, 06/22, 06/23 Original Effective Date: 08/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, all of the following must be met:

1. Diagnosis of Homozygous Familial Hypercholesterolemia (HoFH) as evidenced by either genetic or clinical confirmation, as outlined below:
    a. Genetic confirmation: biallelic functional mutations in the low density lipoprotein receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin/kexin type 9 (PCSK9) or LDL receptor adapter protein 1 (LDLRAP1) genes
    b. Clinical confirmation defined as untreated total cholesterol greater than 500 mg/dL or treated LDL-C greater than or equal to 300 mg/dL and one of the following:
        i. Presence of xanthomas before the age of 10 years, or
        ii. Evidence of heterozygous familial hypercholesterolemia in both parents (such as documented history of elevated LDL-C greater than or equal to 190 mg/dL prior to lipid-lowering therapy)
2. Current use of all of the following therapies:

   a. High-intensity statin therapy, defined as atorvastatin 80 mg daily or rosuvastatin 40 mg daily, unless contraindicated or documented statin intolerance
   b. Ezetimibe, unless contraindicated or prior intolerance
   c. PCSK-9 inhibitor (such as evolocumab), unless contraindicated or prior intolerance
3. Documentation of LDL cholesterol levels (taken within the last six months) greater than 100 mg/dL despite at least six months of use of the therapies outlined above

Initial reauthorization requires documentation of at least a 30% reduction in LDL cholesterol levels from pre-treatment levels

EXCLUSION CRITERIA:

1. Concomitant use of evinacumab-dgnb and lometapide (Juxtapid®)
2. Current pregnancy
3. Diagnosis of Heterozygous familial hypercholesterolemia or other hyperlipidemia disorders

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a cardiologist, endocrinologist, or board certified lipidologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes

---

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Evinacumab-dgnb is a monoclonal antibody that binds to and inhibits angiopoietin-like protein 3 (ANGPTL3). Inhibition of ANGPTL3 leads to reductions in LDL-C, HDL-C, and triglycerides (TG). Evinacumab-dgnb reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Evinacumab-dgnb blockade of ANGPTL3 lowers TG and HDL-C by rescuing LPL and EL activities, respectively.

Recommended dose = 15 mg/kg administered by intravenous (IV) infusion every four weeks.

- Administer the diluted solution via IV infusion over 60 minutes through an IV line containing a sterile, in-line or add-on, 0.2 micron to 5 micron filter.
- Do not mix other medications with evinacumab or administer other medications concomitantly via the same infusion line.

FDA APPROVED INDICATIONS:
Adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged five years and older, with homozygous familial hypercholesterolemia (HoFH).

Limitations of Use:

- The safety and effectiveness have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- The effects on cardiovascular morbidity and mortality have not been determined.

POSITION STATEMENT:
Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder affecting approximately 1 in every 300,000 to 400,000 people.6 This genetic disorder results from a gene mutation that effects the catabolism of low density lipoproteins (LDL) and therefore elevates the LDL levels in the blood. The most common mutation that causes HoFH is a loss of function mutation in the low-density lipoprotein receptor (LDLR) gene. Other possible mutations are in the apolipoprotein B (apo B) gene (APOB3500), LDL receptor adapter protein 1 (LDLRAP1) and the proprotein covertase subtilisin kexin 9 (PCSK9) gene – this is a gain of function mutation[6,7].

HoFH is characterized by premature cardiovascular disease due to persistently high levels of LDL cholesterol (LDL-C). Therefore, early diagnosis and treatment is crucial to delay cardiovascular disease in these patients[6,8].

Diagnosis of HoFH can be made through genetic testing or clinical criteria such as baseline LDL levels, physical manifestatins and family history. The European Atherosclerosis Society (EAS)[6] criteria for HoFH is defined as one of the following: 1) genetic confirmation of two mutant alleles of the LDLR, Apo(b), PCSK9, or LDLR adaptor protein 1 gene locus; or 2) an untreated LDL-C >500 mg/dL or treated LDL-C ≥300 mg/dL together with either cutaneous or tendon xanthoma before 10 years of age or untreated elevated LDL-C levels consistent with HeFH in both parents. They also indicate lower LDL-C levels do not exclude HoFH. A scientific statement from the American Heart Association (AHA) has proposed a slightly different definition provided in the table below[8].

Homozygous Familial hypercholesteromia Diagnostic Category from AHA 2015 Scientific Statement

Clinical Criteria	With Genetic Testing Performed
LDL-C ≥400 mg/dL and one or both parents having clinically diagnosed FH, positive genetic testing for a known LDL-C–raising (LDLR, Apo[b], PCSK9) gene defect, or autosomal-recessive FH	Presence of two identical (HoFH) or nonidentical (compound HeFH) abnormal LDL-C–raising gene defects, including the rare autosomal-recessive type
If LDL-C >560 mg/dL or LDL-C >400 mg/dL with aortic valve disease or xanthomata at <20 years of age	Occasionally, HoFH will have LDL-C <400 mg/dL

American Heart Association/American College of Cardiology Guidelines (2018)
For patients with primary severe hypercholesterolemia (LDL-C ≥190 mg/dL) initiation of a high intensity statin is recommended. If a high intensity statin is not tolerated then the maximally tolerated statin therapy is recommended. If LDL-C remains ≥100 mg/dL or there is <50% reduction in LDL-C on maximally tolerated statin therapy, the addition of ezetimibe is recommended. If LDL-C remains ≥100 mg/dL consider the addition of a PCSK9 inhibitor. Bile acid sequestrates may be considered in patients who are not eligible for PCSK9 inhibitor.

Clinical evidence for evinacumab
Raal FJ et al. (ELIPSE HoFH Trial) (PubMed ID # 32813947*)*

- Randomized, Double-Blind, Placebo-Controlled

- Study Duration: 24 weeks
    - Patients receiving placebo during the initial 24 week study period were eligible to enroll in 24 week open label study
- Patient population: Patients (N=65)
    - Key inclusion criteria: Patients with homozygous familial hypercholesterolemia, ≥12 years old, patients were required to be receiving stable lipid-lowering therapy at the maximally tolerated dose, LDL-C ≥70 mg/dL. If undergoing LDL apheresis – must have initiated at least three months prior to screening and on a stable schedule or stable settings for at least eight weeks.
        - HoFH diagnosis was based on either genetic or clinical criteria results
            - Genetic diagnosis: a documented variant in two LDLR alleles or the presence of homozygous or compound heterozygous variants in apolipoprotein B (APOB) or PCSK9. Patients who had compound heterozygosity or homozygosity for variants in the gene encoding LDL receptor adaptor protein 1 (LDLRAP1) were also eligible.
            - Clinical diagnosis: untreated total cholesterol level of more than 500 mg per deciliter (12.9 mmol per liter), with either the presence of cutaneous or tendinous xanthomas before the age of 10 years or documentation of an untreated total cholesterol level of more than 250 mg per deciliter (6.5 mmol per liter) in both parents.
    - Key exclusion criteria: Use of nutraceuticals or over-the-counter therapies known to affect lipids without stable doses for at least four weeks prior to screening, newly diagnosed diabetes (within three months prior to randomization visit) or poorly controlled diabetes (HbA1c > 9%), significant cardiac history within three months of screening, pregnant or breastfeeding women, sexually active women not willing to practice highly effective birth control during study period and follow-up.
- Intervention: 2:1 randomization to either evinacumab 15 mg/kg IV every four weeks plus other lipid-lowering therapies or to the placebo group of lipid-lowering therapies alone
- Primary endpoint: Percent change from baseline in the LDL-C level at week 24
- Secondary endpoint: Percentage of participants with ≥30% reduction in calculated low-density lipoprotein cholesterol (LDL-C) at week 24
- Results:

- Baseline Characteristics: 60% of participants were between 18-44 years old, mean age 41.7±15.5, 74% of participants were white
  - Diagnosis: 68% via genotyping, 32% via clinical diagnosis
  - Cholesterol (mg/dL)
    - Calculated LDL: 255.1±165.2
    - Total cholesterol: 322.3±163.1
  - Adjunct therapies in the evinacumab group:
    - By individual therapy: 93.8% on a statin, 75.4% on ezetimibe, 76.9% on PCSK9 inhibitor, 21.5% on lomitapide, 33.8% undergoing apheresis
    - Combination therapies:
      - Ezetimibe + PCSK9 inhibitor + statin: 44.1% of participants
      - Ezetimibe + lomitapide + PCSK9 inhibitor + statin: 10.8% of participants
      - At least three lipid-lowering therapies: 63.1% of participants
- Efficacy:
  - Primary endpoint: At week 24, patients in the evinacumab group had a 47.1% reduction from baseline in the LDL-C level, as compared with a 1.9% increase in the placebo group, for a between-group least-squares mean difference of -49.0 percentage points (95% confidence interval [CI], -65.0 to -33.1; P<0.001)
  - Secondary endpoint: at week 24, 83.7% of patients in the evinacumab group had a ≥30% reduction in calculated LDL cholesterol, as compared with 18.2% in the placebo group.
- Safety:
  - Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and in 81% of those in the placebo group. No patients discontinued treatment due to an adverse event.
  - Serious adverse events during the treatment period occurred in two patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt. Both patients recovered.
  - No cardiovascular events were reported in either group during the double-blind treatment period.
  - An influenza-like illness was reported in five of 44 patients (11%) in the evinacumab group and in no patients in the placebo group.

        - An increase in the level of either alanine or aspartate aminotransferase was reported in two of 44 patients (5%) in the evinacumab group and in two of 21 patients (10%) in the placebo group, increases that were less than three times and five times the upper limit of the normal range, respectively.
- GRADE evidence rating: Low
    - Strengths:
        - A majority of patients were stable on baseline lipid lowering therapies, including ~54% of patients on at least triple therapy
        - Study was multi-site and multi-country, used an intention to treat analysis, included patient's undergoing apheresis
        - Baseline characteristics were well matched between groups
    - Limitations:
        - Study has small patient population, was too short in duration to assess clinical outcomes and was placebo-controlled (for initial 24 weeks)
        - Baseline patient population was mostly white and only included two patients under the age of 18 years

REFERENCE/RESOURCES:

1. Evkeeza™ (evinacumab-dgnb) injection for intravenous use [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; March 2023.
2. Evinacumab-dgnb. IBM Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Accessed April 2, 2021
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143.
4. Raal FJ, Rosenson RS, Reeskamp LF, et al. ELIPSE HoFH Investigators. Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020;383(8):711-720.
5. Rosenson RS, Burgess LJ, Ebenbichler CF, Evinacumab in Patients with Refractory Hypercholesterolemia. N Engl J Med. 2020;383(24):2307-2319.
6. Raal FJ, Hovingh GK Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018;277:483-492.Cuchel M, Bruckert E, Ginsberg HN, *et al*; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous

familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J*. 2014 Aug 21;35(32):2146-57.

7. Sturm AC, Knowles JW, Gidding SS, *et al*; Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2018 Aug 7;72(6):662-680.
8. Gidding SS, Champagne MA, de Ferranti SD, *et al*.; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation* 2015;132:2167-92.

Brand Name	Generic Name	HCPCS Code
Evkeeza® Vial	evinacumab-dgnb	J1305

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND071.0623	**ENDOCRINE & METABOLIC DRUGS** **HORMONE REPLACEMENT THERAPY** See Table 1 for Medications
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/15, 03/16, 07/16, 03/17, 3/18, 05/18, 07/18, 01/19, 02/19, 03/19, 02/20, 03/21, 07/21, 03/22, 03/23, 05/23 (JLS) P&T Committee Meeting Date: 02/15, 08/15, 04/16, 08/16, 04/17, 04/18, 06/18, 07/18, 02/19, 02/19 , 04/19, 04/20, 04/21, 08/21, 04/22, 04/23, 06/23 Original Effective Date: 09/15 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page:1 of 9

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B – criteria based on Local Coverage Determination - L36569

POLICY CRITERA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of testosterone replacement therapy (new starts), must meet all the following criteria
    a. One of the following confirmed diagnoses:
        i. Diagnosis of gender dysphoria or gender identity disorder OR
        ii. Diagnosis of clinical hypogonadism, defined as meeting the following (1-3):
            1) At least two separate serum testosterone levels taken on two different days in the morning (when testosterone secretion is highest), and / or two morning levels of “free” or bioavailable testosterone) indicating low testosterone levels
            2) Elevated luteinizing hormone (LH) or follicle-stimulating hormone (FSH) levels.
            3) Presence of low testosterone associated symptoms (such as decreased energy, sleep disturbances, anemia, hot flushes, etc)

   b. Documented trial and failure (defined as inability to reach therapeutic levels or fluctuations in levels resulting in symptoms) of both of the following:
      i. Generic formulary topical testosterone (such as generic topical testosterone 1% or generic topical testosterone 1.62% pump); and
      ii. Generic injectable testosterone cypionate.
2. For patients established on the requested testosterone replacement therapy (within the previous year): Documentation of positive response to therapy and ongoing monitoring of hormone levels
3. For estrogen replacement therapy: The use of a subcutaneous pellet formations of estrogen is considered investigational for all indications.

EXCLUSION CRITERIA:

- Use for improvement of sexual signs and symptoms (such as decreased libido, sexual dysfunction)
- Use in patients with breast cancer or untreated prostate cancer

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMIT:
Testopel® is limited to a maximum of six pellets per insertion
Medicare may only cover the number of pellets actually implanted in the patient (maximum of six pellets); wastage is not covered. Use of additional pellets may be paid on appeal if the documentation supports medical necessity as determined by the FDA approved drug label and the service complies with all Medicare requirements as indicated above.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

PHARMACY PRIOR AUTHORIZATION AND SPEP THERAPY POLICY AND CRITERIA ORPTCEND071	ENDOCRINE & METABOLIC DRUGS HORMONE REPLACEMENT THERAPY See Table 1 for Medications

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Each testosterone replacement therapy (TRT) product is approved for use in adult males for conditions associated with a deficiency or absence of endogenous testosterone, commonly referred to as hypogonadism. The condition is further classified into primary hypogonadism, failure of the testicles to produce testosterone, and secondary (hypogonadotropic) hypogonadism, central defects in the hypothalamus or pituitary gland, both leading to low testosterone levels. In primary hypogonadism, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are generally at normal or elevated levels; where as in secondary hypogonadisms levels are decreased. There are various administration routes available for TRT, including transdermal patch, topical gels, buccal formulations, implantable pellets and intramuscular injections (short & long acting) of which all have been proven effective in increasing testosterone levels.

Note: All TRT products are Drug Enforcement Administration (DEA) Controlled Substance Class III

FDA APPROVED INDICATIONS:
Replacement therapy in congenital or acquired conditions associated with a deficiency or absence of endogenous testosterone, such as:

- Primary hypogonadism: testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals.
- Secondary (hypogonadotropic) hypogonadism: idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation.

POSITION STATEMENT:
Testosterone Replacement Therapy (TRT)

- There is no evidence demonstrating any one TRT product is safer or more effective than other therapeutic alternatives. All products were proven effective based on pharmacokinetic data.
- Total serum testosterone level must be measured to confirm diagnosis of hypogonadism.
- According to the 2018 Endocrine Society Guidelines: For {total serum testosterone} laboratories that are not CDC certified and do not participate in an accuracy-based quality control program, the reference range may vary

considerably depending on the assay and reference population used. Using the lower limit of the range established in local laboratories may not accurately identify men with hypogonadism.

- A harmonized reference range for free testosterone (FT) has not been established, so reference ranges may vary considerably depending on the specific equilibrium dialysis method or the algorithm used to calculate FT. Therefore, until a harmonized reference range is established, the lower limits established by the laboratory may be used.
- Testosterone exhibit diurnal variation levels, with peak levels in the morning and varying levels throughout the day. A confirmed diagnosis of hypogonadism must be measured by morning serum testosterone levels before 10 AM.
- Normal ranges for testosterone vary among laboratories and assays. The Endocrine Society and Center for Disease Control recommends a lower limit of normal testosterone of 264ng/dL for total serum testosterone. The American Urological Association recommends a lower limit of normal total serum testosterone of less than 300ng/dL.
- TRT is contraindicated in men with known or suspected prostate or breast cancer.
- In 2015, the FDA concluded that there is a possible increased cardiovascular risk associated with testosterone use. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not. Labeling changes were required to outline this potential risk.
- The FDA requires manufacturer labeling to reflect the appropriate use of TRT, specifically as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism.
- In 2018, both the Endocrine Society and American Urological Association concluded that the evidence is inconclusive with regards to TRT and concerns for increased cardiovascular risk in hypogonadal men.

Estrogen replacement therapy (ERT)

- Used by biological females typically for the treatment of symptoms of menopause
- Also used for gender-affirming care in biological males
- ERT is available in several different formulations, including estradiol tablets, transdermal patches, injectable, and vaginal applications.
- There are no FDA approved estrogen formulations for pellet insertion; these products are often compounded

REFERENCE/RESOURCES:

1. Relevant package inserts
2. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. Available at http://www.fda.gov/drugs/drugsafety/ucm436259.htm (Accessed March 10, 2023)
3. The International Society for the Study of the Aging Male (ISSAM). Recommendations on the diagnosis, treatment and monitoring of hypogonadism in men. *Aging Male*. 2015;18(1):5–15.
4. Morales A, Bebb RA, Manjoo P et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. *CMAJ*. 2015;187(18):1369-1377.
5. Shalender Bhasin, Juan P Brito, et al, Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline, *The Journal of Clinical Endocrinology & Metabolism*, Volume 103, Issue 5, May 2018, Pages 1715–1744, https://doi.org/10.1210/jc.2018-00229
6. Travison TG, Vesper HW, Orwoll E, Wu F, Kaufman JM, Wang Y, et al. Harmonized Reference Ranges for Circulating Testosterone Levels in Men of Four Cohort Studies in the United States and Europe. J Clin Endocrinol Metab. 2017;102(4):1161-73.
7. American Urological Association. Guidelines on Evaluation and Management of Testosterone Deficiency. Available at https://www.auanet.org/guidelines/testosterone-deficiency-guideline (Accessed March 10, 2023).
8. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination (LCD): Treatment of Males with Low Testosterone (L36539). Available at https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36569&ver=18&keyword=testosterone&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1 (Accessed March 10, 2023).
9. Centers for Medicare & Medicaid Services (CMS). Billing and Coding: Testopel Coverage (A55057). Available at https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=55057&ver=8&keyword=testosterone&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1 (Accessed March 10, 2023).

Table 1: Medications covered by this policy

Brand Name	Benefit
Aveed® testosterone vial	Medical
Testopel® pellet	Medical
Compounded estradioland/or testosterone for use in pellet implantation	Medical

Appendix A: Available testosterone replacement therapies

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
Androgel®				
1%	5 g (4 pumps) applied topically once daily	10 g (8 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered pumps per package)	Applied to right and left upper arms /shoulders and/or right/left abdomen
1.62%	Initial: 40.5 mg (2 pumps) applied topically once daily	81 mg (4 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered pumps per package)	
Androderm® 2 mg/day & 4 mg/day	Apply topically once daily	1 patch per application	• 2 mg: 60 patches • 4 mg: 30 patches	Applied to the back, abdomen, upper arms, or thighs
Aveed®	3 mL by deep gluteal injection every 10 weeks	Same dose as standard	• 750/3 mL solution	Gluteal muscle
Axiron®	Initial: 60 mg (1 pump actuation to each axilla) applied topically once daily	120 mg (2 pumps actuations to each axilla)	• 110 mL (60 metered pumps per package)	Applied to the axilla only.
Fortesta®	40 mg (4 pumps) applied topically once daily	70 mg (7 pumps)	• 60 g canister (120 metered pumps per package)	Applied to front and inner thighs only.
Vogelxo®	50 mg (1 tube or packet or 4 pumps) once daily	100 mg (2 tubes or packets or 8 pumps)	• # 30 – 5 g tubes or packets • 2 x 75 g pumps (120 metered	Applied to the shoulders and/or upper arms only.

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
			pumps per package)	
Testim®	5 g (1 tube) applied topically once daily	10 g (2 tubes)	• #30 – 5 g tubes	Applied to the shoulders and/or upper arms only.
Striant®	1 buccal system tablet (30 mg) applied to gum region twice daily. At 12-hour dosing intervals.	60 mg (2 buccal system tablets)	• 6 blister packs • 10 buccal systems per blister pack	Applied to the gum region only.
Jatenzo®	237 mg orally twice daily	396 mg twice daily	• Capsules are available in three strengths of 158 mg, 198 mg, and 237 mg. Capsules are packaged as 120 units per bottle.	Oral
Kyzatrex®	Recommended starting dose og 200 mg twice daily. Minimum recommended dose is 100 mg once daily.	400 mg twice daily	100 mg, 150 mg, and 200 mg capsules	Oral
Natesto™	1 actuation per nostril (5.5.mg per actuation) INTRANASALLY 3 times a day 6 to 8 hours apart for total daily dose of 33 mg	33 mg/ day – no dose adjustments are recommended. If testosterone levels remain below 300 ng/dL, treatment should be discontinued	Metered dose pump, containing 60 actuations (10 day supply)	Nasal
Xyosted®	Initial: 75mg (1 autoinjector) subcut once weekly, titrate to trough concentration between 350 ng/dL and 650 ng/dL		Autoinjector (carton containing 4 autoinjectors) available as 50mg/0.5ml; 75/0.5ml; or 100mg/0.5ml injectors	Administer subcutaneously in the abdominal region
Testopel®	The number of pellets to be implanted depends upon the minimal	The suggested dosage for androgens varies depending on the	75 mg testosterone pellets	Implanted subcutaneously in hip area or another fatty area

Testosterone Product	Standard Daily Dose	Max Daily Dose	How supplied (per package)	Site of Administration
	daily requirements of testosterone propionate determined by a gradual reduction of the amount administered parenterally. The usual dosage is as follows: implant two 75mg pellets for each 25mg testosterone propionate required weekly.	age, and diagnosis of the individual patient. 150mg to 450mg subcutaneously every 3 to 6 months		
Compounded testosterone (not FDA approved)	Not determined – not FDA approved	Not determined – not FDA approved	Compounded for implantation	Implanted subcutaneously

Appendix 2. Available ERT products

Route of Administration	FDA-Approved Products
Oral	Estradiol tablets (Estrace®) Menest® (esterified estrogens) tablets Premarin® (conjugated estrogens) tablets
Injectable	Estradiol valerate (Delestrogen®) Estradiol cypionate
Implant insertion	Compounded estradiol for pellet insertion (not FDA approved)
Transdermal	Estradiol gel (Divigel®) Estradiol patch (Dotti®, Climara®, Vivelle-DOT® Estradiol cream (Estrace®)
Vaginal	Estradiol (Vagifem®) vaginal tablet Estradiol acetate (Femring®) vaginal ring Premarin® (conjugated estrogens) cream with applicator
Combination Products	Premphase®/Prempro® (conjugated estrogens/medroxyprogesterone) Esterified estrogens/methyltestosterone tablets

BILLING GUIDELINES AND CODING

Per Coding Policy 22.0 HCPCS S-Codes and H-Codes, S-codes are not accepted as billable codes; testosterone pellet (Testopel®) must be billed with the unclassified code. The CPT code for pellet insertion will only be covered when paired with testosterone product.

Testopel® is limited to a maximum of six pellets per insertion. Medicare may only cover the number of pellets actually implanted in the patient (maximum of six pellets); wastage is not covered. Use of additional pellets may be paid on appeal if the documentation supports medical necessity as determined by the FDA approved drug label and the service complies with all Medicare requirements as indicated above.

CPT/HCPCS	Description
11980	Subcutaneous hormone pellet implantation (implantation of estradiol and/or testosterone pellets beneath the skin)
J1071	Injection, testosterone cypionate, 1 mg
J3121	Injection, testosterone enanthate, 1 mg
J3145	Injection, testosterone undecanoate, 1 mg
J3490	Unclassified drugs
J7999	Compounded drug, not otherwise classified
Not to be used for billing	
S0189	Testosterone pellet, 75 mg

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES016.0823	**RESPIRATORY AGENTS** **IL-5 INHIBITORS** See Appendix A for medications covered by policy
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 05/16, 06/16, 05/17, 01/18, 05/18, 09/18, 11/18, 05/19, 07/19, 12/19, 01/20, 4/20, 10/20, 04/21, 07/21, 12/21, 05/22, 04/23, 08/23 (snm) P&T Committee Meeting Date: 05/16, 08/16, 06/17, 02/18, 06/18, 09/18, 12/18, 06/19, 08/19, 12/19, 02/20, 06/20, 12/20, 06/21, 08/21, 12/21b 06/22, 06/23, 08/23 Original Effective Date: 06/16 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 12

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet indication-specific criteria below:
    a. **For eosinophilic asthma:**
        i. Confirmed diagnosis by **one** of the following:
            1) A blood eosinophil count of at least 150 cells/microliter while on high-dose inhaled corticosteroids or daily oral corticosteroids
            2) Fraction of exhaled nitric oxide (FeNO) of at least 20 parts per billion while on high-dose inhaled corticosteroids or daily oral corticosteroids
            3) The patient has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids
            4) History of eosinophilic asthma if currently on daily maintenance treatment with oral glucocorticoids
        ii. In the past three months, patient is adherent to treatment with maximally tolerated doses of both of the following, unless patient

has an intolerance or contraindication to all therapies (This may be verified by pharmacy claims information):
1) Inhaled corticosteroid
2) One of the following:
    a) A long-acting inhaled beta 2-agonist (LABA)
    b) A leukotriene receptor antagonist (LTRA)
    c) A long-acting muscarinic antagonist (LAMA)

iii. Inadequate asthma control despite above therapy, defined as **one** of the following:
1) Asthma Control Test (ACT) score less than 20 or Asthma Control Questionnaire (ACQ) score greater than or equal to 1.5
2) At least two asthma exacerbations requiring oral systemic corticosteroids in the last 12 months
3) At least one asthma exacerbation requiring hospitalization, emergency room or urgent care visit in the last 12 months
4) Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
5) Baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

b. **For Eosinophilic Granulomatosis with Polyangiitis (EGPA),** mepolizumab (Nucala®) may be covered if all the following criteria are met**:**
i. Confirmed diagnosis of EGPA defined as one of the following:
1) The patient meets four of the following:
    a) Asthma (history of wheezing or diffuse high-pitched rales on expiration)
    b) Eosinophilia (greater than 10% eosinophils on white blood cell differential count)
    c) Mononeuropathy (including multiplex), multiple mononeuropathies, or polyneuropathy attributed to a systemic vasculitis
    d) Migratory or transient pulmonary infiltrates detected radiographically
    e) Paranasal sinus abnormality
    f) Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas
2) The patient meets ALL of the following:
    a) Medical history of asthma
    b) Peak peripheral blood eosinophilia greater than 1500 cells/microliter

c) Systemic vasculitis involving two or more extra-pulmonary organs

ii. Relapsing or refractory disease defined as one of the following:
1) History of relapse requiring an increase in glucocorticoid dose, initiation or increase in other immunosuppressive therapy, or hospitalization in the previous two years while receiving at least 7.5 mg/day prednisone (or equivalent)
2) Failure to achieve remission following a standard induction regimen administered for at least three months OR recurrence of symptoms of EGPA while tapering glucocorticoids. Standard treatment regimens include: prednisone [or equivalent] dosed at least 7.5 mg/day in combination with an immunosuppressant such as cyclophosphamide, azathioprine, methotrexate, or mycophenolate mofetil

c. For Hypereosinophilic Syndrome (HES), mepolizumab (Nucala®) may be covered if the following criteria are met:
i. Primary HES without an identifiable non-hematologic secondary cause such as parasitic infections, solid tumors, or T cell lymphoma
ii. Blood eosinophil count of at least 1,000 cells/microliter for at least six months prior to initiation of therapy
iii. Use of conventional HES therapy including one of the following in the past 12 months prior to initiation of therapy:
1) Chronic or episodic oral corticosteroids
2) Immunosuppressive therapy
3) Cytotoxic therapy
iv. History of at least two HES flares within the past 12 months prior to initiation of therapy (defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy)

d. **For Chronic Rhinosinusitis with Nasal Polyp (CRSwNP)**, mepolizumab (Nucala®) may be covered if the following criteria are met:
i. Evidence of nasal polyposis by direct examination, endoscopy, or sinus CT scan
ii. Inadequate response to a three-month trial of intranasal corticosteroids (such as fluticasone) or intolerance or contraindication to ALL intranasal corticosteroids
iii. Patient will continue standard maintenance therapy (such as nasal saline irrigation, intranasal corticosteroids) in combination with mepolizumab

2. For patients established on the requested therapy within the previous year: Response to therapy indicating improvement or stabilization of condition

EXCLUSION CRITERIA:
Concurrent use with anti-IL5 (such as mepolizumab, reslizumab, benralizumab), anti-IgE (such as omalizumab), anti-TSLP (such as tezepelumab), or anti-IL4 (such as dupilumab) monoclonal antibodies

AGE RESTRICTIONS:
For all indications, the patient's age must be within FDA labeling for the requested indication

PRESCRIBER RESTRICTIONS:
- For eosinophilic asthma: must be prescribed by or in consultation with an asthma specialist (such as a pulmonologist, immunologist, or allergist)
- For Eosinophilic Granulomatosis with Polyangiitis: must be prescribed by or in consultation with a pulmonologist, neurologist, or rheumatologist
- For hypereosinophilic syndrome (HES): must be prescribed by or in consultation with hematologist, immunologist, pulmonologist, cardiologist, or neurologist.
- For chronic rhinosinusitis with nasal polyposis: must be prescribed by, or in consultation with, an otolaryngologist, allergist, pulmonologist

COVERAGE DURATION:
Eosinophilic Asthma: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

EGPA, HES, CRSwNP: Initial authorization will be for one year. Reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES016	RESPIRATORY AGENTS IL-5 INHIBITORS See Appendix A for medications covered by policy

INTRODUCTION:
Mepolizumab (Nucala®), reslizumab (Cinqair®) and benralizumab (Fasenra®) are injectable medications given in patients with severe asthma with eosinophilic phenotype as add on therapy to patients that are not controlled with other conventional therapies. Mepolizumab (Nucala®) is also indicated for treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), patients aged 12 years and older with hypereosinophilic syndrome (HES), and adult patients with chronic rhinosinusitis with nasal polyps.

Mepolizumab is an interleukin-5 (IL-5) antagonist monoclonal antibody that reduces the production and survival of eosinophils by blocking the binding of IL-5 to the alpha chain of the receptor complex on the eosinophil cell surface. Mepolizumab is given via subcutaneous injection at a dose of 100 mg once every four weeks for asthma, 300 mg every four weeks for EGPA, and HES . Mepolizumab injection is intended for use under the guidance of a healthcare provider. A patient may self-inject or the patient caregiver may administer mepolizumab injection subcutaneously after the healthcare provider determines it is appropriate.

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα). Dosing for benralizumab is 30 mg administered once every four weeks for the first three doses, and then once every eight weeks thereafter by subcutaneous injection.

Reslizumab is an interleukin-5 (IL-5) antagonist (IgG4, kappa) that blocks the binding of IL-5 to the surface of eosinophils, thus reducing the production and survival of the eosinophil. Reslizumab is given via intravenous over 20-50 minutes at a dose of 3 mg/kg every four weeks.

FDA APPROVED INDICATIONS:
Mepolizumab (Nucala®)
- Add-on maintenance treatment of patients with severe asthma aged six years and older, and with an eosinophilic phenotype
- Add-on maintenance treatment of adult patients 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP) with inadequate response to nasal corticosteroids
- Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)

- The treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for at least six months without an identifiable non-hematologic secondary cause

Limitation of Use:

- Not indicated for the relief of acute bronchospasm or status asthmaticus

Reslizumab (Cinqair®)

- Add-on maintenance treatment of patients with severe asthma aged 18 years and older, and with an eosinophilic phenotype

Limitation of Use:

- Not indicated for treatment of other eosinophilic conditions
- Not indicated for the relief of acute bronchospasm or status asthmaticus

Benralizumab (Fasenra®)

- Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype

Limitation of Use:

- Not indicated for treatment of other eosinophilic conditions
- Not indicated for the relief of acute bronchospasm or status asthmaticus

Both benralizumab (Fasenra®) and mepolizumab (Nucala®) have formulations approved for self-administration.

POSITION STATEMENT:

Asthma

The Global Initiative for Asthma (GINA) guidelines are evidence-based international guidelines that are updated annually. The current guidelines include add-on biologic Type 2 inflammation targeted therapies if available and affordable in patients with exacerbations or poor symptom control despite the use of high dose inhaled corticosteroid (ICS) and long-acting beta agonist (LABA), and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroid (OCS). [21]

Type 2 inflammation is found in approximately 50% of people with severe asthma and is characterized by cytokines, such as interleukin (IL)-4, IL-5, and IL-13, and eosinophilia or increased fractional exhaled nitric oxide (FeNO), and may be accompanied by atopy. Meanwhile, non-Type 2 inflammation is often characterized by increased neutrophils. Type 2 inflammation in patients with mild to moderate asthma improves rapidly with regular use of ICS. However, patients with severe asthma may experience refractory Type 2 inflammatory symptoms with high-dose ICS. It may respond to OCS but serious adverse effects may limit use. Refractory

Type 2 inflammation should be considered in patients who are taking high-dose ICS or daily OCS if any of the following are found:

- Blood eosinophils are 150 cells/microliter or greater
- FeNO 20 ppb or greater
- Sputum eosinophils 2% or greater
- Asthma is clinically allergen-driven

The FDA approval of mepolizumab (Nucala®) for eosinophilic asthma was based on three double-blind, randomized, placebo-controlled studies in patients with severe asthma. The approval trials provide evidence that mepolizumab may reduce the number of annual asthma exacerbations in patients with severe asthma with an eosinophilic phenotype, as well as reduce the daily dose of oral corticosteroids in patients that require daily oral steroids for maintenance therapy. All trials required patients to have a history of 2 or more exacerbations of their asthma in the previous year despite regular use of high-dose inhaled corticosteroids plus an additional controller with or without oral corticosteroids. Additionally, in the MENSA and SIRIUS trials patients had to have blood eosinophils of greater than or equal to 150 cell/microliter at screening or greater than or equal to 300 cell/microliter within 12 months of enrollment. The blood eosinophil levels were derived from exploratory analysis of data from the DREAM trial which suggested that baseline blood eosinophil count of 150 cells/microliter or greater was a potential predictor of treatment benefit. The specific inclusion criteria of these trials limit the populations that may potentially benefit from mepolizumab.[7-9]

The FDA approval of reslizumab (Cinqair®) was based on four double-blind, randomized, placebo-controlled trials in patients with severe asthma on currently available therapies. The studies included patients' ≥ 12 years of age with moderate to severe asthma; three of the four studies (all except Study 4) also required patients to have blood eosinophil levels ≥ 400 cell/mcL despite medium to high dose inhaled corticosteroid (ICS) therapy. The approval trials provide moderate quality of evidence that supports the efficacy of reslizumab in reducing the number of patients experiencing at least one asthma exacerbation in adults (≥18 years) with severe eosinophilic asthma (defined in the trials as a peripheral blood count ≥400 cells/mcL) compared to placebo. There is also moderate evidence that reslizumab is associated with a clinically meaningful improvement in quality life, measured by more patients achieving a 0.5-point reduction in the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire in the trials. Reslizumab did not show a significant reduction in the rate of exacerbation that required hospitalizations or emergency department visits compared with placebo. In the study which did not select patients based on baseline eosinophil levels, there was not a statistically significant increase in FEV_1 values with reslizumab vs. placebo. However, in a

subgroup of patients with baseline eosinophil levels ≥ 400 cell/mcL, the improvement in FEV_1 with reslizumab was significantly greater than with placebo. Reslizumab was studies in patients 12 to 18 years of age, however in the trials the asthma exacerbation rate was higher in adolescent patients treated with reslizumab compared to placebo. [13 -15]

The FDA approval of benralizumab (Fasenra®) was based on three trials including the SIROCCO and CALIMA trials. The SIROCCO and CALIMA studies provide moderate level of evidence that benralizumab as add on- maintenance treatment is more effective than placebo for patients with moderate to severe persistent asthma in patients with high blood eosinophil levels. The BISE study that looked at benralizumab in patients with mild to moderate persistent asthma did not reach the minimum clinically important difference in its primary endpoint. Therefore, the results of this trial supports guidelines that biologicals for treatment of asthma are most appropriate for patients with moderate to severe disease as add on for patients that have failed to respond to standard of care medication.[17-20]

There have been no direct comparisons among these three anti-IL-5 therapies for the treatment of eosinophilic asthma. Therefore, without direct comparison it is unknown if one agent is more effective than the others. In addition, the safety and efficacy of anti-asthma monoclonal antibodies (such as mepolizumab, reslizumab, benralizumab, dupilumab, and omalizumab) given in combination have not been established.

Numerical asthma control tools for assessment of asthma symptom control:[21]

- Asthma Control Test (ACT): Scores range from 5 to 24 (higher is better controlled symptoms). Scores of 20 to 25 is classified as well-controlled asthma; 16 to 19 as not well-controlled, and 5 to 15 as very poorly controlled asthma. The ACT includes a patient self-assessed level of asthma control, frequency of shortness of breath, use of rescue medications, and the effect on daily function due to asthma. The minimum clinically important difference is 3 points
- Asthma Control Questionnaire (ACQ): Scores range from 0 to 6 (higher score is worse control). A score of 0.0 to 0.75 is classified as well-controlled asthma; 0.75 to 1.5 is a “gray zone,” and 1.5 or greater as poorly controlled asthma. ACQ score is calculated as the average of 5 to 7 items that includes five symptom questions. ACQ-7 includes a score for pre-bronchodilator FEV1, in addition to questions on symptoms and use of rescue medications. The minimum clinically important difference is 0.5 points.

Eosinophilic Granulomatosis with Polyangiitis

The approval of mepolizumab for eosinophilic granulomatosis with polyangiitis (EGPA) was based on a placebo-controlled, multicenter, 52-week trial. In this trial mepolizumab led to significantly more accrued weeks of remission (Birmingham Vasculitis Activity Score 0 and prednisone less than or equal to 4mg/day), than placebo (odds ratio [OR] 5.91; 95% CI 2.68-13.03) and a higher percentage of participants in remission at weeks 36 and 48 (OR 16.74; 95% CI 3.61-77.56). Patients had to have a diagnosis of relapsing or refractory eosinophilic granulomatosis with polyangiitis at least six months previously, and had been taking a stable dose of prednisolone or prednisone with a majority of patients having previously taken immunosuppressive agents.[16]

Hypereosinophilic Syndrome

The approval of mepolizumab for hypereosinophilic syndrome (HES) was based on a randomized, double-blind, placebo-controlled, multicenter 32-week study. The incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with NUCALA (50% reduction) (OR 0.28, 95% CI 0.12-0.64, p-value 0.002). Treatment with mepolizumab resulted in a statistically significant 66% reduction in the annualized rate of HES flares compared with placebo. Patients had to have a diagnosis of primary HES for at least six months and been on stable HES therapy for four weeks prior to randomization (including chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy).[25]

Chronic Rhinosinusitis with Nasal Polyps

The approval of mepolizumab for chronic rhinosinusitis with nasal polyps (CRSwNP) was based on a randomized, double-blind, placebo-controlled, multicenter 52 week trial. The study included patients receiving background nasal corticosteroid for at least eight weeks with recurrent and symptomatic CRSwNP, and had at least one surgery for removal of nasal polyps within the previous 10 years. At the end of the 52 week treatment period, patients treated with mepolizumab had a statistically significant improvement in bilateral NPS (mean difference vs placebo, -0.93 [95% CI, -1.31, -0.55]) and nasal obstruction VAS score (mean difference vs placebo, -1.86 [95% CI, -2.53,-1.19]). In addition, the proportion of patients who had surgery was significantly reduced by 57% in patients treated with mepolizumab vs placebo, HR = 0.43 (95% CI 0.25,0.76).[26]

REFERENCE/RESOURCES:

1. Mepolizumab (Nucala®) [package insert]. Philadelphia, PA Glaxo SmithKline LLC; 2023 Mar.

2. Cinqair® [package insert]. West Chester, PA: Teva Respiratory, LLC; 2020 Jun.
3. Fasenra® [package insert]. Wilmington, EL: AstraZeneca Pharmaceuticals, LP; 2021 Feb.
4. Mepolizumab (Nucala®) In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 21, 2023.
5. Cinqair® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 21, 2023.
6. Fasenra® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 21, 2023.
7. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012 Aug 18; 380(9842):651-9.
8. Oldhoff, JM, Darsow, U, Werfel, T, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. Allergy. 2005 May;60(5):693-6.
9. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014 Sep 25; 371(13):1198-207.
10. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med. 2014 Sep 25; 371(13):1189-97.
11. Flood-Page, P, Swenson, C, Faiferman, I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. American journal of respiratory and critical care medicine. 2007 Dec 1; 176(11):1062-71.
12. [Asthma in Adults and Adolescence] In: DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. Updated January 19 2016. Accessed [3/8/2016].
13. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015; 3(5):355-366. doi:10.1016/S2213-2600(15)00042-9.
14. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M, Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels: a Randomized Phase 3 Study, CHEST (2016), doi: 10.1016/j.chest.2016.03.032.

15. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M, Phase 3 Study of Reslizumab in Patients with Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts, CHEST (2016), doi: 10.1016/j.chest.2016.03.018.
16. Wechsler M, Akuthota P. Jayne D et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017; 376:1921-1932.
17. Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of Fasenra for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo controlled phase 3 trial. Lancet. 2016;388:2115-2127.
18. Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo controlled phase 3 trial. Lancet. 2016;388:2128-2141
19. Ferguson GT, FitzGerald JM, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial Lacet Respir Med. 2017; 5:568-76.
20. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med. 2017 Sep 8. [Epub ahead of print].
21. Global Initiative for Asthma. Global initiative for asthma management and prevention (2023 update). Available at: http://www.ginasthma.org. Accessed on May 9, 2023.
22. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 2020; 146:1217.
23. Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. J Allergy Clin Immunol. 2023;151(2):386-398. doi:10.1016/j.jaci.2022.10.026
24. Orlandi, RR, Kingdom, TT, Smith, TL, et al. International consensus statement on rhinology and allergy: rhinosinusitis. Int Forum Allergy Rhinol. 2021; 11: 213– 739. https://doi.org/10.1002/alr.22741
25. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized,

placebo-controlled trial. J Allergy Clin Immunol. 2020 Dec;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037. Epub 2020 Sep 18. PMID: 32956756; PMCID: PMC9579892.

26. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2021 Oct;9(10):1141-1153. doi: 10.1016/S2213-2600(21)00097-7. Epub 2021 Apr 16. PMID: 33872587.

APPENDIX A

Brand Name	Generic Name	HCPCS Code
Cinqair® Vial	reslizumab	J2786
Fasenra® Syringe	benralizumab	J0517
Nucala® Vial	mepolizumab	J2182
Nucala® Auto Injct / Syringe	mepolizumab	J2182

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO019.0623	**BIOLOGICAL** **IMMUNE GAMMA GLOBULIN (IgG)** See Table 2 for Specific Products
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: P&T Committee Meeting Date: 06/23 Original Effective Date: 08/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 15

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit. Off-label uses may be approved according to the clinical criteria outlined in the below policy.

REQUIRED MEDICAL INFORMATION:
Initial Authorization for ALL indications:
1. The medical diagnosis is an FDA approved indication or is listed as a covered medical condition below and any indication specific criteria in the policy is met **AND**
2. Requested dosage, frequency and length of therapy are supported by FDA-approved labeling, accepted compendia and/ or evidence-based practice guidelines (See Table 1). If request is for a non-standard dose, frequency or length, medical rational should be provided and exceptions will be considered on a case by cases basis. *Dosing is subject to audit.*

Re-Authorization for ALL indications:
1. Documentation of response to therapy and any indication specific re-authorization criteria listed below is met

Indication-Specific Requirements:

Primary immune deficiency disorders such as agammaglobulinemia, hypogammaglobulinemia (common variable immunodeficiency), Hyper-IgM (X-linked or autosomal recessive hypogammaglobulinemia), Wiskott-Aldrich syndrome

1. The patient has one of the following:
    a. The patient has a total IgG less than 200 mg/dL at baseline prior to immune globulin therapy
    b. The patient has abnormal Bruton tyrosine kinase (BTK) gene or absence of BTK protein
    c. The patient has an absence of B lymphocytes
    d. The patient meets all of the following:
        i. One of the following:
            1) The patient has selective IgG subclass deficiency [Defined as deficiency of one or more IgG subclasses (e.g., IgG1, IgG2, IgG3, or IgG4) more than two standard deviations (SD) below age-specific mean, assessed on two separate occasions during infection free period
            2) The patient has specific antibody deficiency (SAD) with normal levels of both immunoglobulin and total IgG subclasses
            3) The patient has hypogammaglobulinemia (defined as total IgG less than 700 mg/dL OR more than two SDs below mean for the patient's age at baseline prior to immune globulin therapy)
        ii. The patient has a lack of response or inability to mount an adequate response to protein and/or polysaccharide antigens (such as inability to make IgG antibody against either diphtheria and tetanus toxoids, or pneumococcal polysaccharide vaccine, or both)
        iii. The patient has evidence of recurrent, persistent, severe, difficult-to-treat infections (such as recurring otitis media, bronchiectasis, recurrent infections requiring IV antibiotics)

Reauthorization:

1. Documentation that treatment has been effective in reducing the number or severity of clinical infections

Prevention of infections in patients with B-cell chronic lymphocytic leukemia (CLL):

1. Documented pre-treatment endogenous IgG less than 700 mg/dL OR more than two standard deviations below mean for the patient's age

OR

2. History of recurrent, severe bacterial infections requiring antibiotics and/or hospitalization

Kawasaki Disease:

1. Documentation that use is for acute treatment given in conjunction with aspirin and within 10 days of the onset of symptoms

Idiopathic or Immune Thrombocytopenic Purpura (ITP):

(Platelet counts expressed per microliter and should be obtained within the past 30 days)

For children with ITP:

1. Documentation of one of the following:
    a. Platelet count less than 20,000 and significant mucous membrane bleeding
    b. Platelet count less than 10,000 and minor purpura
    c. Rapid increase in platelets required due to planned surgery, dental extractions, or other procedures likely to cause blood loss

Pregnant Women with ITP:

1. Documentation of one of the following:
    a. Platelet count is less than 100,000
    b. Past history of splenectomy
    c. Past history of delivered infant with autoimmune thrombocytopenia

Adult Patients with ITP:

1. Documentation of one of the following:
    a. Platelet count of less than 30,000
    b. Platelet count less than 50,000 with acute bleeding or high-risk of bleeding
    c. To defer or avoid splenectomy
    d. Rapid increase in platelets required due to planned surgery, dental extractions, or other procedures likely to cause blood loss (platelet count goal is generally greater than 50,000)
2. Documentation that IGG product will be used in combination with corticosteroid therapy or corticosteroid therapy is contraindicated

Dermatomyositis and polymyositis:

1. Documented trial, failure, intolerance or contraindication to systemic corticosteroids (such as prednisone or methylprednisolone)

AND

2. Documented trial, failure, intolerance or contraindication to immunosuppressant therapy (e.g., methotrexate, azathioprine, cyclosporine, 6-mercaptopurine, chlorambucil, cyclophosphamide)
   AND
3. Documentation of severe symptoms/disability despite previous therapy with above agents

Reauthorization: Documented response to therapy

Chronic inflammatory demyelinating polyneuropathy (CIDP):

1. Documentation of severe disability
   AND
2. One of the following:
   a. Documented trial, failure, intolerance or contraindication to systemic corticosteroids (such as prednisone or methylprednisolone)
   b. Documentation of pure motor CIDP

Autoimmune Hemolytic Anemia:

1. Documented trial, failure, intolerance or contraindication to systemic corticosteroids (such as prednisone or methylprednisolone)
   AND
2. Documented trial, failure, intolerance or contraindication to another conventional therapy for autoimmune hemolytic anemia (e.g., splenectomy, cyclophosphamide, azathioprine, cyclosporine)

Guillain-Barre Syndrome:

1. Documentation that symptom onset is within two weeks or symptoms are severe (such as being unable to ambulate independently)
   AND
2. Documented trial, failure, intolerance or contraindication to plasma exchange

Multifocal motor neuropathy:

1. Confirmed diagnosis: motor involvement of at least two nerves (for more than one month) without symptoms of sensory abnormalities
   AND
2. Documentation of severe disease/disability

Multiple Sclerosis:

1. Documentation of relapsing/remitting disease

AND

2. Documented trial, failure, intolerance or contraindication to at least two conventional therapies (such as glatiramer, interferon beta, dimethyl fumarate)

Myasthenia Gravis:

Myasthenic exacerbation:

1. Evidence of myasthenic exacerbation, defined by at least one of the following symptoms in the last month:
    a. Difficulty swallowing
    b. Acute respiratory failure
    c. Major functional disability responsible for the discontinuation of physical activity

Refractory disease:

1. Documentation that patient has severely impaired function due to myasthenia gravis

AND

2. Documented trial, failure, intolerance or contraindication to at least two of the following conventional therapies:
    a. Acetylcholinesterase inhibitors (such as pyridostigmine)
    b. Corticosteroids (such as prednisone, methylprednisolone)
    c. Immunosuppressive agents (such as azathioprine, cyclosporine, mycophenolate)
    d. Plasma exchange

Allogenic Bone Marrow Transplantation or Hematopoietic Stem Cell Transplant (HSCT) Recipients:

1. Documentation of one of the following:
    a. Therapy is requested for use within 100 days after transplantation (transplantation date must be documented)

    OR

    b. Documentation that patient has an IgG less than 400 mg/dL with a history of recurrent infections

Autoimmune mucocutaneous blistering disease: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane (cicatricial) pemphigoid, epidermolysis bullosa acquisita, pemphigoid gestationis, linear IgA bullous dermatosis

1. Documentation of biopsy proven disease

AND

2. One of the following:
   a. Documented trial, failure or contraindication to systemic corticosteroids with concurrent immunosuppressive treatment (such as azathioprine, cyclophosphamide, mycophenolate mofetil). **OR**
   b. Patient has rapidly progressive disease in whom a clinical response could not be affected quickly enough using conventional agents. In such situations documentation that IgG therapy will be given with conventional treatment(s) and only used until the conventional therapy can take effect is required.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS):

1. Clinical documentation must be provided detailing patient's primary symptom complex along with baseline clinical testing(s) using validated instrument(s)

AND

2. A clinically appropriate trial of two or more less-intensive treatments was either not effective, not tolerated, or did not result in sustained improvement in symptoms, as measured by a lack of clinically meaningful improvement on a validated instrument directed at the patient's primary symptom complex. For example, treatments may include appropriate limited course of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, selective serotonin reuptake inhibitors (SSRIs), behavioral therapy, or short-course antibiotic therapy). These trials may be done concurrently.

Reauthorization in PANDAS/PANS:

1. Documentation that a reevaluation at three months post treatment have been performed by an appropriate specialist

AND

2. Documentation of objective clinically meaningful improvement posttreatment as defined by an improvement in the clinical testing with a validated instrument

Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD)

1. Documentation of severe residual deficits following an initial attack, to prevent further disability (for example, to preserve vision in patients with residual monocular blindless after an initial attack)

OR

2. As maintenance treatment for patients who have experienced at least one relapse following an initial attack

Reauthorization for MOGAD: Documented positive response to therapy as demonstrated by recovery of function from previous attack or reduction in frequency or severity of attacks.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an appropriate specialist (such as a neurologist for multiple sclerosis; immunologist, hematologist or infections disease expert for primary immunodeficiency; neurologist, psychiatrist, or rheumatologist for PANDAS/PANS)

COVERAGE DURATION:
Generally, initial authorization is up to six months subject to criteria and reauthorization is up to one year subject to criteria. See Table 1 for indication specific coverage duration

TABLE 1

Indication	Coverage Duration	Recommended Dose for Adult Patients*
Primary or secondary Immunodeficiency	Initial authorization: up to six months Reauthorization: up to one year	Initial dosing: 400-600 mg/kg IV every three to four weeks or equivalent scIG weekly
ITP	Initial authorization: up to six months Reauthorization: up to one year	For acute ITP: Up to 1,000 mg/kg/day IV for one to two days. For chronic ITP: 2000 mg/kg IV per month given over two to five days May be repeated monthly as needed to prevent exacerbation
Kawasaki disease	two weeks (IVIG is typically not effective after 10 days post diagnosis)	400 mg/kg IV for five days or a single dose of 2000 mg/kg IV

Prevention infection in B-cell CLL	Initial authorization: up to six months Reauthorization: up to one year	400 mg/kg IV every three to four weeks
Dermatomyositis and Polymyositis	Initial authorization: up to six months Reauthorization: up one year	Initial: 2,000 mg/kg IV per month given over two to five days. Maintenance dose: Up to 2000 mg/kg IV per month adjusted to maintain clinical response (general 500-1000 mg/kg IV every three to four weeks)
CIPD	Initial authorization: up to six months Reauthorization: up to one year	2000 mg/kg IV per month given over two to five days. Dosing interval may need to be adjusted in patients with severe comorbidities
Guillain-Barre Syndrome	Initial authorization: one month Reauthorization: up to three months	400 mg/kg IV once daily for two to five days. May be repeated in up to three monthly infusions.
Autoimmune Hemolytic Anemia	Initial authorization and reauthorization: one month	1000 mg/kg IV per day for five days May require retreatment
Multifocal motor neuropathy	Initial authorization: up to six months Reauthorization: up to one year	2,400 mg/kg IV per month given over two to five days, may be repeated monthly to prevent exacerbation
Multiple Sclerosis	Initial authorization: up to six months Reauthorization: up to one year	No standard dose has been determined
Myasthenia Gravis	For Myasthenic Crisis: Initial and reauthorization approved for one month	Myasthenic Crisis: Single treatment 2000 mg/kg IV divided over two to five days

	For Refractory disease: Initial authorization: up to six months Reauthorization: up to one year	Refractory disease: 2000 mg/kg IV every three to eight weeks adjusted to maintain clinical response
Allogenic Bone Marrow Transplantation or Hematopoietic Stem Cell Transplant (HSCT) Recipients	Initial authorization: up to 100 days post-transplant	500 mg/kg IV once weekly for the first 90 days post-transplant
Autoimmune mucocutaneous blistering disease	Initial authorization: up to six months Reauthorization: up to one year	2000 mg/kg IV divided over two to five days then monthly
PANDAS/PANS	Initial authorization: up to three months Reauthorization: up to one year	No standard dose has been determined
MOGAD	Initial authorization: up to six months Reauthorization: up to one year	Loading dose of 0.4 g/Kg/day for five consecutive days, followed by treatment every four weeks with a dose of 0.4 g/kg to 2 g/kg

* Dosing may vary between products, please refer to FDA approved label. The following recommendations are not all inclusive. For SCIG products please refer to FDA-label and conversion guidelines. **Dosing for intravenously infused medications may be subject to audit.**

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO019	BIOLOGICAL IMMUNE GAMMA GLOBULIN (IgG) See Table 2 for Specific Products

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Immunoglobulins (IgG) are major effector protein molecules of the immune system. Intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) are purified preparations of IgG derived from pooled human serum. The broad range of antibodies contained in these products have specific action against bacterial and viral antigens. In many circumstances, the specificity of a given Immunoglobulin antibody is unknown. IVIG products have 100% bioavailability, but the rate of degradation is dependent upon the serum IgG level (the higher the serum level, the faster the degradation). SCIG formulations typically have 2/3 the bioavailability of the IVIG products, and therefore may require higher monthly doses to achieve the same response. Product selection will vary depending on the characteristics of the patient and it is generally recommended to stay with the same product unless there is a compelling reason to switch.

Table 2: Immune gamma globulin product availability

HCPCS Code	Product Name	Administration	Indications
J1568	Octagam®	IV	PID, D/P (10% strength)
J1566	Gammagard S/D®	IV	PID, B-cell CLL, ITP, Kawasaki disease (peds)
J1561	Gamunex-C®	IV or SC	PID, ITP, CIDP
J1561	Gammaked®	IV or SC	PID, ITP, CIDP
J1459	Privigen®	IV	PID, ITP, CIDP
J1556	Bivigam®	IV	PID
J1557	Gammaplex®	IV	PID, ITP
J1572	Flebogamma Dif®	IV	PID
J1569	Gammagard Liquid®	IV or SC	PID, MMN
J1559	Hizentra®	SC infusion only (via pump)	PID, CIDP
J1575	HyQvia®	IV or SC	PID

J1460/J1560	Gamastan S-D®	IM injection	Post-exposure to varicella, measles, rubella Hepatitis A prevention
J1555	Cuvitru®	SC infusion only (via pump)	PID
J1558	Xembify® (Immune Globulin-klhw)	SC infusion only (via pump)	PID
J1554	Asceniv® (Immune Globulin-slra)	IV	PID
J1576	Panzyga® (Immune Globulin-ifas)	IV	ITP, CIDP, PID
J1551	Cutaquig® (Immune Globulin-hipp)	SC infusion only (via pump)	PID

PID: primary immunodeficiency; B-cell CLL: prevention of bacterial infections associated with CLL; ITP: immune thrombocytopenic purpura; CIDP: chronic Inflammatory demyelinating polyradiculoneuropathy; MMN: multifocal motor neuropathy; D/P: Dermatomyositis/polymyositis

FDA INDICATIONS:

- Prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with chronic B cell lymphocytic leukemia
- Immune thrombocytopenic purpura (ITP)
- Kawaskai Syndrome
- Primary humoral immunodeficiency diseases **(Medicare Part B always)**. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)
- Hepatitis A prevention
- Post-exposure to varicella, measles and rubella
- Dermatomyositis

POSITION STATEMENT:

- IVIG preparations with low IgA content are used to minimize reactions in patients with hypogammaglobulinemia and concurrent IgA deficiency or when anti-IgA antibodies are present in a recipient.
- Renal dysfunction and acute renal failure have been associated with many of the licensed IVIG products. Sucrose containing IVIG products have had a higher incidence of renal dysfunction when infused at a rate greater than the FDA maximum infusion rate recommendation. Non-sucrose containing IVIG products may be indicated in high-risk patients.
- Dosing adjustments are based on clinical response and IgG levels. Target IgG trough levels maintained above 500 gm/dL has been considered sufficient to prevent most system infections in patients with hypogammaglobulinemia
    - IgG trough levels > 800 mg/dL may have the potential to improve pulmonary outcomes
- In patients with severe hypogammaglobulinemia or agammaglobinemia, IgG levels (trough) should be checked every 3-6 months in growing children and every 6 – 12 months in adults.
- Subcutaneous (SC) administration of immune globulin is considered an alternative to intravenous administration of immune globulin when used for one of the covered indications. In some patients, the SC administration can reduce the occurrence of adverse events.
- There are no randomized, controlled comparative trials that show any differences between the currently available agents. The available products differ in the methods used for preparation and viral inactivation, storage requirement, and dosage form (lyophilized versus liquid) although these differences are not clinically significant. Various pharmaceutical characteristics may alter the potential for adverse effectives in select, specific patient populations, such as sodium content, osmolality, IgA content, sugar content and latex content. Consideration for the patient's age, medical history, and concurrent disease states must be taken when selecting a product.
- Immune globulin therapy is used for many different conditions. For specific indications FDA label, compendia and/ or evidence-based practice guidelines should be consulted.
- The off-label use of IVIG in pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and pediatric acute onset neuropsychiatric syndrome (PANS) is based on expert opinion and low-quality observational studies showing some patients may benefit from therapy. However, due to the severe impact of symptoms associated with PANDAS/PANS on child health, growth and development, and the lack of known effective treatments, coverage of IVIG is recommended by the Health Evidence Review Commission (HERC) when recommended by the patient's primary care provider (PCP) and a

pediatric subspecialist and after less-intensive therapies were not effective, were not tolerated or did not result in sustained improvement in symptoms.[21]

- Please refer to HERC guidance on recommended symptom specific validated instruments for clinical assessment. [21]
- While the efficacy for using IVIG in MOGAD is extremely limited, two retrospective studies have shown a potential for lowering the rate of relapse[22,23]. The National Multiple Sclerosis Society makes recommendations for the use of IVIG in MOGAD[25]. For initial attacks, IVIG is typically used in cases of very severe or refractory cases, after treatment with high-dose corticosteroids. Plasma exchange may also be used. While 40-50% of patients only have one attack with good recovery following, some patients may experience residual deficits following their initial attack or may relapse. For these patients, long-term maintenance treatment may include maintenance IVIG, rituximab, azathioprine, or IL-6 targeting treatments. There is limited data available on the use of any of these therapies in MOGAD, and none have been approved by the FDA for use in this condition.

For Medicare, in addition, see further criteria for determination of Medicare B vs Medicare D coverage determination for a Medicare PA request.

REFERENCE/RESOURCES:

1. Individual product prescribing information accessed May 2022
2. Hays WS, Inc. Intravenous Immunoglobulin for Multiple Sclerosis October 14, 2005
3. HaysWS, Inc. Intravenous Immunoglobulin for Neurological Diseases. February 2, 2006
4. Zulay JP et al. Long-term follow up of multifocal motor neuropathy with conduction block under treatment. *J. Neurol 1997*; 62(4): 391-4.
5. Azulay JP et al. intravenous immunoglobulin treatment in patients with Motor neuron syndromes associated with anti-GM1 antibodies. *Neurology 1994;* 44: 429-32.
6. Conley ME et al. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immuodeficiency) and ESDI (European Society for Immunodeficiencies). *Clin Immunol* 1999; 93: 190-7.
7. Bonilla, FA et al. Practice Parameters for Diagnosis and Management of Primary Immunodeficiencies. *Ann Allergy Asthma Immunol.* 2005 May; 94(5 Supp 1): S1-63.
8. Immune Globulin. DrugPoint Summary. Micromedex. Truven Health Analytics, Inc. Greenwood Village, CO. Available at: http://www.micromedexsolutions.com. Accessed March 12, 2014

9. Orange JS, Hossny EM, Weiler CR et al. Use of intravenous immunoglobulin in human disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006; 117:S525-53.
10. DynaMed [database online]. Ipswich (MA): EBSCO Information Services. http://www.ebscohost.com.liboff.ohsu.edu/DynaMed/. Accessed November 20, 2014.Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010 Jan 14; 115(2):168-86.
11. Immune Globulin. In: AHFS Drug Information STAT!Ref Online Electronic Medical Library. Bethesda, MD: American Society of Health-System Pharmacists. Updated periodically; Accessed January 22, 2105].
12. Patwa HS, Chaudry V, Katzberg H, et al. Evidenced-based guidelines: intravenous immunoglobulin in the treatment of neuromuscular disorders: reports of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2012; 78(13);1009-1015.
13. Perez EE, Orange JS, Bonilla F, et all. Update on the use of immunoglobulin in human disease: a review of evidence. J allergy Clin Immunol, 2017: 139:21-46
14. UpToDate Online. Subcutaneous and intramuscular immune globulin therapy. Accessed 11/2017.
15. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. Arch Dermatol. 2003;139:1051-1059.
16. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis-Executive Summary. Neurology. 2016 Jul 26; 87(4): 419-25.
17. Oaklander AL, Lunn MP, Hughes RA, van Schaik IN, Frost C, Chalk CH. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. Cochrane Database Syst Rev. 2017;1 CD010369.
18. Sriaroon P, Ballow M. Immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am. 2015; 35: 713–730.
19. Mahdi-Rogers M, Brassington R, Gunn AA, van Doorn PA, Hughes RA. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev. 2017;5 CD003280.
20. Hacohen Y, Banwell B. Treatment Approaches for MOG-Ab-Associated Demyelination in Children. Current Treatment Options in Neurology. January

2019. 21(1):2. DOI: 10.1007/s11940-019-0541-x. Accessed on October 7, 2021.

21. Health Evidence Review Commission (HERC). Coverage Guidance: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS). Approved 5/19/2022. Available at: https://www.oregon.gov/oha/HPA/DSI-HERC/EvidenceBasedReports/PANDAS-PANS_Coverage-Guidance_FINALapproved_5-19-2022.pdf (Accessed September 20, 2022)
22. Chen JJ, Flanagan EP, Bhatti MT, et al. Steroid-sparing maintenance immunotherapy for MOG-IgG associated disorder. Neurology. (2020) 95:e111–e20. doi: 10.1212/WNL.0000000000009758
23. Chen JJ, Huda S, Hacohen Y, et al. Association of maintenance intravenous immunoglobulin with prevention of relapse in adult myelin oligodendrocyte glycoprotein antibody-associated disease. JAMA Neurol. (2022). doi: 10.1001/jamaneurol.2022.0489
24. Sechi E, Cacciaguerra L, Chen JJ, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD): A Review of Clinical and MRI Features, Diagnosis, and Management. Frontiers in Neurology. June 2022; 13. https://doi.org/10.3389/fneur.2022.885218
25. "Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOGAD)." National Multiple Sclerosis Society, Aug 2022. Accessed May 7, 2022. Available at: https://www.nationalmssociety.org/What-is-MS/Related-Conditions/MOGAD#:~:text=Treatment%20for%20MOGAD,-There%20are%20several&text=Intravenous%20(infusion%20through%20the%20vein,liquid%20part%20of%20the%20blood
26. *Billing and Coding: Immune Globulin Intravenous (IVIg) A57194*. CMS.gov Centers for Medicare & Medicaid Services. Retrieved May 10, 2023, from https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=57194
27. *Intravenous Immune Globulin for the Treatment of Autoimmune Mucocutaneous Blistering Diseases.* CMS.gov Centers for Medicare & Medicaid Services. Retrieved May 10, 2023, from https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?NCDId=158
28. *Billing and Coding: Intravenous Immune Globulin (IVIg)-NCD 250.3 A54643.* CMS.gov Centers for Medicare & Medicaid Services. Retrieved May 10, 2023, from https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=54643&ver=9&=

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCONC102B.1223	**ANTINEOPLASTIC AGENTS** **INJECTABLE ANTI-CANCER MEDICATIONS** See Appendix A for Medications covered by policy
Effective Date: 3/1/2024	**Review/Revised Date**: 04/16, 07/16, 12/16, 01/17, 08/17,12/17, 04/18, 12/18, 01/19, 08/19, 01/20, 01/20, 06/20, 07/20, 09/20, 12/20, 01/21, 03/21, 05/21, 07/21, 08/21, 12/21, 01/22, 05/22, 08/22, 01/23, 06/23, 08/23, 10/23, 11/23 (JLS)
Original Effective Date: 10/16	**P&T Committee Meeting Date**: 04/16, 08/16, 02/16, 02/17, 06/17, 08/17, 10/17, 02/18, 04/18, 12/18, 02/19, 06/19, 08/19, 10/19, 12/19, 02/20, 04/20, 06/20, 08/20, 10/20, 12/20, 02/21, 04/21, 06/21, 08/21, 10/21, 12/21, 02/22, 06/22, 08/22, 10/22, 12/22, 02/23, 06/23, 08/23, 10/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

For bevacizumab given via intravitreal injection: See payment policy 97.0 Compound Drugs Administered in the Physician's Office

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts):
    a. Use must be for a FDA approved indication or indication supported by National Comprehensive Cancer Network guidelines with recommendation 2A or higher
    b. For non-preferred trastuzumab products (see Appendix A): Documented trial and failure, intolerance, or contraindication to the use of both of the preferred products, Ogivri® (trastuzumab-dkst) and Trazimera® (trastuzumab-qyyp)
    c. For non-preferred bevacizumab products (see Appendix A): Documented trial and failure, intolerance, or contraindication to the use of both of the preferred products, Mvasi® (bevacizumab-bvzr) and Zirabev® (bevacizumab-awwb)

2. For patients established on the requested product (within the previous year): documentation of adequate response to the medication must be provided.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with an oncologist

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Medications used in the treatment of cancer pose a risk for serious side effects; their efficacy is indeterminate outside of indications for which clinical trial evidence available. Additionally, many medications to treat cancer are high in cost. Prior authorization review of oncology medication allows for an assessment of safety and efficacy data for medication(s) requested for a member.

FDA APPROVED INDICATIONS:
Refer to Micromedex® for FDA approved indications of individual medications.

POSITION STATEMENT:

Use of oncology medications outside of the FDA approved indication may be supported by clinical trial data. National Comprehensive Cancer Network (NCCN) provides evidence-based Clinical Practice Guidelines in Oncology (NCCN Guidelines®) steered by consensus from a panel of subspecialists. FDA labeled and non-FDA approved indications are included. Guidelines are reviewed annually and updated as new data becomes available. The NCCN Drugs & Biologics Compendium (NCCN Compendium®), based directly on NCCN Guidelines®, lists indications for each individual medication for which there is a recommendation for use, with the category of recommendation (see description below) included. The NCCN Guidelines® and NCCN Compendium® are intended to aid clinicians and payers in decisions regarding treatment of cancer.

National Comprehensive Cancer Network (NCCN) Categories for Recommendations

	Description of Evidence and Consensus
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

The NCCN Compendium® is one reference utilized in Providence Health Plan's coverage determination process, based on the operational policy: Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

REFERENCE/RESOURCES:

1. About the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). https://www.nccn.org/professionals/physician_gls/default.aspx Accessed January 13, 2022.
2. NCCN. Development and Update of Guidelines. https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines Accessed January 5, 2023.
3. Micromedex: DRUGDEX® System [Internet database]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc.; Updated periodically.

Appendix A

Medication Brand Name	Generic Name	HCPCS Code
Bevacizumab		
Preferred products		
Mvasi®	bevacizumab-awwb	Q5107
Zirabev®	bevacizumab-bvzr	Q5118
Non-preferred products (STEP THERAPY APPLIES)		
Alymsys®	bevacizumab-maly	Q5126
Avastin®	bevacizumab	J9035
Vegzelma	bevacizumab-adcd	Q5129
Trastuzumab		
Preferred products		
Ogivri®	trastuzumab-dkst	Q5114
Trazimera®	trastuzumab-gyyp	Q5116
Non-preferred products (STEP THERAPY APPLIES)		
Herceptin®	trastuzumab	J9355
Herceptin Hylecta®	trastuzumab and hyaluronidase-oysk	J9356
Herzuma®	trastuzumab-pkrb	Q5113
Kanjinti	trastuzumab-anns	Q5117
Ontruzant®	trastuzumab-dttb	Q5112
All other medications covered by policy		
Abraxane®	paclitaxel, albumin bound	J9264
Adcetris®	brentuximab vedotin	J9042
Adstiladrin®	nadofaragene firadenovec-vncg	J9029
Aliqopa®	copanlisib	J9057
Alkeran®	melphalan	J9245
Arranon®	nelarabine	J9261
Arzerra®	ofatumumab	J9302
Asparlas®	calaspargase pegol-mknl	J9118
Azedra®	Iobenguane iodine-131	A9590

Bavencio®	avelumab	J9023
Beleodaq®	belinostat	J9032
Belrapzo®	bendamustine HCl	J9036
Bendamustine HCl	bendamustine HCl	J9058
Bendeka®	bendamustine	J9034
Besponsa®	inotuzumab ozogamicin	J9229
Blenrep®	belantamab mafodotin-blmf	J9037
Blincyto®	blinatumomab	J9039
Columvi®	Glofitamab-gxbm	J9999 C9399
Cosela®	trilaciclib dihydrochloride	J1448
Cyramza®	ramucirumab	J9308
Dacogen®	decitabine	J0893/J0894
Danyelza®	naxitamab-gqgk	J9348
Darzalex™	daratumumab	J9145
Darzalex Faspro®	daratumumab and hyaluronidase-fihj	J9144
Elahere	mirvetuximab soravtansine-gynx	J9063
Elzonris®	tagraxofusp-erzs	J9269
Empliciti®	elotuzumab lyophilized	J9176
Enhertu® (not interchangeable with other trastuzumab products)	fam-trastuzumab deruxtecan-nxki	J9358
Epkinly®	Epcoritamab-bysp	J9999
Erbitux®	cetuximab	J9055
Evomela	melphalan hcl/betadex sulfobutyl ether sodium	J9246
Faslodex®	fulvestrant	J9393/J9394/J9395
Folotyn®	pralatrexate	J9307
Fyarro®	pralatrexate	J9331
Halaven®	eribulin mesylate	J9179
Imfinzi®	durvalumab	J9173

Imjudo®	tremelimumab-actl	J9347
Imlygic®	talimogene laherparepvec for intralesional injection	J9325
Istodax®	romidepsin	J9315
Ixempra®	ixabepilone	J9207
Jelmyto®	Mitomycin pyelocalyceal solution	J9281
Jemperli®	Dostarlimab	J9272
Jevtana®	cabazitaxel	J9043
Kadcyla® (not interchangeable with other trastuzumab products)	ado-trastuzumab emtansine	J9354
Keytruda®	pembrolizumab	J9271
Kimmtrak®	Tebentafusp-tebn	J9274
Kyprolis®	carfilzomib	J9047
Libtayo®	cemiplimab-rwlc	J9119
Lumoxiti®	moxetumomab pasudotox-tdfk	J9313
Lunsumio®	Mosunetuzumab-axgb	J9350
Lutathera®	lutetium lu^{177} dotatate	A9513
Margenza®	margetuximab-cmkb	J9353
Monjuvi®	tafasitamab-cxix	J9349
Mylotarg®	gemtuzumab ozogamicin	J9203
Onivyde®	liposomal irinotecan	J9205
Opdivo®	nivolumab	J9299
Opdualag®	nivolumab/relatilimab-RMBW	J9298
Padcev®	enfortumab vedotin-ejfv	J9177
Pedmark®	Sodium thiosulfate	J0208
Pepaxto®	Melphalan flufenamide	J9247
Perjeta®	pertuzumab	J9306
Phesgo®	pertuzumab, trastuzumab, hyaluronidase-zzxf	J9316

Pluvicto®	Lutetium lu-177 vipivotide tetraxetan	A9607
Polivy®	Polatuzumab vedotin-piiq	J9309
Portrazza®	necitumumab	J9295
Poteligeo®	mogamulizumab-kpkc	J9204
Rylaze®	asparaginase erwinia chrysanthemi (recombinant)-rywn	J9021
Rybrevant®	Amivantamab	J9061
Sarclisa®	isatuximab	J9227
Synribo®	omacetaxine subcutaneous injection	J9262
Tecentriq®	atezolizumab	J9022
Temodar® IV	temozolomide	J9328
Tivdak	Tisotumab vedotin-tftv	J9273
Torisel®	temsirolimus	J9330
Treanda®	bendamustine	J9033
Trodelvy®	sacituzumab govitecan-hziy	J9317
Vectibix®	panitumumab	J9303
Velcade®	bortezomib	J9041, J9046, J9048, J9049
Vidaza®	azacitidine	J9025
Vivimusta®	bendamustine HCl	J9056
Vyxeos®	daunorubicin/cytarabine liposomal	J9153
Xofigo®	radium-223	A9606
Yervoy®	ipilimumab	J9228
Yondelis®	trabectedin	J9352
Zaltrap®	ziv-aflibercept	J9400
Zepzelca®	lurbinectedin	J9223
Zynlonta®	loncastuximab tesirine	J9359
Zynyz®	Retifanlimab-dlwr	J9999

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH037.1223	**MISCELLANEOUS PRODUCTS** **INTERLEUKIN – 1 INHIBITORS** **Ilaris®** (canakinumab injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 02/10, 02/11, 12/11, 04/13, 04/14, 04/15, 06/15, 03/16, 03/17, 05/18, 02/19, 09/19, 08/20, 02/21, 05/21, 07/21, 09/22, 08/23, 12/23 (BS)
Original Effective Date: 10/08	**P&T Committee Meeting Date**: 10/08, 04/09, 02/10, 12/11, 04/13, 04/14, 04/15, 06/15, 04/16, 04/17, 06/18, 04/19, 10/19, 10/20, 02/21, 06/21, 08/21, 10/22, 10/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet the indication-specific criteria outlined below:
    a. Cryopyrin-Associated Periodic Syndrome (CAPS) including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) confirmed by both of the following:
        i. Laboratory evidence of genetic mutation NLRP-3 (Nucleotide-binding domain, leucine rich family (NLR) pyrin domain containing 3) or CIAS1 (Cold-Induced Auto-inflammatory Syndrome-1), **AND**
        ii. Classic symptoms associated with Familial Cold Auto-Inflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS) – recurrent intermittent fever and rash typically associated with natural or artificial cold
    b. Familial Mediterranean Fever (FMF):
        i. Diagnosis confirmed by laboratory evidence of genetic mutation in Mediterranean fever gene, MEFV.
        ii. Documented trial and failure, contraindication or intolerance to colchicine

iii. Classic symptoms associated with FMF (febrile episodes, pain in the abdomen, chest, or arthritis of large joints).

c. Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD):
   i. Laboratory evidence of genetic mutation MVK (mevalonate kinase),
   ii. Classic symptoms associated with HIDs (abdominal pain, lymphadenopathy, aphthous ulcers)

d. Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) confirmed by:
   i. Laboratory evidence of genetic mutation TNFRSF1A (tumor necrosis factor receptor super family)
   ii. Classic symptoms associated with TRAPs (abdominal pain, skin rash, musculoskeletal pain, eye manifestations)

e. Still's Disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease, must meet ONE of the following criteria:
   i. Documentation of trial and failure, intolerance, or contraindication to non-steroidal anti-inflammatory drugs (NSAIDS) OR
   ii. Presence of Macrophage Activation Syndrome

f. Gout flares:
   i. Classic symptoms associated with gout flares (monoarticular inflammation, severe pain, redness, swelling)
   ii. Confirmed diagnosis, defined as one of the following:
      a. Presence of uric acid crystals in inflamed synovial fluid, joint, or tophus
      b. Score greater or equal to 8 on gout clinical diagnostic rule
   iii. Documentation of inadequate response to therapy with all the following on contraindication/intolerance to all therapies:
      a. Colchicine (at least three days)
      b. Nonsteroidal anti-inflammatory drugs (NSAIDs) (at least one week)
      c. Corticosteroid therapy (at least one week)

2. For patients established on therapy (within the previous year): Documentation submitted of improvement of symptoms (such as fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis for CAPS). Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy.

EXCLUSION CRITERIA:
Combination therapy with another therapeutic immunomodulator (TIM) agent

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Canakinumab (Ilaris®) works by blocking the action of the inflammatory protein interleukin-1. Canakinumab is dosed based on body weight and must be administered by a healthcare professional.

FDA APPROVED INDICATIONS:
Canakinumab (Ilaris®):

- Cryopyrin-Associated Periodic Syndromes (CAPS): Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children four years of age and older.
- Periodic Fever Syndromes: Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF) in adults and children two years of age and older.
- Still's Disease: Active Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult Onset Still's Disease (AOSD) in patients aged two years and older.
- Gout flares: where non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and repeated courses of corticosteroids are not appropriate in adults.

POSITION STATEMENT:

Cryopyrin-Associated Periodic Syndromes (CAPS)

CAPS are rare, genetic interleukin-1 associated autoinflammatory disorders that arise from mutations in the NLRP3 gene which encodes cryopyrin protein. CAPS includes the subtypes FCAS, MWS, and NOMID. Although these are three separate diagnoses, they are recognized as being the same disease, differentiated only by the severity of their severity with FCAS being the mildest and NOMID being the most severe phenotype. A combination of genetic analysis and clinical symptoms are recommended by the EULAR/American College of Rheumatology taskforce for the differentiation of CAPS from other similar disorders. Characteristic signs/symptoms of CAPS include urticaria-like rash, cold/stress-triggered episodes, sensorineural hearing loss, chronic aseptic meningitis, and skeletal abnormalities.

Approximately 833 subjects have been treated with canakinumab in blinded and open-label clinical trials in CAPS and other diseases. The first trial included three phases, patients with the MWS phenotype of CAPS. The first phase was an 8-week open label period, 71% of patients had complete clinical response one week after initiation of treatment and 97% by week eight. Complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10mg/l. Phase 2 was a 24 week randomized withdrawal period with canakinumab (n=15) or placebo (m=16). 81% of patients randomized to placebo experienced disease flare. Disease flare was defined as CRP and/or SAA values greater than 30mg/l and either a score of mild or worse PHY or a score of minimal or worse for PHY and SKD. All 15 canakinumab patients had absent or minimal disease activity. The third phase was a 16-week open label period where placebo patients were reintroduced to canakinumab and canakinumab patients were continued. A second study included patients four to 74 years of age with both MWS and FCAS. This was an open label study that showed clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week. CRP and SAA normalized within eight days of treatment in most patients.

Periodic Fever Syndromes (PFS) (includes Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF))

A recent study has provided evidence to support canakinumab for the following Periodic Fever Syndromes: Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF). The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD,

and FMF was demonstrated in a 4-Part study (TRAPS, HIDS/MKD, and FMF Study 1) consisting of three separate, disease cohorts (TRAPS, HIDS/MKD and FMF) which enrolled 185 patients aged greater than 28 days. Patients in each cohort entered a 12-week screening period (Part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (Part 2) where they received either 150 mg canakinumab (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment from the time of the resolution of the index flare.

Goals in FMF are to prevent acute attacks, minimize inflammation in between attacks, and to prevent the development and progression of amyloidosis. Colchicine is recommended as a prophylactic treatment in all patients with FMF. Interleukin-1 inhibitors are the preferred second-line therapy for patients who do not respond or do not tolerate colchicine.

Still's Disease (SD) (includes Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)

SJIA is a unique type of JIA which manifests with fever and rash as well as visceral involvement. Approximately 40% of patients with SJIA present with Macrophage Activation Syndrome (MAS) which may be life-threatening. The American College of Rheumatology (ACR) recommends an interleukin-1 or interleukin-6 inhibitor as initial treatment of SJIA with or without MAS. For patients with SJIA without MAS, non-steroidal anti-inflammatory drugs (NSAIDs) may also be used for initial monotherapy.

Two phase III randomized controlled trials were performed to assess canakinumab in its treatment of SJIA in eligible patients aged 2 to 19 years with SJIA, including those with active systemic features and arthritis. A 29-day single-dose, randomized, double-blind, placebo-controlled study compared canakinumab group (n=43) to a placebo group (n=41). At baseline among 84 patients, a total of 53 (63%) were on methotrexate therapy, 48 (57%) patients had prior use of a biologic agent (i.e. anakinra, tocilzumab, and other biologics), and 59 (70%) patients were on stable prednisone therapy. By day 15 of the study, 36 (84%) of 43 patients from the canakinumab group compared to 4 (10%) of 41 patients in the placebo group achieved an endpoint of a JIA American College of Rheumatology (ACR) 30 response. These responses were sustained until the end of study.

A two-part (open-label and withdrawal phased) study initially treated 177 patients with canakinumab during the open label phase for 12 to 32 weeks. During the withdrawal phase, those who achieved JIA ACR 50 response (n=128) were randomized into either the canakinumab group (n=50) or placebo group (n=50). At baseline, a total of 93 (53%) of patients were on methotrexate therapy, 116 (66%) of patients had prior use of a biologic agent (i.e. anakinra, tocilzumab, and other biologics), and 128 (72%) of patients were on stable prednisone therapy. During the withdrawal phase, 39 (74%) patients form the canakinumab group compared to 24 (25%) patients in the placebo group achieved no flare of disease. By the end of the withdrawal phase, 31 of 50 (62%) patients form the canakinumab group compared to 17 of 50 (34%) patients in the placebo group achieved inactive disease. There was also an average reduction of glucocorticoid dose from 0.34mg to 0.05mg per kilogram per day. Additionally, 42 of 128 (33%) patients were able to discontinue glucocorticoids after tapering.

The efficacy of canakinumab in adults with AOSD is based on the pharmacokinetic exposure and extrapolation of the established efficacy in SJIA patients. Efficacy was also assessed in a randomized, double-blind, placebo-controlled study that enrolled 36 patients (22 to 70 years old) diagnosed with AOSD. The efficacy data were generally consistent with the results of a pooled efficacy analysis of SJIA patients.

Gout Flares

Gout flares is intensely painful and disabling. This condition affects a single joint and usually resolved completely within a few days to several weeks. However, symptoms may improve faster with treatment. The American College of Rheumatology (ACR) currently recommends colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic glucocorticoids as treatment options for gout glares, and should be started as soon as possible after the onset.

The efficacy of canakinumab was demonstrated in three 12-week, randomized, double-blind, active-controlled studies in patients with gout flares for whom NSAIDs and/or colchicine were contraindicated, not tolerated or ineffective, and who had experienced at least three gout flares in the previous year. In Study 1 (NCT01029652), patients were randomized to receive canakinumab 150 mg subcutaneous (N = 115) or triamcinolone acetonide 40 mg intramuscular (N = 115) at baseline and thereafter treated upon a new flare. In Study 2 (NCT01080131), patients were randomized to receive canakinumab 150 mg subcutaneous (N =112) or triamcinolone acetonide 40 mg intramuscular (N =114) at baseline and thereafter treated upon a new flare. In study 3 (NCT01356602), patients were randomized to receive canakinumab 150 mg subcutaneous (N =265) or triamcinolone acetonide 40 mg intramuscular (N =132) at baseline. All three studies' primary endpoints were: 1) patient's assessment of gout flare pain intensity at the most affected joint at 72 hours

post-dose measured on a 0-100 mm visual analogue scale (VAS), 2) the time to first new gout flare. Results were consistent throughout the three studies, pain intensity of the most affected joint (0-100 mm VAS) at 72 hours post-dose was consistently lower for patients treated with canakinumab compared with triamcinolone acetonide in patients unable to use NSAIDs and colchicine. The pain intensity for patients unable to use NSAID and colchicine are presented in the following format, (mean canakinumab vs. mean triamcinolone; difference in 95% confidence interval in pain intensity 72 hours post dose): 21.4 vs. 38.4; -17.0 mm (-32.3, -1.6) [study 1], 24.1 vs. 33.1; -9.1 mm (-18.9, 0.8) [study 2], 20.8 vs. 40.3 19.5 mm (-28.6, -10.3) [study 3].

Canakinumab carries a safety warning for serious infections. Live vaccines should be avoided in patients receiving canakinumab. Other common adverse reactions include nasopharyngitis, diarrhea, influenza, headache, nausea, upper respiratory tract infections, abdominal pain and injection site reactions.

REFERENCE/RESOURCES:

1. Ilaris® (canakinumab) prescribing information. East Hanover, NJ: Novartis Pharmaceuticals, Inc. June 2020.
2. Canakinumab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically
3. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367(25):2396-2406.
4. Kastner DL. Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com. Accessed October 13, 2016
5. Verbsky J. Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases. In: Kliegman RM, St Geme JW, Blum NJ, eds. Nelson Textbook of Pediatrics. Philadelphia: Elsevier; 2002:1292-1304.e1 (Accessed September 10, 2022)
6. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81:907-921.
7. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis,

and Systemic Juvenile Idiopathic Arthritis. *Arthritis Rheum*. 2022;74(4):553-569.

8. Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Annals of the Rheumatic Diseases. 2012;71(11):1839-1848.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP046.1223	**TOPICAL PRODUCTS** **IZERVAY®** (avacincaptad pegol sodium pf vial)
Effective Date: 2/1/2024	**Review/Revised Date**:
Original Effective Date: 02/24	**P&T Committee Meeting Date**: 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 3	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:
1. Documentation of diagnosis of geographic atrophy (GA) confirmed by clinical exam or diagnostic imaging (such as Color Fundus Photography, Fundus Autofluorescence, Near Infrared Reflectance Imaging, Optical Coherence Tomography)
2. Documentation that GA is secondary to age-related macular degeneration (AMD)
3. If active choroidal neovascularization (CNV) present, documentation must be submitted attesting that treatment with the requested medication is medically necessary and appropriate monitoring of CNV will be conducted such as a comprehensive eye exam within three months of starting the requested therapy

EXCLUSION CRITERIA:
- Active ocular or periocular infections in the requested eye being treated.
- History of endophthalmitis, retinal detachments, or increased intraocular pressure in the requested eye being treated.

AGE RESTRICTIONS:
May be approved for patients aged 50 years and older.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP046	TOPICAL PRODUCTS **IZERVAY®** (avacincaptad pegol sodium pf vial)

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an ophthalmologist.

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.
Reauthorization will not be allowed.

QUANTITY LIMIT: 4 mg/30 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Avacincaptad pegol (Izervay®) is a complement C5 inhibitor indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Avacincaptad pegol is the second FDA-approved treatment for geographic GA with an FDA approval for treatment up to 12 months.[1-3]

FDA APPROVED INDICATIONS:
Indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).[1-3]

POSITION STATEMENT:

- GA is an advanced form of AMD affecting more than 5 million people worldwide, including 22% of people over 90 years old. GA is responsible for 10-20% of all incidences of legal blindness caused by AMD. Risk factors for GA include genetic polymorphisms, advanced age (especially over 85 years old), smoking, and presence of early AMD to GA in the fellow eye. Genes that may play a significant role in GA include: Complement Factor H (CFH), Complement Factor B (CFB),

Complement 2 (C2), Complement 3 (C3), and ARMS2. Polymorphisms in six complement genes (CFH, CFI, C2/CFB, C3, C9) account for almost 60% of the AMD genetic risk. Symptoms of GA can include scotomas (large dark or blind spots in the visual field), difficulty recognizing faces, decreased reading speed (measured in words per minute, wpm), impaired dark adaptation, low luminance deficit (LLD), impaired contrast sensitivity, and difficulty driving at night.[5]

- Per expert opinion consultation, GA can occur in both wet and dry AMD.
- Most recent guidelines for GA include Age-Related Macular Degeneration Preferred Practice Pattern guideline, published in 2019, which states that at the time there was no proven therapy to prevent or treat GA.[6]
- The first treatment approved by the FDA for treatment of geographic atrophy (GA) secondary to age-related macular degeneration was Pegcetacoplan-pf vial (Syfovre®), a complement C3 inhibitor.[7]
- Avacincaptad pegol (Izervay®) was approved based off two randomized, multi-center, double-masked, sham-controlled trials (GATHER1 and GATHER2). GATHER1 and GATHER2 demonstrated that avacincaptad pegol reduces the GA growth rate over 12 months in patients with GA due to AMD. However, avacincaptad pegol did not have an impact on best corrected visual acuity (BCVA).[4]
- Patients who completed the second year of GATHER2 will be enrolled in the ongoing open-label extension for an additional 18 months of treatment and safety monitoring for GA secondary to AMD. Therapy duration of avacincaptad pegol (Izervay®) past 12 months will be evaluated once submitted to the FDA after additional research is conducted.[4]

REFERENCE/RESOURCES:

1. Izervay Package insert. Parsippany, NJ. IVERIC bio, Inc. August 9, 2023.
2. Izervay In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed November 2, 2023.
3. Izervay In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed November 2, 2023.
4. Izervay (avacincaptad pegol) vial monograph. Prime Therapeutics. Updated on August 16, 2023.
5. Geographic atrophy. Pathways and targets for geographic atrophy. Geographic Atrophy (accessed 2023 March 13).
6. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration preferred practice pattern. *American Academy of Ophthalmology*. 2019;127(1):1-65.
7. Syfovre® package insert. Waltham, MA: Apellis Pharmaceutical, Inc; 2023 Feb.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND STEP THERAPY CRITERIA ORPTCOTH048.1023	**MISCELLANEOUS PRODUCTS** **KORSUVA®** (difelikefalin acetate vial)
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 09/23 (JN) P&T Committee Meeting Date: 08/22, 10/23 Original Effective Date: 10/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts), all the following must be met:

1. Diagnosis of moderate to severe pruritis associated with chronic kidney disease. Moderate to severe pruritis is defined as a score of 4 or higher on the Worst Itching Intensity numerical scale (WI-NRS) or pruritis that is severe enough to impair quality of life
2. Undergoing hemodialysis for at least three months
3. Prescriber attestation that the following have been optimized:
    a. Dialysis
    b. Laboratory abnormalities such as parathyroid, phosphate, magnesium
    c. Use of topical emollients
4. Documented inadequate response to at least two weeks trial of an oral antihistamine, or intolerance/ contraindication to antihistamine therapy
5. Documented inadequate response to at least two weeks trial of pregabalin or gabapentin, or intolerance/ contraindication to both pregabalin and gabapentin
6. Dose and frequency are in accordance with FDA-approved labeling

For patients established on therapy (within the previous year), all the following must be met:

1. Undergoing hemodialysis
2. Documentation of positive response to therapy, defined as an improvement of at least three points on the WI-NRS from baseline or improvement in quality of life
3. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
Use with peritoneal dialysis

AGE RESTRICTIONS:
May be approved for patients aged eighteen years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a nephrologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:
Difelikefalin acetate (Korsuva™) is an injectable kappa opioid receptor (KOR) agonist for treatment of chronic kidney disease–associated pruritus (CKD-aP), also known as uremic pruritus. Difelikefalin mechanism of action as an antipruritic is thought to be due to pharmacological actions of KOR agonists on peripheral sensory neurons and immune cells.

FDA APPROVED INDICATIONS:
Moderate-to-severe pruritis associated with chronic kidney disease, in adults undergoing hemodialysis

Limitations of Use:
Difelikefalin acetate (Korsuva™) has not been studied in patients on peritoneal dialysis and is not recommended for use in this population.

POSITION STATEMENT:
Around half of patients on hemodialysis are thought to experience pruritus with approximately 20-40% suffering from moderate to severe pruritus[4-7]. CKD-aP is characterized as a generalized and intractable itch that can have a significant impact on quality of life relating to impaired sleep, anxiety, depression, discomfort, and increased risk of infection from skin damage sustained by scratching. Patients with pruritus, undergoing hemodialysis (HD), are reported to have a higher rate of all-cause mortality relative to hemodialysis patients without pruritus. [5-7] Diagnosis of CKD-aP requires elimination of non-uremic causes of pruritus.

There are no formal clinical guidelines available for CKD-aP and no other FDA approved treatment. Initial treatment strategies for patients with CKD-aP should include optimization of dialysis, correction of any laboratory abnormalities (specifically parathyroid, calcium, magnesium and phosphate) and use of topical emollients and/or analgesics.[5,7] Another commonly used therapy is oral antihistamines. Most utilized oral antihistamines include diphenhydramine and hydroxyzine.[4,5,7] If sedation is a limiting use factor, second generation antihistamines may be considered for trial during the day with first generation use overnight. A Cochrane review (2020) found that gabapentin and pregabalin appear to reduce itch in patients with chronic kidney disease.[4] Other agents reviewed were found to either not improve itch, did not work well, or required further study.

Efficacy of Korsuva® was evaluated in two randomized, double blind, placebo-controlled, phase 3 trials (KALM-1 and KALM-2). These trials utilized the Worst Itching Intensity numerical scale (WI-NRS). Scores range from 0 "no itch" to 10 "worst itch imaginable". Scores of 4 or higher are consider indicative of moderate-to-severe pruritus.

- Patient population: Patients (N=848) ≥ 18 years of age with end-stage renal disease receiving HD at least three times weekly for three months with moderate-to-severe pruritus.
    - In KALM-1 mean baseline weekly mean WI-NRS score was 7 on a scale of 0-10

    - In KALM-1 approximately 40% of study participants were on concomitant antipruritic agents with oral antihistamines being the most common
- Intervention: difelikefalin 0.5 mcg/kg (target dry body weight) three times weekly after each dialysis session

These trials demonstrated improvement in itch intensity [>3 point improvement in Worst Itching Intensity numerical scale (WI-NRS) as well as a >4 point improvement (secondary endpoint requested by FDA)] and itch related quality of life in patients undergoing hemodialysis.[5-8]

- Safety:
    - Warnings and Precautions: Central nervous system (CNS) effects such as dizziness, somnolence, mental status chances and gait disturbances. These are more common when initiating therapy and in the elderly.
    - Likely low potential for abuse
    - Has not been studied in peritoneal dialysis

As of April 1, 2022, difelikefalin (J0879) qualifies for the Transitional Drug Add-on Payment Adjustment (TDAPA) for Medicare Part B services. The TDAPA payment applies for two years.

REFERENCE/RESOURCES:

1. Korsuva™ package insert. Stamford, CT: Cara Therapeutics, Inc; Dec 2021.
2. Difelikefalin In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed Sept. 11, 2023
3. Difelikefalin In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-
4. Hercz D, Jiang SH, Webster AC. Interventions for itch in people with advanced chronic kidney disease. *Cochrane Database Syst Rev*. 2020 Dec 7;12(12).
5. Center for Drug Evaluation and Research. Multi-Discipline Review: Summary Review, Office Director, Cross Discipline Team Leader Review, Clinical Review, Non-Clinical Review, Statistical Review, Clinical Pharmacology Review. Application number:214916Orig1s000. Korsuva (difelikefalin). Accessed June 30, 2022.
6. Fishbane S, Jamal A, Munera C, et al. A Phase 3 Trial of Difelikefalin in Hemodialysis Patients with Pruritus. *N Engl J Med*. 2020;382:222-32.
7. IPD Analytics. RxBrief: Nephrology. Treatment Update: Chronic Kidney Disease-Associated Pruritus. Published November 2021.

8. Wooldridge TD, Mccafferty K, Schoemig M, *et al*. Efficacy and Safety of Difelikefalin for Moderate-to-Severe CKD-Associated Pruritus: A Global Phase 3 Study in Hemodialysis Patients (KALM-2). American Society of Nephrology: Hemodialysis and Home Hemodialysis: Research Abstracts. Abstract FR-OR24. October 23, 2020.
9. CMS.gov. MLN Matters. Quarterly Update to the End-Stage Renal Disease Prospective Payment System (ESRD PPS). Available at https://www.cms.gov/files/document/mm12583-quarterly-update-end-stage-renal-disease-prospective-payment-system-esrd-pps.pdf. Accessed August 2, 2022

Appendix A.

Brand Name	Generic Name	Q-Code/J-Code
Korsuva®	difelikefalin acetate	J0879

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCANA024.0823	**ANALGESICS & ANESTHETICS** **KRYSTEXXA®** (pegloticase for injection)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/11, 04/12, 06/13, 10/13, 06/14, 06/15, 05/16, 05/17, 05/18, 05/19, 05/20, 05/21, 05/22, 07/23 (CJD) P&T Committee Meeting Date: 04/11, 04/12, 06/13, 10/13, 06/14, 06/15, 05/16, 05/17 , 05/18, 05/19, 06/20. 06/21, 06/22, 08/23 Original Effective Date: 06/11 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page: 1 of 4

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial therapy, all the following criteria must be met:
1. Diagnosis of chronic gout
2. Documentation of inadequate response, intolerance or contraindication to both of the following at maximum medically appropriate doses:
    a. Xanthine oxidase inhibitor (such as allopurinol)
    b. Uricosuric agent (such as probenecid).

    Note: Inadequate response is defined as inability to achieve uric acid levels of less than 6 mg/dL after at least three months of continuous therapy.
3. Documentation of symptomatic gout, as defined by one or more of the following, despite therapies outlined in criterion 2 above:
    a. At least two gout flares per year
    b. Non-resolving tophi

Reauthorization requires documentation of a decreased uric acid level from baseline

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a rheumatologist.

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for six months.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Krystexxa® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patient's refractory to conventional therapy. Pegloticase mechanism of action is acting as a recombinant uricase to catalyze the oxidation of uric acid and lowering serum uric acid levels

FDA APPROVED INDICATIONS:
Krystexxa® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patient's refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Krystexxa® is not recommended for the treatment of asymptomatic hyperuricemia.

POSITION STATEMENT:
The 2020 American College of Rheumatology (ACR) guideline for the management of gout strongly recommends initiation urate-lowering therapy (ULT) in patients with any of the following:

1. One or more subcutaneous tophi
2. Radiographic damage (any modality) attributable to gout
3. Frequent gout flares (>2/year)

Treatment with allopurinol is strongly recommended as the first-line ULT agent, even in patients with moderate-to-severe chronic kidney disease. Anti-inflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) should be initiated concomitantly with ULT and continued for three to six months. Treatment with ULT is recommended to target a uric acid level of <6 mg/dL and it is recommended to continue treatment with ULTs indefinitely if well tolerated and not burdensome for the patient.

The guidelines recommend strongly against the use of pegloticase as a first-line therapy due to costs and adverse event profile. Additionally, the guideline only recommends switching to pegloticase therapy if the patient continues to have gout flares (at least two per year) or non-resolving tophi despite therapy with xanthine oxidase inhibitors (e.g., allopurinol, febuxostat) and uricosurics (e.g., probenacid)

Krystexxa® was studied in two multicenter, randomized, double-blind, placebo-controlled studies. Patients with chronic, symptomatic gout. This was defined as at least three gout flares in the previous 18 months, at least 1 gout tophus, or gouty arthritis. Patients had serum uric acid levels of at least 8 mg/dL despite therapy with allopurinol. Patients were randomized to receive pegloticase 8 mg every two weeks or every four weeks or placebo in a 2:2:1 ratio. The primary endpoint was the proportion of patients who achieved uric acid levels of less than 6 mg/dL for at least 80% of the time during months three and six. About 40% of patients receiving pegloticase achieved the primary endpoint compared to none in the placebo group. Of note, patients receiving every four week dosing regimens experienced a higher frequency of anaphylaxis and infusion reactions.

Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are contraindicated for use of this therapy due to the risk of hemolysis and methemoglobinemia. Patients at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened prior to treatment.

Krystexxa® has a boxed warning for anaphylaxis and infusion reactions. These reactions can occur with any infusion (including the first infusion) and generally manifests within two hours of administration. There is a Risk Evaluation and

Mitigation Strategy (REMS) program intended to inform healthcare providers about anaphylaxis, infusion reactions, and contraindications of use.

REFERENCE/RESOURCES:

1. Krystexxa® Prescribing Information, Crealta Pharmaceuticals LLC Glendale, WI Feb. 2020.
2. Uloric® Prescribing Information, Takeda Pharmaceuticals America. Deerfield, IL. Feb. 2019.
3. Reinders MK, Jansen TL. New Advances in the treatment of gout: review of pegloticase. Ther Clin Risk Mgt. 2010;6:543-550.
4. Hershfield. Treating gout with pegloticase, a PEGylated urate oxidase, provides insight into the importance of uric acid as an antioxidant in vivo. Proc Natl Acad Sci USA 2010 Aug 10;107(32):14351-14356.
5. American College of Rheumatology. 2020 American College of Rheumatology Guideline for the Management of Gout. Available at https://www.rheumatology.org/Portals/0/Files/Gout-Guideline-Final-2020.pdf (Accessed May 1, 2022).

Brand Name	Generic Name	HCPCS Code
Krystexxa®	pegloticase	J2507

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCCNS062.0823	**CENTRAL NERVOUS SYSTEM DRUGS** **LEMTRADA®** (alemtuzumab for intravenous injection)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/16, 09/16, 06/17, 07/18, 06/19, 02/20, 07/20, 07/21, 06/22, 08/23 (JN) P&T Committee Meeting Date: 04/15, 08/16, 10/16, 08/17, 08/18, 08/19, 02/20, 08/20, 08/21, 08/22, 08/23 Original Effective Date: 06/15 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts) for multiple sclerosis (MS), all the following criteria must be met:

1. Documentation of confirmed diagnosis of relapsing form of multiple sclerosis or active secondary progressive disease. Note: this therapy is not indicated for use in clinically isolated syndrome (CIS).
2. The patient has highly active disease defined as ONE of the following:
    a. Greater than or equal to two relapses in the previous year
    b. The patient has greater than or equal to one gadolinium enhancing lesion on MRI
    c. Presence of significant T2 lesion burden defined as ONE of the following:
        i. Greater than ten (10) T2 lesion burden as documented with MRI
        ii. Significant increase in T2 lesion load compared with a previous MRI
        iii. T2 lesion(s) located in spinal cord or brainstem
3. Inadequate response (after at least six months of continuous therapy) to ocrelizumab (Ocrevus®)

4. One of the following:
    a. Inadequate response (after at least six months of continuous therapy) or intolerance to one (1) of the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, or generic teriflunomide
    b. FDA labeled contraindication to ALL the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, or generic teriflunomide
5. Dose and frequency are in accordance with FDA-approved labeling

For patients established on therapy (within the previous year), the following must be met:
1. Documentation of positive clinical response to therapy
2. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
In combination with other disease modifying therapy indicated for the treatment of multiple sclerosis

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist

COVERAGE DURATION:
Authorization will be approved for one year. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Alemtuzumab (Lemtrada®) is a medication given intravenously for patients with relapsing forms of multiple sclerosis (RRMS) to reduce the number of relapses. It is a CD52-direct cytolytic monoclonal antibody that binds to and kills immune cells which attack myelin in those affected by multiple sclerosis.

Alemtuzumab (Lemtrada®) is given in two treatment courses over a two year period. The first course is 12 mg/day IV on five consecutive days, followed by 12 mg/day IV on three consecutive days, 12 months after first treatment course. Subsequent treatment courses of 12 mg daily for three days may be administered, as needed, at least 12 months after the last treatment course dose.

FDA APPROVED INDICATIONS:
Treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults.

Because of its safety profile, the use should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS

Limitations of use: Lemtrada® is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile

POSITION STATEMENT:
Alemtuzumab was initially approved in 2001 by the FDA under the trade name Campath® for first-line treatment in patients with B-cell chronic lymphocytic leukemia (B-CLL). It was also used in various types of hematological malignancies, transplant rejection, demyelinating disorders and for transplant conditioning.
Efficacy

- The FDA approval of alemtuzumab (Lemtrada®) was based on two active-controlled, randomized, rater-blinded, 2-year studies comparing alemtuzumab to high-dose interferon beta-1a (IFNB/Rebif®) efficacy in patients with RRMS.
- Both studies enrolled patients with confirmed RRMS and active disease (defined as ≥ 2 relapses in the prior 2 years and ≥ 1 relapse in the prior year). One study enrolled patients who were treatment naïve and the other was conducted in patients who relapsed while treated with interferon beta or glatiramer. The co-primary efficacy endpoints in both studies were relapse rate and time to 6-month sustained accumulation of disability (SAD) based on the Expanded Disability Status Scale (EDSS).

CARE-MS 1

- The study enrolled 581 patients who were treatment-naïve to DMT, EDSS score ≤ 3 and MS symptom onset within 5 years.

- The study reports a relapse rate of 39% in IFNB treated patients and 18% in alemtuzumab 12 mg/day treated patients by Year 2 (p<0.0001).
- The percentage of patients experiencing *6-months SAD* at 2 years was 8% of alemtuzumab-treated patients compared with 11% in the IFNB group. However, the difference did not achieve statistical significance (p=0.22).

CARE-MS 2

- The study enrolled 840 patients who had relapsed on prior non-IFNB1a DMT after receiving that therapy for ≥ 6 months, EDSS score ≤ 5 and MS symptom onset within 10 years.
- The study reports a relapse rate of 52% of IFNB treated patients and 26% of alemtuzumab 12 mg/day treated patients by year 2 (p<0.0001).
- The percentage of patients experiencing *6-months SAD* at 2 years was 12.7% in the alemtuzumab group compared with 21.1% in the IFNB group (p=0.0084)

While the study results appear to favor alemtuzumab (Lemtrada®) in RRMS, major limitations in the studies were identified which render the quality of evidence of uncertain validity and/or usefulness. The major limitation to the studies was the lack of user blinding of the study drugs. Although measures were taken to ensure rater-blinding, chance of bias cannot be ruled out favoring the study drug alemtuzumab. Other limitations include reporting bias (e.g., concomitant use of DMTSs was not reported in the literature), lack of intent-to-treat analysis, and protocol amendment after study had begun. Additionally, the current FDA labeling only provides dosing recommendation for the first two treatment courses. There is no recommendation for re-dosing at this time and the durability of the drug beyond 2 years remains to be determined.

Safety

Several Boxed Warnings in the labeling for Lemtrada®:

- Serious, sometimes fatal, autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease
- Serious and life-threatening infusion reactions
- Serious and life-threatening stroke (including ischemic and hemorrhagic stroke) has been reported within 3 days of administration
- Increased risk of malignancies, including thyroid cancer, melanoma, and lymphoproliferative disorders

The clinical safety experience with alemtuzumab (Lemtrada®) in MS included 1,486 patients and >5,400 patient-years of collective follow-up. Common adverse events reported in clinical trials include but are not limited to infusion-associated reactions, frequent infections including herpes viral infections and thyroid gland disorders.

- Patients should be monitored for complete blood count with differential, renal function, and thyroid function at baseline and at periodic intervals for 48 months

following the last treatment course of alemtuzumab to detect early signs of potentially serious adverse effects.

- Due to the potential high risks associated alemtuzumab (Lemtrada®), a Risk Evaluation and Mitigation Strategy (REMS) program is in place to ensure the safe use of Lemtrada®. Key elements include certifications of prescribers, dispensing pharmacies and infusion sites; patient education and limited drug access to authorized patients; and monitoring of patients to identify autoimmune conditions and malignancies.

There are many disease-modifying therapies (DMTs) available for the treatment of MS and its subtypes. DMTs are typically used to reduce relapse rates and prevent new lesions in the CNS. The American Academy of Neurology 2018 Guidelines for the use of DMT recommend that DMT be initiated in patients "with relapsing forms of MS with recent clinical relapses or MRI activity." The guidelines do not prefer specific DMTs other than to say that "clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS." Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 1).

Table 1. DMT Evidence for Lowering Relapse Rate[9]

Very Low	Low	Moderate	Strong
Immunoglobulins	Cyclophosphamide	Azathioprine	Alemtuzumab
Methotrexate	Mycophenolate Mofetil	Interferon beta-1b	Cladribine
Rituximab			Dimethyl Fumarate†
Corticosteroids			Fingolimod†
			Glatiramer Acetate†
			Interferon beta-1a
			Mitoxantrone
			Natalizumab
			Ocrelizumab
			Pegylated Interferon
			Teriflunomide†

† Generic Available

REFERENCE/RESOURCES:

1. Lemtrada™(alemtuzumab) injection prescribing information. Cambridge, MA: Genzyme Corporation. 2023 May.
2. Alemtuzumab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. Coles AJ, Wing M, Smith S, et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. Lancet 1999; 354: 1691–95.
4. Hill-Cawthorne GA, Button T, Tuohy O, et al. Long term lymphocyte reconstitution after alemtuzumab treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry 2012; 83: 298–304.
5. Cohen JA, Coles AJ, Arnold DL. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. 2012 Nov 24;380(9856):1819-28 (CARE-MS 1)
6. Coles AJ, Twyman CL, Arnold DL. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Nov 24;380(9856):1829-39. (CARE-MS 2)
7. Hartung HP, Arnold DL, Cohen AJ, Coles AJ, Fox EJ, et al. Efficacy and safety of alemtuzumab in patients with relapsing-remitting MS who relapsed on prior therapy: four-year follow-up of CARE-MS II study. Joint Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) - European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Meeting Boston, MA.2014
8. Coles AJ, Arnold DL, Cohen AJ, Fox EJ, Giovannoni G, et al. Efficacy and safety of alemtuzumab in treatment-naive patients with relapsing-remitting MS: four-year follow-up of the CARE-MS I study. Joint Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) - European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Meeting Boston, MA.2014
9. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777–788.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP025.0623	**TOPICAL PRODUCTS** **LUXTURNA®** (voretigene neparvovec-RZYL injection)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 02/18, 09/18, 02/19, 10/19, 10/20, 05/21, 05/22, 05/23 (JN) P&T Committee Meeting Date: 04/18, 09/18, 4/19, 12/19, 12/20, 06/21, 06/22, 06/23 Original Effective Date: 06/18 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
All the following must be met:

1. Confirmed biallelic RPE65 gene mutation, and
2. Has not previously had the intended treatment eye treated with gene therapy for retinal dystrophy RPE65 mutations, and
3. Documentation by an ophthalmologist within the previous six months of BOTH of the following:
    a. Presence of sufficient viable retinal cells in the intended treatment eye as evidenced by an area of retina within the posterior pole of more than 100 micrometer thickness shown on optical coherence tomography, and
    b. The member has remaining light perception in the intended treatment eye

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Approved for 12 months of age and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an ophthalmologist from a certified Luxturna® administration site

COVERAGE DURATION:
Authorization is limited to one treatment course per eye per lifetime. Approval duration will be for six months.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Voretigene neparvovec works by delivering a normal copy of the gene encoding RPE65 protein to retina cells of persons with reduced or absent levels of biologically active RPE65.

FDA APPROVED INDICATIONS:
Biallelic RPE65 mutation-associated retinal dystrophy

POSITION STATEMENT:
RPE65-mediated Inherited Retinal Disease (IRD) is a group of rare, blinding conditions caused by genetic mutations. Mutations that affect both copies of the gene RPE65 (biallelic mutations) cause Leber Congenital Amaurosis, type 2 (LCA2), Early Onset Severe Retinal Dystrophy (EOSRD) and Severe Early Childhood-onset Retinal Dystrophy (SECORD), Retinitis Pigmentosa type 20 (RP20), and other

phenotypes. It is estimated that 1000-3000 persons in the US have RPE65 mediated IRDs.

If two different RPE65 pathogenic variants are detected (heterozygous state), confirmatory testing may be required to determine whether the 2 different pathogenic variants are found in different copies or in the same copy of the RPE65 gene (cis vs trans configuration). The presence of two different RPE65 pathogenic variants in separate copies of the RPE65 gene (trans configuration) is considered biallelic. The presence of two different RPE65 pathogenic variants in only 1 copy of the RPE65 gene (cis configuration) is not considered biallelic.

Biallelic mutations in the RPE65 gene produces a defective enzyme needed for regeneration of light reacting proteins in the retina. People living with RPE65-mediated IRD often experience night blindness, due to a decrease in light sensitivity in childhood or early adulthood and nystagmus (involuntary back-and-forth eye movements). As the disease progresses, individuals may experience loss in their peripheral vision, developing tunnel vision, and eventually, they may lose their central vision as well, resulting in total blindness. Vision-dependent activities of daily living and independent navigation also becomes severely limited as the disease progresses. There are currently no therapies available that alter the natural history of this disease.

In an open-label, phase 3, controlled trial, 31 patients were randomized in a 2:1 ratio to receive sub-retinal voretigene neparvovec into both eyes or control, with baseline mobility assessments using the multi-luminance mobility test (MLMT). The MLMT was designed to quantify a patient's ability to navigate around obstacles in varying environmental illuminations. At the end of one year, there was a statistically significant improvement in mean MLMT change scores in the intervention arm compared to the control group. Using both eyes, eleven of the 21 (52%) subjects in the voretigene treatment group had an MLMT score change of two or greater, while one of the ten (10%) subjects in the control group had an MLMT score change of two. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level. An MLMT score change of two or greater is considered a clinically meaningful benefit in functional vision. A median MLMT score change of two was observed for intervention group at Day 30 after drug administration, this effect was sustained over the remaining follow-up visits throughout a two-year period. Patients who had more advanced disease (or vision of 20/800 or worse) did not experience improvement.

Study inclusion criteria required the presence of sufficient viable retinal cells as defined by an area of retina within the posterior pole of greater than 100 µm

thickness shown on optical coherence tomography or greater than 2 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole.

Voretigene neparvovec is not recommended for patients younger than 12 months of age, because the retinal cells are still undergoing cell proliferation during that time.

REFERENCE/RESOURCES:

1. [Luxturna®] package insert. Philadelphia, Pennsylvania. June 2022.
2. [Luxturna] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed May 7, 2023.
3. [Luxturna] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed May 7, 2023.
4. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017 Aug 26,390(10097):849-860.
5. American Association for Pediatric Opthalmology and Strabismus. Leber Congenital Amaurosis. Available at: https://aapos.org/glossary/leber-congenital-amaurosis. Accessed May 2, 2021.
6. American Academy of Opthalmology. Leber Congenital Amaurosis. Available at: http://eyewiki.org/Leber_Congenital_Amaurosis. Accessed May 2, 2021.
7. Johnson S, Buessing M, O'Connel T, Pitluck S, Ciulla TA. Cost-effectiveness of Voretigene Neparvovec-rzyl vs Standard Care for RPE65-Mediated Inherited Retinal Disease. *JAMA Ophthalmol*. 2019, 137(10): 1115-1123.

Brand Name	Generic Name	HCPCS Code
Luxturna®	voretigene neparvovec-RZYL	C9032

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNUT001B.0423	**NUTRITIONAL PRODUCTS MEDICAL NUTRITION**
Effective Date: 6/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/99, 08/0, 09/01, 05/02, 12/03, 12/04, 12/05, 06/07, 10/08, 10/09, 10/10, 12/11, 04/12, 08/12 , 08/13 , 10/13, 08/14, 08/15, 07/16, 07/17, 08/18, 07/19, 07/20, 10/20, 03/21, 03/22, 02/23 (MTW) P&T Committee Meeting Date: 08/00, 08/00, 09/01, 05/02, 08/02, 12/03, 12/04, 12/05, 06/07, 10/08, 10/09, 10/10, 12/11, 04/12, 08/12, 08/13, 08/14, 08/15, 08/16, 08/17, 08/18, 08/19, 08/20, 12/20, 04/21, 04/22, 04/23 Original Effective Date: 09/98 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Medically-Accepted Indications

REQUIRED MEDICAL INFORMATION:

For coverage of enteral nutrition, member must have a diagnosis listed in Table 1, or must meet the following criteria:

1. Documentation of a medical condition that prevents food from reaching the digestive tract (such as head and neck cancer with reconstructive surgery, central nervous system disease that interferes with neuromuscular mechanisms of ingestion) or disease of the small bowel that impairs digestion and/or absorption of an oral diet (such as inflammatory bowel disease, surgical resection of small bowel, cystic fibrosis, chronic pancreatitis, advanced liver disease)

AND

2. Documentation that the condition is of long and indefinite duration as deemed by the judgment of the attending provider or substantiated in the medical records

AND

3. Adequate nutrition must not be possible by dietary adjustment and/or oral supplements

AND

4. For in-line digestive enzyme cartridge requests, must have a diagnosis of exocrine pancreatic insufficiency (EPI)

Reauthorization:
The assessment and treatment plan must demonstrate that adequate nutrition (at least 75% of required intake) is not possible by dietary adjustment and/or oral supplementation.

EXCLUSION CRITERIA:

- Food thickeners, baby food, and other regular grocery products that can be blenderized and used with the enteral system
- Electrolyte-containing fluids
- Self-blenderized formulas
- Oral administration of enteral nutrition products

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for up to one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Enteral nutrition therapy is the provision of nutrition directly into either the stomach or small intestine through a feeding tube. The enteral nutrition benefit will include all related supplies, equipment and nutrients. Skilled assessment of nutritional status will be done at a frequency consistent with the member's diagnosis and general nutritional condition.

POSITION STATEMENT:

- Enteral nutrition therapy is a covered benefit when it is determined to be medically necessary to prevent or treat malnutrition and nutritional needs which cannot be met by oral intake alone. Enteral nutrition will be covered under the member's medical benefit (for Medicare members, this is their Part B benefit). Medicare considers enteral nutrition as a prosthetic device, which requires that a member must have a permanently inoperative internal body organ or function thereof. Therefore, enteral therapy is not normally covered under Part B in situations involving temporary impairments. The medical policy and criteria are developed based on Medicare and ASPEN guidelines.
- Medicare requires that a beneficiary has a permanent impairment for coverage of enteral nutrition under the prosthetic device benefit, as outlined in the Medicare Benefit Policy Manual. However, this does not require a determination that there is no possibility that the beneficiary's condition may improve sometime in the future. If the medical record, including the judgment of the treating practitioner, indicates that the impairment will be of long and indefinite duration, the test of permanence is considered met.
- For Medicare members, enteral and parenteral nutritional therapies are not covered under Part B in situations involving temporary impairments. Orally administered enteral nutrition products, related supplies and equipment will be denied non-covered, no benefit.
- Some patients require supplementation of their daily protein and caloric intake. Nutritional supplements are often given as a medicine between meals to boost protein-caloric intake or the mainstay of a daily nutritional plan. Nutritional supplementation is not covered under Medicare Part B.
- As mandated by Medicare, dispensing of nutritional therapy is limited to a one-month supply at any one time.

Relizorb™

- Exocrine pancreatic insufficiency (EPI) occurs in 85-95% of patients with cystic fibrosis. This leads to fat malabsorption and negatively impacts growth in children and BMI in adults, both of which are important in maintenance of pulmonary function. In 2008, The Cystic Fibrosis Foundation Subcommittee on Growth and Nutrition made a recommendation for using pancreatic enzyme replacement therapy (PERT) for the treatment of cystic fibrosis-related pancreatic insufficiency in both children and adults18. Approximately 44% of patients with cystic fibrosis are unable to meet their nutritional requirements orally and require enteral nutrition19, and while PERT is the standard of care in patients with pancreatic insufficiency, there is a lack of clinical trial data on its use in patients using enteral nutrition. Additionally, no standardized recommendations have been published regarding the use of pancreatic enzyme therapy with enteral feeding. The Cystic Fibrosis Foundation does not recommend for or against a specific method of providing pancreatic enzyme therapy during enteral tube feeding in individuals with

cystic fibrosis20. Due to the relatively short duration of action of PERT (45 to 60 minutes), individuals typically take it orally before and after enteral feeding, and during if possible, which can be challenging for continuous overnight enteral feeding. Others crush or dissolve pancreatic enzymes in the enteral formula, however there is no evidence of efficacy with this, and it is against most manufacturer guidelines19.

- Relizorb™ is a single-use digestive enzyme (i.e., lipase) cartridge to be used in conjunction with enteral feeding sets. Approved by the FDA in 2016, it is designed to mimic digestive enzymes normally secreted by the pancreas to break down fats in enteral formula for absorption. Relizorb™ is indicated for use in pediatric patients (ages 5 years and older) and adult patients to hydrolyze fats in enteral formula. In a clinical trial by Freeman, et al (N=34), patients were given either 11 days of placebo cartridges or Relizorb™ and found a significant change in omega-3 fat levels in the blood. However, this study was small in scale, did not measure clinical outcomes, and was short in duration. In 2021 a retrospective analysis evaluating the effectiveness of Relizorb™ in enterally fed patients with cystic fibrosis was published. Baseline anthropometric data were obtained, and subsequent measurements of height, weight, and body mass index (BMI) were collected at 6 and 12 months. Inclusion criteria were met by 100 patients (ages 0-45 years old). The data showed significant improvements in height and weight z-scores (in patients >2 years of age [n = 93]) at 6 months, which increased or was sustained through 12 months, and improvement trend seen in BMI21. The frequency of achieving the 50th percentile increased steadily for weight and BMI from baseline to 12 months but not for height. Although additional literature is needed to determine safety, efficacy, and place in therapy, current evidence shows that Relizorb™ may be beneficial in some patients with cystic fibrosis and exocrine pancreatic insufficiency who are unable to manage their pancreatic insufficiency with the use of pancreatic enzyme replacement therapy.

HCPCS CODES

The following table includes codes that may be eligible for coverage under this policy. This list may not be all inclusive and does not guarantee coverage. This information is for reference purposes only.

Prior Authorization Required	
HCPCS Code	**Description**
B4104	Additive for enteral formula (e.g., fiber) – not separately payable
B4105	In-line cartridge containing digestive enzyme(s) for enteral feeding, each

B4149	Enteral formula, manufactured blenderized natural foods with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4150	Enteral formula, nutritionally complete with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4152	Enteral formula, nutritionally complete calorically dense (equal to or greater than 1.5 kcal/ml) with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4153	Enteral formula, nutritionally complete, hydrolyzed proteins (amino acids and peptide chain), includes fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4154	Enteral formula, nutritionally complete, for special metabolic needs, excludes inherited disease of metabolism, includes altered composition of proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4155	Enteral formula, nutritionally incomplete/modular nutrients, includes specific nutrients, carbohydrates (e.g., glucose polymers), proteins/amino acids (e.g., glutamine, arginine) fat (e.g., medium chain triglycerides) or combination, administered through an enteral feeding tube, 100 calories = 1 unit
B4157	Enteral formula, nutritionally complete, for special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4158	Enteral formula, for pediatrics, nutritionally complete with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit
B4159	Enteral formula, for pediatrics, nutritionally complete soy based with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit
B4160	Enteral formula, for pediatrics, nutritionally complete calorically dense (equal to or greater than 0.7 kcal/ml) with intact nutrients, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4161	Enteral formula, for pediatrics, hydrolyzed/amino acids and peptide chain proteins, includes fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
B4162	Enteral formula, for pediatrics, special metabolic needs for inherited disease of metabolism, includes proteins, fats, carbohydrates, vitamins and minerals, may include fiber, administered through an enteral feeding tube, 100 calories = 1 unit
No Prior Authorization Required	
A5200	Percutaneous catheter/tube anchoring device, adhesive skin attachment
A9270	Non-covered item or service

B4034	Enteral feeding supply kit; syringe fed, per day, includes but not limited to feeding/flushing syringe, administrative set tubing, dressings, tape
B4035	Enteral feeding supply kit; pump fed, per day, includes but not limited to feeding/flushing syringe, administrative set tubing, dressings, tape
B4036	Enteral feeding supply kit; gravity fed, per day, includes but not limited to feeding/flushing syringe, administrative set tubing, dressings, tape
B4081	Nasogastric tubing with stylet
B4082	Nasogastric tubing without stylet
B4083	Stomach tube-levine type
B4087	Gastronomy/Jejunostomy tube, standard, any material, any type, each
B4088	Gastronomy/Jejunostomy tube, low profile, any material, any type, each
B9002	Enteral nutrition infusion pump, any type
B9998	NOC for enteral supplies
Not Covered	
B4100	Food thickener, administered orally, per ounce
B4102	Enteral formula, for adults, used to replace fluids and electrolytes (e.g., clear liquids) 500ml = 1 unit
B4103	Enteral formula, for pediatrics, used to replace fluids and electrolytes (e.g., clear liquids) 500ml = 1 unit

Table 1

Nutrition HCPCS codes will not require Prior Authorization when billed with any of the following diagnosis codes:

ICD-10 Code	Description
C01	Malignant neoplasm of base of tongue
C02	Malignant neoplasm of other and unspecific parts of tongue
C03	Malignant neoplasm of gums
C04	Malignant neoplasms of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of cheek mucosa
C07	Malignant neoplasm of parotid gland
C08	Malignant neoplasm of submandibular gland
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of pyriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of pharynx
C15	Malignant neoplasm of esophagus
C16	Malignant neoplasm of stomach
C76.0	Malignant neoplasm of head, face, and neck

E70.0, E70.1	Phenylketonuria
E70.21	Tyrosinemia
E70.41	Histidinemia
E71.0	Maple syrup disease
E72.11	Homocystinuria
E72.23	Citrullinemia
E84.0-E84.9	Cystic fibrosis
G80.0-G80.9	Cerebral palsy
G12.21	Amyotrophic lateral sclerosis

REFERENCE/RESOURCES:

1. Bankhead R, Boullata J, Brantley S et al. Enteral Nutrition Practice Recommendations. JPEN J Parenter Enteral Nutr. 2009 Mar-Apr;33(2):122-67.
2. FDA 510(k) approval letter. July 12, 2017. RELiZORB. Alcresta Therapeutics, Inc. FDA website. https://www.accessdata.fda.gov/cdrh_docs/pdf16/K163057.pdf. Accessed November 3, 2020.
3. FDA Device Classification under Section 513(f)(2)(de novo) database. FDA website. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN150001. Accessed November 3, 2020.
4. Freeman S, Orenstein D, Black P. et al. Increased Fat Absorption for Enteral Formula Through an In-line Digestive Cartridge in Patients with Cystic Fibrosis. J Pediatr Gastroenterol Nutr. 2017 Jul:65 (1):97-101.
5. Pancreatic Enzymes Clinical Care Guidelines. Last updated 2016. CFF website. https://www.cff.org/Care/Clinical-Care-Guidelines/Nutrition-and-GI-Clinical-Care-Guidelines/Pancreatic-Enzymes-Clinical-Care-Guidelines/. Accessed July 18, 2018.
6. Schwarzenberg SJ, Hempstead SE, McDonald CM, et al. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. J Cyst Fibros. 2016; 15(6): 724 – 735. DOI: 10.1016/j.jcf.2016.08.004.
7. *Enteral nutrition L38955*. CMS.gov Centers for Medicare & Medicaid Services. (n.d.). Retrieved March 7, 2022, from https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38955
8. Enteral Nutrition – Policy Article. CMS.gov Centers for Medicare & Medicaid Services. (n.d.). Retrieved February 16, 2023, from https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=58833&ver=11&keyword=nutrition&keyw

ordType=starts&areaId=s44&docType=NCA,NCD,MCD,6,3,5,1,F&contractOption=name&contractorName=5&sortBy=relevance&bc=1

9. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-Based Practice Recommendations for Nutrition-Related Management of Children and Adults with Cystic Fibrosis and Pancreatic Insufficiency: Results of a Systematic Review, Journal of the American Dietetic Association. 2008;108(5):832-839. https://doi.org/10.1016/j.jada.2008.02.020.
10. Freedman SD. Options for Addressing Exocrine Pancreatic Insufficiency in Patients Receiving Enteral Nutrition Supplementation. Am J Manag Care. 2017;23:-S0. https://www.ajmc.com/view/options-for-addressing-exocrine-pancreatic-insufficiency-in-patients-receiving-enteral-nutrition-supplementation-article
11. Schwarzenberg SJ, Hempstead SE, McDonald CM, et. al. Enteral Tube Feeding for Individuals With Cystic Fibrosis: Cystic Fibrosis Foundation Evidence-Informed Guidelines. J Cyst Fibros. 2016. Nov;15(6):724-735.PMID: 27599607.
12. Sathe, Meghana N.∗; Patel, Dhiren†; Stone, Archie‡; First, Eric‡. Evaluation of the Effectiveness of In-line Immobilized Lipase Cartridge in Enterally Fed Patients With Cystic Fibrosis. Journal of Pediatric Gastroenterology and Nutrition 72(1):p 18-23, January 2021. | DOI: 10.1097/MPG.0000000000002984

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCCNS065.0823	**CENTRAL NERVOUS SYSTEM DRUGS** **MEDICALLY ADMINISTERED MULTIPLE SCLEROSIS AGENTS** See Table 1 for Applicable Medications
Effective Date: 11/1/2023	Review/Revised Date:
	P&T Committee Meeting Date: 08/23
	Original Effective Date: 10/23
	Approved by: Oregon Region Pharmacy and Therapeutics Committee
Robert Gluckman, M.D. **Chief Medical Officer**	Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initiation of therapy for **multiple sclerosis (MS)**, all the following criteria (1-2) must be met:

1. Must have one of the following confirmed diagnoses:
    a. Relapsing-remitting multiple sclerosis (RRMS)
    b. Secondary progressive multiple sclerosis (SPMS)
    c. Clinically isolated syndrome (CIS)
    d. For Ocrevus only: Primary progressive MS
2. Documentation of ONE of the following (a b, c, or d) for RRMS, SPMS, CIS:
    a. Documentation the patient has highly active disease defined as ONE of the following:
        i. Greater than or equal to two relapses in the previous year
        ii. The patient has greater than or equal to one gadolinium enhancing lesion on MRI
        iii. Presence of significant T2 lesion burden defined as ONE of the following:
            1) Greater than ten (10) T2 lesion burden as documented with MRI

2) Significant increase in T2 lesion load compared with a previous MRI
3) T2 lesion(s) located in spinal cord or brainstem

b. The patient has been treated with at least three multiple sclerosis agents from different drug classes
c. Inadequate response (after at least six months of continuous therapy) or intolerance to one of the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, or generic teriflunomide
d. FDA labeled contraindication to ALL of the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, and generic teriflunomide

For **patients established on therapy** (within the previous year), the following must be met: Documentation of positive clinical response to therapy

EXCLUSION CRITERIA:
Concurrent use with other disease modifying agents for multiple sclerosis

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a neurologist.

COVERAGE DURATION:
Initial authorization will be approved for one year. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCCNS065	CENTRAL NERVOUS SYSTEM DRUGS MEDICALLY ADMINISTERED MULTIPLE SCLEROSIS AGENTS See Table 1 for Applicable Medications

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:
Ublituximab-xiiy (Briumvi®), a B-cell therapy with CD20-directed cytolytic monoclonal antibody for treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ublituximab-xiiy is administered every 24 weeks (6 months).

Ocrelizumab (Ocrevus®), a B-cell therapy with CD20-directed cytolytic monoclonal antibody for treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults, and primary progressive MS in adults.

FDA APPROVED INDICATIONS:
Ublituximab (Briumvi®) is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Ocrelizumab (Ocrevus®) is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults, and primary progressive MS in adults.

Table 1. Medically infused multiple sclerosis medications

Drug	Class	RRMS	SPMS	CIS	Other
ublituximab (Briumvi®)	Recombinant monoclonal antibody, binds to CD52, natural killer cells, monocytes, and macrophages	X	X	X	
Ocrelizumab (Ocrevus®)	Immune modulator, binds to CD-20	X	X	X	Primary progressive MS

MOA = mechanism of action, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis, CIS = clinically isolated syndrome

POSITION STATEMENT:

Guidelines for Multiple Sclerosis include the American Academy of Neurology Publication "Comprehensive Systematic Review Summary: Disease-Modifying Therapies for Adults with Multiple Sclerosis" published in 2018 and a consensus paper by the Multiple Sclerosis Coalition titled "The Use of Disease-Modifying Therapies in Multiple Sclerosis" published in 2019. Guidelines state that initiating a disease modifying therapy (DMT) should be offered to patients as early as possible. The choice of initial DMT should be individualized to consider safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability. When switching therapies after failure of an agent, disease activity, adherence, AE profiles, and mechanisms of action should be considered when selecting a new agent to start. For advanced, aggressive, or highly active disease guidelines recommend fingolimod (Gilenya®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), or alemtuzumab (Lemtrada®). Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 2).[5]

Table 2. DMT Evidence for Lowering Relapse Rate[5]

Very Low	Low	Moderate	Strong
Immunoglobulins	Cyclophosphamide	Azathioprine	Alemtuzumab
Methotrexate	Mycophenolate Mofetil	Interferon beta-1b	Cladribine
Rituximab			Dimethyl Fumarate†
Corticosteroids			Fingolimod†
			Glatiramer Acetate†
			Interferon beta-1a
			Mitoxantrone
			Natalizumab
			Ocrelizumab
			Pegylated Interferon
			Teriflunomide†

† Generic Available

REFERENCE/RESOURCES:

1. Briumvi package insert. Morrisville, NC: TG Therapeutics, Inc; 2023 Jan.
2. Ocrevus package insert. San Francisco, CA: Genentech, Inc; 2023 March.
3. Briumvi. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
4. Ocrevus. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777–788.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH021M.0224	**MISCELLANEOUS PRODUCTS** **MEDICALLY INFUSED THERAPEUTIC IMMUNOMODULATORS (TIMs)** See Table 1 for Applicable Medications
Effective Date: 4/1/2024	**Review/Revised Date**: 01/17, 02/17, 03/17, 09/17, 01/17, 03/18, 05/18, 11/18, 01/19, 03/19, 09/19, 12/19, 01/20, 04/20, 09/20, 05/21, 07/21, 9/21, 11/21, 05/22, 08/22, 09/23, 02/24 (BS)
Original Effective Date: 02/17	**P&T Committee Meeting Date**: 02/17, 02/17(cv), 03/17(cv), 04/17, 02/18, 03/18 (cv), 06/18, 12/18, 02/19, 04/19, 06/19, 10/19, 12/19 (cv), 02/20, 06/20, 10/20, 10/20 (off-cycle), 06/21, 08/21, 10/21, 10/21 (CV), 12/21, 06/22, 08/22, 10/22, 10/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 16	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit. Drug Compendia supported indications may be covered.

REQUIRED MEDICIAL INFORMATION:

1. For **all requests**, the patient must have an FDA labeled indication for the requested agent, or use to treat the indication is supported in drug compendia (such as the American Hospital Formulary Service-Drug Information (AHFS-DI) or Truven Health Analytics' DRUGDEX® System.)
   AND
2. The requested agent will not be given concurrently with another therapeutic immunomodulator (TIMs) agent or apremilast (Otezla®)
   AND
3. One of the following:
   a. For patients already established on the requested TIMs agent within the previous year: Documentation of response to therapy (such as slowing of disease progression or decrease in symptom severity and/or frequency)
   b. Patients not established on the requested TIMs agent (new starts), must meet ALL of the following indication-specific criteria (note: if indication is not listed below, the requested drug may be covered if it is an FDA approved indication for the requested drug):

i. Requests for non-preferred infliximab products (Remicade® and Avsola®) will require documentation of failure, intolerance or contraindication to the preferred infliximab products, Inflectra® and Renflexis®, in addition to the indication-specific criteria below. Accepted contraindications include: contraindications listed in the package insert or a documented allergic reaction to an ingredient found only in the preferred biosimilar product(s).

ii. For moderate to severe **ulcerative colitis:**
    1) Preferred infliximab products (Inflectra® and Renflexis®) or vedolizumab (Entyvio®) may be covered
    2) For non-preferred agents: documentation of failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®) or vedolizumab (Entyvio®)

i. For moderate to severe **Crohn's disease:**
    1) Preferred infliximab products (Inflectra® and Renflexis®) or vedolizumab (Entyvio®) may be covered
    2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®) or vedolizumab (Entyvio®)

ii. For **rheumatoid arthritis**:
    1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as methotrexate, leflunomide, hydroxychloroquine, sulfasalazine)
    2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

iii. For moderate to severe **plaque psoriasis:**
    1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as methotrexate, tazarotene, topical corticosteroids, calcitriol)
    2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

iv. For **psoriatic arthritis**:
    1) For all agents: Documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as methotrexate, leflunomide, sulfasalazine)

2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

v. For **ankylosing spondylitis**:
   1) Preferred infliximab products (Inflectra® and Renflexis®) may be covered
   2) For non-preferred agents: documentation of trial, failure, intolerance, or contraindication to a preferred infliximab product (Inflectra® or Renflexis®)

vi. For **giant cell arteritis**: Tocilizumab (Actemra®) may be approved with documentation of trial and failure, intolerance, or contraindication to at least one conventional therapy (such as systemic corticosteroid therapy)

vii. For **systemic sclerosis (SSc-ILD)**, tocilizumab (Actemra®) may be covered if the patient has interstitial lung disease, as evidence by high-resolution computed tomography (HRCT)

viii. For **immune checkpoint inhibitor related toxicities**, a preferred infliximab products (Inflectra® and Renflexis®) may be covered if one of the following criteria are met:
   1) Moderate to severe diarrhea or colitis unresponsive to high-dose systemic corticosteroids
   2) Moderate to severe pneumonitis if no improvement after 48 hours of high-dose systemic corticosteroids
   3) Severe (stage 3) or life-threatening (stage 4) renal failure or elevated serum creatinine if toxicity remains greater than stage 2 after 4-6 weeks of corticosteroids
   4) Myocarditis if unresponsive to high-dose systemic corticosteroids
   5) Moderate, severe, or life-threatening inflammatory arthritis unresponsive to corticosteroids or anti-inflammatory agents
   6) Grade 1-4 uveitis that is refractory to high-dose systemic corticosteroids

ix. For **sarcoidosis**, a preferred infliximab product (Inflectra® or Renflexis®) may be covered if one of the following criteria are met:
   1) Trial and failure, contraindication, or intolerance to corticosteroids (such as prednisone, methylprednisolone)
   2) Trial and failure, contraindication, or intolerance to one immunosuppressant (such as methotrexate, cyclophosphamide, azathioprine)

Note:
- Conventional therapy requirements may be waived if the patient has previously used another therapeutic immunomodulator agent OR apremilast (Otezla®) for the same indication.
- Conventional therapy and preferred agent requirements may be waived with clinically appropriate medical rationale.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
For patients not established on the requested TIMs agent: Must be prescribed by, or in consultation with, a specialist for the respective indication, such as:
- Rheumatoid arthritis, ankylosing spondylitis: must be prescribed by, or in consultation with, a rheumatologist
- Psoriasis: must be prescribed by, or in consultation with, a dermatologist
- Psoriatic arthritis: must be prescribed by, or in consultation with, a dermatologist or rheumatologist
- Inflammatory Bowel Disease: must be prescribed by, or in consultation with, a gastroenterologist
- Giant Cell Arteritis: must be prescribed by, or in consultation with, a rheumatologist or neurologist
- Systemic sclerosis-associated interstitial lung disease: must be prescribed by, or in consultation with, a pulmonologist or rheumatologist
- Immune checkpoint inhibitor related diarrhea/colitis: must be prescribed by, or in consultation with, an oncologist, gastroenterologist, pulmonologist, ophthalmologist or rheumatologist
- Sarcoidosis: must be prescribed by, or in consultation with a pulmonologist, ophthalmologist, neurologist, cardiologist, rheumatologist or dermatologist

COVERAGE DURATION:
- For immune checkpoint inhibitor related diarrhea/colitis: Authorization will be approved for three months
- For all other indications: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy

document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Therapeutic Immunomodulators (TIMs) have become standard of care in patients with moderate to severe, chronic inflammatory diseases where conventional therapies have not been adequate. These agents work by targeting specific steps in the inflammatory and immune cascade.

Table 1. Therapeutic Immunomodulators (TIMs) covered by this policy

Drug	HCPCS Code
Preferred Agents	
Infliximab-dyyb (Inflectra®)	Q5103
Infliximab-abda (Renflexis®)	Q5104
vedolizumab (Entyvio®)	J3380
Non-Preferred Agents[t]	
Infliximab (Remicade®)	J1745
Infliximab-axxq (Avsola®)	Q5121
tocilizumab (Actemra®)	J3262
abatacept (Orencia®)	J0129
tildrakizumab-asmn (Ilumya®)	J3245
golimumab IV (Simponi Aria®)	J1602
Certolizumab (Cimzia® lyophilized powder vial)	J0717
Agents Indicated for Induction Dosing Only	
ustekinumab (Stelara®)*	J3358
risankizumab-rzaa (Skyrizi® vial)**	J2327

*intravenous ustekinumab is indicated for a one-time induction dose for Crohn's disease and ulcerative colitis. Subcutaneous ustekinumab is eligible for coverage, and is considered a preferred product under the pharmacy benefit. Medical benefit induction doses will be covered upon approval of a pharmacy benefit prior authorization.

**intravenous risankizumab-rzaa is indicated for three induction doses for Crohn's disease. Subcutaneous risankizumab-rzaa is eligible for coverage, and is considered a preferred product

under the pharmacy benefit. Medical benefit induction doses will be covered upon approval of a pharmacy benefit prior authorization.
ŧAny self-administered TIMs agent that is requested for coverage through the medical benefit will be subject to requirements outlined in this policy.

FDA APPROVED INDICATIONS:

Table 2. Infusible therapeutic immunomodulators (TIMs) and their respective FDA-approved Indications

Drug	MOA	RA	CD	UC	Ps	PsA	AS	Other
abatacept (Orencia®)	T-cell inhibitor	X				X (age 2+)		PJIA (age 2+) aGVHD (age 2+)
certolizumab (Cimzia®)	Anti-TNF	X	X		X	X	X	NRAS
golimumab IV (Simponi Aria®)	Anti-TNF	X				X (age 2+)	X	PJIA (age 2+)
infliximab (Remicade®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-dyyb (Inflectra®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-abda (Renflexis®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
infliximab-axxq (Avsola®)	Anti-TNF	X	X (age 6+)	X (age 6+)	X	X	X	
risankizumab-rzaa (Skyrizi®)	IL-23 inhibitor		X[2]					
tildrakizumab-asmn (Ilumya®)	IL-23 inhibitor				X			
tocilizumab (Actemra®)	IL-6 inhibitor	X						GCA, PJIA/SJIA (age 2+), CRS (age 2+)
ustekinumab (Stelara® IV)	IL-12/23 inhibitor		X[1]	X[1]				
vedolizumab (Entyvio®)	α4β7 inhibitor		X	X				

[1]Intravenous ustekinumab is indicated for a one-time induction dose for Crohn's disease and ulcerative colitis
[2]Intravenous Risankizumab-rzaa is indicated for a one-time induction dose for Crohn's disease

Abbreviations: MOA = mechanism of action; RA = rheumatoid arthritis; SJIA = Systemic juvenile idiopathic arthritis; CD = Crohn's disease; UC = ulcerative colitis; Ps = psoriasis; PsA = psoriatic

arthritis; AS = ankylosing spondylitis; GCA = giant cell arteritis; PJIA = Polyarticular Juvenile Idiopathic Arthritis; CRS = cytokine release syndrome; SSc-ILD = systemic sclerosis-associated interstitial lung disease; NRAS = non-radiographic axial spondyloarthritis; aGVHD = acute graft versus host disease

POSITION STATEMENT:

Preferred use of biosimilar medically infused therapeutic immunomodulators

Biosimilars have been approved for use in the United States for several disease states that are currently treated with therapeutic immunomodulators. The United States Food and Drug Administration (FDA) defines a biosimilar as a "biological product that is highly similar to and had no clinically meaningful differences from an existing FDA-approved reference product." The Companies have chosen to favor the use of biosimilar products to provide quality clinical care to our members in the most cost-effective manner.

Infliximab

There are currently three approved biosimilars for infliximab: Inflectra® (infliximab-dyyb), Renflexis® (infliximab-abda), and Avsola® (infliximab-axxq). These agents have been FDA approved for all indications that the reference product (Remicade®) has been approved for. Therefore, it is clinically appropriate to use these agents instead of Remicade®. Additionally, there have been several moderate-to-high quality studies that support non-medical switching from Remicade® to infliximab biosimilars.

The NOR-SWITCH trial was a prospective, randomized double-blind study of 482 patients with inflammatory diseases in Norway. Disease states included in this study were: Crohn's disease (CD), ulcerative colitis (UC), spondylarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis. This study included patients who had been treated on the reference drug Remicade® for an average of 6.9 years before switching to the biosimilar Inflectra®. Inflectra® was shown to be non-inferior to Remicade® when switching after at least six months of Remicade treatment. There were no significant differences between the groups in terms of safety, objective measures of disease activity, infliximab trough levels, or immunogenicity (anti-drug antibodies). There was a discontinuation rate of 4% for the Remicade® group and 3% for the Inflectra® group. A notable limitation of the NOR-SWITCH study is that it was not powered to make conclusions about treatment outcomes in the individual indications that were studied, so it is possible that outcomes for certain subgroups may differ. To address this limitation, the authors conducted an open-label extension (OLE) and further subgroup analysis of the inflammatory bowel disease cohorts of the original NOR-SWITCH study. In the OLE, 100 patients who had been in the Remicade® arm of the initial study were switched in an unblinded fashion to Inflectra®. The author's found no difference in clinical outcomes with this

open-label switch, adjusted risk of disease worsening with switch to Inflectra for Crohn's disease 7.9% (95% CI –5.2 to 21) and ulcerative colitis 12.4% (-0.1 to 25). Both CD and UC outcomes had wide confidence intervals due to the low number of disease worsening events that occurred. Overall, the NOR-SWITCH study and subsequent open-label extension demonstrates that non-medical change of therapy from Remicade® to a biosimilar is not expected to have an inferior outcome to continuing Remicade®. [2,3]

Bergqvist et al conducted a prospective, observational, open-label study switching 313 consecutive patients receiving Remicade® for inflammatory bowel disease to Inflectra®. This was a multi-center study performed in County of Skåne, Sweden that was funded by a variety of non-industry sponsored grants. All but one of these patients was in the maintenance phase of therapy (i.e., there was one patient still in the induction phase of therapy) and the average time on Remicade® was 4.6 years (range 0.4-16.6 years) for CD and 3.6 years (range 0.2-9.6 years) for UC. At baseline, 33.8% of CD patients and 28.4% of UC patients had clinical disease activity, although no patients would have been considered to have relapsed disease. Comparisons were made between baseline and follow-up clinical disease scores [Harvey-Bradshaw Index (CD) and Simple Clinical Colitis Activity Index (UC)], objective biomarkers [e.g., fecal calprotectin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), etc.], and patient quality of life (Short Health Scale composite scores). The authors found no differences between groups after switching to Inflectra®. In a similar analysis to NOR-SWITCH, 14.0% of patients in the CD group and 13.8% in the UC group had clinical worsening after the switch. This is lower than what was reported in NOR-SWITCH and acts to refute non-inferiority concerns some have expressed regarding NOR-SWITCH. The overall number of patients in remission at baseline increased from 68.2% to 78.9% for CD and 66.2% to 71.6% for UC; these were not statistically significant results.[4]

The DANBIO registry study observed the effects of a nationwide non-medical switch from Remicade® to Inflectra® in Denmark. Patients (n=802) were identified as switching from Remicade® to Inflectra®; these patients had an average treatment duration of 6.8 years on Remicade®. The authors found no differences in clinical outcomes between the three months before and after the mandated switch. There were similar one-year retention rates between the Inflectra® switch group and a historic Remicade® cohort, 84.1% (95% CI 81.3-86.5) and 86.2% (95% CI 84.8-88.8), respectively. The authors note that compared to the blinded NOR-SWITCH study, the discontinuation rate was higher in this analysis possibly due to the "nocebo" effect in addition to loss of efficacy and side effects. The nocebo effect is the negative counterpart to the placebo effect wherein an active therapy or sham

therapy causes a negative outcome based on psychological factors (e.g., negative expectations associated with a change in therapy).[5]

Smolen *et al* conducted a randomized, double-blind, switching study as a continuation of a phase III study of Renflexis® in patients with moderate-to-severe rheumatoid arthritis. Patients (n=396) who completed the initial study which randomized 1:1 initial treatment with Renflexis® vs Remicade® agreed to participate in the follow-up switching study. In the switching study, patients who received Remicade® in the initial study (n=195) were randomized to receive either continued Remicade® (n=101) or switched to Renflexis® (n=94) at week 54 of treatment. Clinical outcomes, safety, and immunogenicity were followed through week 78. Overall, no differences were found between the groups for any of the measured efficacy, safety, or immunogenicity outcomes.[6]

Based on the above moderate-to-high quality studies, a switch from Remicade® to an infliximab biosimilar is expected to have similar clinical efficacy, safety, and immunogenic outcomes as remaining on Remicade®, even in patients who have been long established on Remicade®. Therefore, in the absence of a contraindication, adverse event, or clinical failure of the preferred biosimilar infliximab agents, it is appropriate to transition members from Remicade® to more cost-effective formulations of infliximab.

Inflammatory Bowel Disease

Crohn's Disease (CD)

Based on the available evidence and national practice guidelines, TIMs are effective agents in inducing and maintaining remission in severe, active CD. These agents are typically used when conventional therapies (e.g., corticosteroids, mesalamine, 6-MP and azathioprine) have failed to induce remission. Overall, there is insufficient direct comparative evidence for the efficacy of TIMs in the treatment of severe, active CD; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.

The American Gastroenterological Association (AGA), in their 2021 guidelines, defines moderate to severe luminal Crohn's disease as any of the following:

- CDAI score of at least 220
- High risk of adverse disease-related complications, such as surgery, hospitalizations, and disability based on a combination of structural damage, inflammatory burden, and impact on quality of life

The AGA recommends the use of infliximab, adalimumab, ustekinumab, or vedolizumab over certolizumab for the induction of remission in patients without previous use of TIMs agents. In primary non-responders to TNF agents, they

recommend use of ustekinumab to induce remission (vedolizumab may be considered). For those that loss response to infliximab, they recommend adalimumab or ustekinumab to induce remission (vedolizumab may be considered). For patients with moderate to severe disease, biologic therapy is recommended to induce remission instead of 5-aminosalicylates and/or corticosteroids.[7]

Ulcerative Colitis (UC)
Based on the available evidence and national practice guidelines, TIMs are effective agents in inducing and maintaining remission in moderate to severe UC. These agents are typically used when conventional therapies (e.g., aminosalicylates, topical mesalamine, corticosteroids, 6-mercaptopurine, and azathioprine) have failed to induce remission. Infliximab may be more consistently efficacious for inducing remission and mucosal healing than adalimumab. Vedolizumab is a non-anti-TNF therapy option for the treatment of UC. Overall, there is insufficient direct comparative evidence for the efficacy of TIMs in the treatment of moderate to severe UC; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.

In 2020, the Institute for Clinical and Economic Review (ICER) published a report on TIMs for UC, assessing the following therapies: adalimumab, golimumab, infliximab and biosimilars, tofacitinib, and ustekinumab. All agents were found to be clinically superior than placebo, and all were found to be comparable to adalimumab. It was noted that vedolizumab was "found to produce greater rates of clinical response and remission over adalimumab, the market leader, in both patients who had used TIMs previously ("biologic-experienced") as well as those who did not ("biologic-naïve")." No agents were found to be cost-effective at current drug costs, but infliximab and its biosimilars represent the best value for money for UC.[8]

The AGA, in their 2020 guidelines, defines moderate to severely active UC as any of the following:

- Patients deemed to be at high-risk for colectomy
- Mayo Clinic Score 6–12, with Mayo Endoscopic Subscore 2 or 3
- Severely active endoscopic disease, with ulcers
- Patients with corticosteroid dependence, or refractory to oral corticosteroids

The AGA recommends infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment; however, they suggest the use of infliximab or vedolizumab over adalimumab for the induction of remission in patients without previous use of TIMs agents. They do not recommend the use of tofacitinib in this setting, unless in a clinical trial. In primary non-responders to infliximab, they

suggest use of ustekinumab or tofacitinib rather than vedolizumab or adalimumab for induction of remission. [9]

Guidelines:

- American Gastroenterological Association: http://www.gastro.org/guidelines
- American College of gastroenterology: https://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/

Rheumatologic Disorders

Rheumatoid arthritis (RA)

Based on the available evidence and national practice guidelines, TIMs are effective agents in treating moderate to severe RA. These agents are typically used when non-biologic disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, have failed. There is limited direct comparative evidence for the efficacy of TIMs in the treatment of moderate to severe RA; all FDA approved agents have shown to be superior to placebo.

In 2017, the Institute for Clinical and Economic Review (ICER) published a review of the Targeted Immune Modulators for Rheumatoid Arthritis. They reviewed the following therapies:

- TNFα inhibitors: adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), golimumab (Simponi® and Simponi Aria®), infliximab (Remicade®):
- CD20-directed cytolytic B-cell antibody: rituximab (Rituxan®)
- T-cell inhibitor: abatacept (Orencia®)
- IL-6 inhibitors: tocilizumab (Actemra®,), sarilumab (Kevzara™)
- JAK inhibitors: tofacitinib (Xeljanz®), baricitinib (Olumiant™)

Using a network meta-analysis, the review suggests that all agents are superior to conventional DMARD monotherapy. There have been some head-to-head trials conducted between the TIMs agents and adalimumab was found to be inferior to monotherapy with tocilizumab or sarilumab in terms of achieving clinical remission or ACR responses; these agents were rated as B+ over adalimumab (Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit). Abatacept was given the same B+ rating over infliximab. Tofacitinib is considered more costly and less effective than adalimumab.[11]

In 2020, ICER published an updated report including newer JAK Inhibitors and biosimilars used for Rheumatoid Arthritis. The review concludes that the JAK inhibitors upadacitinib and tofacitinib are superior to conventional DMARD therapy.

These agents both received an A rating over DMARDs (high certainty of substantial net health benefit) in TIM-naïve patients and B+ in TIM-experienced patients. Upadacitinib was rated B+ over adalimumab, tofacitinib was rated C (comparable) to adalimumab, and the infliximab biosimilar (Inflectra®) was rated C to Remicade® in TIM-naïve patients.[12]

Juvenile Idiopathic Arthritis (JIA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA)
Based on the available evidence and national practice guidelines, TIMs are effective agents in treating these conditions. There is limited and/or insufficient direct comparative evidence for the efficacy of TIMs in these conditions; all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.[10]

Guidelines:

- American College of Rheumatology: https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines

Dermatologic Disorders
Plaque psoriasis (Ps)
Based on the available evidence and national practice guidelines, TIMs are effective agents in treating moderate to severe plaque psoriasis and are generally initiated when standard conventional therapies (e.g., topical therapy and phototherapy) are inadequate. Low quality evidence suggests that ustekinumab, secukinumab, and ixekizumab may have better efficacy than etanercept, but there were sufficient limitations identified to render the evidence of uncertain validity. At this time, all FDA approved agents have shown to be superior to placebo and are considered to have comparable efficacy.[13,14]

Guidelines:

- American Academy of Dermatology: https://www.aad.org/practicecenter/quality/clinical-guidelines

Immune checkpoint inhibitor (ICI) related diarrhea/colitis
Diarrhea and colitis, inflammatory arthritis, and elevated serum creatinine are a few common symptoms of treatment with ICI therapy. The National Comprehensive Cancer Network (NCCN) recommends addition of infliximab when there is no response to other conventional therapy (if applicable). [15]

REFERENCE/RESOURCES:

1. Relevant package inserts
2. Jørgensen KK, Olsen IC, Goll GL et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304-16.
3. Jørgensen KK, Goll GL, Sexton J. Efficacy and safety of CT-P13 in inflammatory bowel disease after switching from originator infliximab: exploratory analyses from the NOR-SWITCH main and extension trials. BioDrugs. 2020;34:681-94.
4. Bergqvist V, Kadivar M, Molin D et al. Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease. Ther Adv Gastroenterol. 2018;11:1-13.
5. Glintborg B, Sørensen IJ, Loft AG et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis 2017;76:1426-31.
6. Smolen JS, Choe JY, Prodanovic N et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Ann Rheum Dis. 2018;77:234-40.
7. Feuerstein JD, Ho EY, Schmidt E et al. American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. *Gastroenterology* 2021;160:2496–2508.
8. ICER. An assessment of treatments for ulcerative colitis. Available at https://icer.org/assessment/ulcerative-colitis-2020/ (Accessed October 11, 2023)
9. Feuerstein JD, Isaacs KL, Schneider MS et al. American Gastroenterological Association (AGA) Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology 2020;158:1450–1461.
10. American College of Rheumatology (ACR). ACR Guideline for the Treatment of Rheumatoid Arthritis, 2015. Available at https://www.rheumatology.org/Portals/0/Files/ACR%202015%20RA%20Guideline.pdf (Accessed October 11, 2023)
11. Institute for Clinical and Economic Review (ICER). Rheumatoid Arthritis: Final Report. Available at https://icer-review.org/material/ra-final-report/ (Accessed October 11, 2023)

12. ICER. Rheumatoid Arthritis: An assessment of JAK inhibitors. Available at https://icer.org/assessment/rheumatoid-arthritis-2019/ (Accessed October 11, 2023)
13. Oregon State University Drug Use Research & Management Program. Drug Class Update: Targeted Immune Modulators for Autoimmune Diseases. Available at https://www.orpdl.org/durm/meetings/meetingdocs/2021_10_07/finals/BiologicsAutoimmune_ClassUpdate.pdf (Accessed October 11, 2023)
14. American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF). Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. Available at https://www.jaad.org/article/S0190-9622(18)33001-9/fulltext. Accessed (October 11, 2023)
15. National Comprehensive Cancer Network (NCCN). NCCN Guidelines Management of Immunotherapy-Related Toxicities Version 2.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf (Accessed October 11, 2023)

Appendix 1. Contraindication(s) for TIMs agents

TIMs Agent	Contraindication(s)
Abatacept (Orencia®)	None
Certolizumab (Cimzia®)	History of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria
Golimumab (Simponi Aria®)	None
Infliximab (Remicade®) and infliximab biosimilars	Doses > 5 mg/kg in moderate to severe heart failure; hypersensitivity reaction to infliximab, its inactive components, or to any murine proteins
Risankizumab-rzaa (Skyrizi®)	History of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients
Tildrakizumab-asmn (Ilumya®)	Previous serious hypersensitivity reaction to tildrakizumab or to any of the excipients
Tocilizumab (Actemra®)	Hypersensitivity to Actemra®
Ustekinumab (Stelara®)	Clinically significant hypersensitivity to ustekinumab or to any of the excipients
Vedolizumab (Entyvio®)	Known serious or severe hypersensitivity reaction to Entyvio® or any of its excipients

Appendix 2. Conventional Agent Prerequisites by Indication

Compendial Supported Indications	Conventional Agent Prerequisites
Rheumatoid arthritis (RA)	methotrexate leflunomide hydroxychloroquine sulfasalazine
Polyarticular juvenile idiopathic arthritis (PJIA)	methotrexate leflunomide sulfasalazine
Psoriasis (PS)	methotrexate topical corticosteroids coal tar products anthralin calcipotriene calcitriol acitretin tazarotene cyclosporine methoxsalen tacrolimus pimecrolimus PUVA (phototherapy)
Psoriatic arthritis	methotrexate

Compendial Supported Indications	Conventional Agent Prerequisites
	leflunomide sulfasalazine
Uveitis	difluprednate oral prednisone periocular/intraocular glucocorticoid injection Accept but do not offer: azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, cyclophosphamide
Giant Cell Arteritis	Systemic corticosteroid therapy

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH051.1223	**MISCELLANEOUS PRODUCTS** **MEDICATIONS FOR RARE INDICATIONS – MEDICARE PART B** See Table 3 for Applicable Medications
Effective Date: 2/1/2024	**Review/Revised Date**:
Original Effective Date: 02/24	**P&T Committee Meeting Date**: 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Both of the following must be met:
1. Confirmation of FDA-labeled indication (appropriate lab values and/or genetic tests must be submitted – (See Table 1)
    a. For Nulibry®: Diagnosis of molybdenum cofactor deficiency (MoCD) Type A confirmed by a mutation in the *MOCS1* gene OR suspected molybdenum cofactor deficiency (MoCD) Type A
    b. For Veopoz®: Confirmation of CD55 loss-of-function mutation detected by genetic testing

AND

2. Dosing is within FDA-labeled guidelines OR documentation has been submitted in support of therapy with a higher dose for the intended diagnosis such as high-quality peer reviewed literature, guidelines, other clinical information

REAUTHORIZATION CRITERIA:
The following must be met:
1. Documentation of successful response to therapy

AND

2. Dosing is within FDA-labeled guidelines OR documentation has been submitted in support of therapy with a higher dose for the intended diagnosis such as high-quality peer reviewed literature, guidelines, other clinical information

AND

3. For Nulibry®: Genetic testing to confirm mutation in the *MOCS1* gene (Nulibry® should be discontinued if the MoCD Type A diagnosis is not confirmed by genetic testing)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with a specialist in the respective disease state.

COVERAGE DURATION:
For Nulibry®: Initial authorization will be approved for three months. Reauthorization will be approved for 12 months.

For all other medications: Initial authorization will be approved for one year and reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
In the United States, Congress defines a rare disease as one that affects fewer than 200,000 people[5]. Congress recognized that people with rare diseases often did not have many treatment options, so it created the Orphan Drug Act (ODA) of 1983 to

incentivize drug developers to create medications for these populations[4]. Since then, a significant number of drugs have emerged on the market for use in rare indication with more to come. On June 29, 2017, The Food and Drug Administration (FDA) unveiled a strategic plan to reduce its backlog of orphan drug requests to expedite the process.[6]

POSITION STATEMENT:
The purpose of this policy is to ensure safe and effective therapy for patients with rare diseases. A list of rare diseases can be found at National Institute of Health (NIH) website[2] and a list of orphan drugs can be found at the FDA website[3].

Table 1. Pertinent Lab Values, Genetic Testing, and Diagnostic Testing

Disease and Drugs	Lab Values/Genetic Testing/Diagnostic Testing
Primary HLH • emapalumab-lzsg vial (Gamifant®)	Diagnosis of primary HLH based on a molecular diagnosis OR family history consistent with primary HLH OR 5 out of the following 8 criteria fulfilled:[22] 1. Fever 2. Splenomegaly 3. Cytopenias affecting 2 of 3 lineages in the peripheral blood: hemoglobin less than 9 g/dL, platelets less than 100 x 109/L, neutrophils less than 1 x 109/L 4. Hypertriglyceridemia (fasting triglycerides greater than 3 mmol/L or equal or greater than 265 mg/dL) and/or hypofibrinogenemia (equal or less than 1.5 g/L) 5. Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy 6. Low or absent NK-cell activity 7. Ferritin equal or greater than 500 mcg/L 8. Soluble CD 25 equal or greater than 2400 U/mL
Molybdenum cofactor deficiency (MoCD) Type A • fosdenopterin vial (Nulibry®)	*MOCS1 gene*[26] • MOCS1 gene mutations cause type A
CHAPLE disease (also known as CD55-deficient protein-losing enteropathy) • pozelimab-bbfg (Veopoz®)	Ultra-rare genetic disorder characterized by history of protein-losing enteropathy (PLE) and diagnosed with genetic confirmation of biallelic CD55 loss of function mutation[32-33]

Table 2. FDA Indication(s)[1]

Drug	FDA Indication(s)
emapalumab-lzsg vial (Gamifant®)	Treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.
fosdenopterin vial (Nulibry®)	To reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.
pozelimab-bbfg vial (Veopoz®)	Adult and pediatric patients one year of age and older with CD55-deficient protein-losing enteropathy (PLE), also known as CHAPLE disease.

REFERENCE/RESOURCES:

1. Current package insert for each listed drug
2. National Institute of Health. Genetic and Rare Diseased Information Center (GARD). Accessed June 8, 2023. Available from https://rarediseases.info.nih.gov/
3. Food and Drug Administration. Search Orphan Drug Designations and Approvals. https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm (accessed August 28, 2022).
4. Orphan Drugs, 21 C.F.R § 316 (1992)
5. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Rare Disease at FDA (2020). Accessed August 28, 2022. Available from https://www.fda.gov/patients/rare-diseases-fda
6. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Orphan Drug Modernization Plan (2018). Accessed August 28, 2022. Available from https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-modernization-plan
7. Progeria Research Foundation. PRF by the numbers. Published September 30, 2020. Accessed February 23, 2021. https://www.progeriaresearch.org/wp-content/uploads/2020/10/PRF-By-the-Numbers_-FINAL-October2020.pdf.
8. Introne WJ, Merideth MA. Hutchinson-Gilford progeria syndrome. In: UpToDate, Hand JL (Ed), UpToDate, Waltham, MA, Jan 2021. Accessed September 9, 2021.
9. National Organization for Rare Disorders. Hutchinson-Gilford Progeria Syndrome. Updated 2021. Accessed September 9, 2021. https://rarediseases.org/rare-diseases/hutchinson-gilford-progeria/.

10. Food and Drug Administration Center for Drug Evaluation and Research Integrated Review.2020. Accessed September 9, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213969Orig1s000IntegratedR.pdf
11. Atwal P, et al. Molybdenum cofactor deficiency. Mol Genet Metab. 2016;117:1-4. doi: 10.1016/j.ymgme.2015.11.010.
12. Mechler K, Mountford WK, Hoffmann GF, Ries M. Ultra-orphan diseases: a quantitative analysis of the natural history of molybdenum cofactor deficiency. Genet Med. 2015 Dec;17(12):965-70. doi: 10.1038/gim.2015.12. Epub 2015 Mar 12. PMID: 25764214.
13. Medline Plus. Molybdenum cofactor deficiency. Updated https://medlineplus.gov/genetics/condition/molybdenum-cofactor-deficiency/#resources. Accessed September 9, 2021.
14. Food and Drug Administration. Center for Drug Evaluation and Research Integrated Review. 2021 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf. Accessed September 9, 2021.
15. Garonzi C, Chinello M, Cesaro S. Emapalumab for adult and pediatric patients with hemophagocytic lymphohistiocytosis. Expert Rev Clin Pharmacol. 2021;14(5):527-534. doi:10.1080/17512433.2021.1901576
16. Urea cycle Treatment Guidelines. Urea Cycle Disorders Consortium. Accessed November 13, 2023. Available at: Treatment Guidelines | Urea Cycle Disorders Consortium (rarediseasesnetwork.org).
17. N-acetylglutamate synthetase deficiency. NORD. April 14, 2016. Accessed November 13, 2023. Available at: N-Acetylglutamate Synthetase Deficiency - Symptoms, Causes, Treatment | NORD (rarediseases.org).
18. Stone WL, Basit H, Master SR. Gaucher Disease. StatPearls. June 7, 2022. Accessed November 13, 2023. Available at: Gaucher Disease - StatPearls - NCBI Bookshelf (nih.gov).
19. Rett Syndrome Diagnosis. International Rett Syndrome Foundation. Accessed November 13, 2023. Available at: Rett Syndrome Diagnosis - International Rett Syndrome Foundation.
20. ACT sheets and algorithms. American College of Medical and Generics and Genomics. Accessed November 13, 2023. Available at: ACT Sheets and Algorithms (acmg.net).
21. Lenders M. and Brand E. Fabry disease: the current treatment landscape. *Drugs*. 2021: 81(6):635-645. Available at: Fabry Disease: The Current Treatment Landscape - PMC (nih.gov).
22. Rosee PL, Horne A, Hines M, et al. Recommendations for the management of meophagocytic lymphohistiocytosis in adults. *Blood*. 2019: 133(23):2465-2477. Available at: Recommendations for the management of

hemophagocytic lymphohistiocytosis in adults | Blood | American Society of Hematology (ashpublications.org).

23. Activated phosphoinositide 3-kinase delta syndrome (APDS). NORD. April 4, 2023. Accessed November 13, 2023. Available at: Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS) - Symptoms, Causes, Treatment | NORD (rarediseases.org).
24. Statland JM, Fontaine B, Hanna MG, et al. Review of the diagnosis and treatment of periodic paralysis. *Muscle Nerve*. 2018. 57(4):522-530. Available at: Review of the Diagnosis and Treatment of Periodic Paralysis - PMC (nih.gov).
25. Araujo-Vilar D. and Santini F. Diagnosis and treatment of lipodystrophy: a step-by-step approach. J Endocrinol Invest. 2019. 42(1):61-73. Available at: Diagnosis and treatment of lipodystrophy: a step-by-step approach - PMC (nih.gov).
26. Molybdenum cofactor deficiency (MoCD) TypeA. Child Neurology Foundation. July 2021. Accessed November 13, 2023. Available at: Molybdenum Cofactor Deficiency (MoCD) Type A - Child Neurology Foundation.
27. Friedreich ataxia. NIH. Accessed November 13, 2023. Available at: Friedreich Ataxia | National Institute of Neurological Disorders and Stroke (nih.gov).
28. Hereditary orotic aciduria. NORD. September 6, 2018. Available at: Hereditary Orotic Aciduria - Symptoms, Causes, Treatment | NORD (rarediseases.org).
29. Stone W, Basit H, Master S. Gaucher Disease. StatPearls. June 7, 2022. Accessed November 13, 2023. Available at: Gaucher Disease - StatPearls - NCBI Bookshelf (nih.gov).
30. Gaucher disease diagnosis and treatment. National Gaucher Foundation. Accessed November 13, 2023. Available at: Gaucher Disease Diagnosis & Treatment | National Gaucher Foundation.
31. Progeria. Cleveland Clinic. Accessed November 13, 2023. Available at: Progeria (Hutchinson-Gilford Progeria Syndrome — HGPS): Symptoms & Causes (clevelandclinic.org).
32. Ozen A, Comrie WA, Ardy RC et al. CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis. *N Engl J Med* 2017; 377:52-61.
33. U.S. National Library of Medicine ClinicalTrials.gov. An Open-Label Efficacy and Safety Study of Pozelimab in Patients With CD55-Deficient Protein-Losing Enteropathy (CHAPLE Disease). Available at https://www.clinicaltrials.gov/study/NCT04209634?term=NCT04209634&rank=1 (Accessed January 23, 2024)

Table 3. HCPS Coding

Brand Name	Generic Name	HCPCS Code
Gamifant®	emapalumab-lzsg vial	J9210
Nulibry®	fosdenopterin vial	J3490
Veopoz®	pozelimab-bbfg vial	J3590/C9399

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC106.0823	**ANTINEOPLASTIC AGENTS** **OMISIRGE®** (omidubicel-onlv suspension)
Effective Date: 10/1/2023	Review/Revised Date:
	P&T Committee Meeting Date: 08/23
	Original Effective Date: 10/23
	Approved by: Oregon Region Pharmacy and Therapeutics Committee
Robert Gluckman, M.D. **Chief Medical Officer**	Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
A one-time authorization will be approved when the following criteria are met:

1. Documentation of provider determination that patient is eligible for allogeneic hematopoietic stem cell transplant
2. Patient has a hematologic malignancy planned for umbilical cord blood transplantation following myeloablative conditioning
3. Documentation that patient does not have a matched related donor (MRD), matched unrelated donor (MUD), mismatched unrelated donor (MMUD), or haploidentical donor readily available
4. Patient must not have received a prior allogeneic hematopoietic stem cell transplant

EXCLUSION CRITERIA: None

AGE RESTRICTIONS:
May be approved for patients aged 12 years and older

PRESCRIBER RESTRICTIONS:

Must be prescribed by, or in consultation with, an oncologist, immunologist, or hematologist.

COVERAGE DURATION:
Authorization will be limited to one treatment course per lifetime.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:
Omisirge® (Omidubicel-onlv) is a nicotinamide (NAM) modified allogeneic hematopoietic progenitor cell therapy derived from cord blood used as an allogeneic stem cell donor source. Omisirge® is a cell suspension for intravenous infusion. A single dose consists of:

- a Cultured Fraction (CF): a minimum of 8.0×10^8 total viable cells of which a minimum of 8.7% is CD34+ cells and a minimum of 9.2×10^7 CD34+ cells, and
- a Non-cultured Fraction (NF): a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 CD3+ cells

FDA APPROVED INDICATIONS:
For use in adults and pediatric patients 12 years and older with hematologic malignancies who are planned for umbilical cord blood transplantation following myeloablative conditioning to reduce the time to neutrophil recovery and the incidence of infection.

POSITION STATEMENT:

- Hematopoietic cell transplantation (HCT) is the infusion of hematopoietic cells to eliminate disease and achieve adequate hematopoietic immune function

and is potentially curative for patients with certain types of hematologic malignancies and other diseases that cannot be cured with conventional treatments. HCT can be autologous or allogeneic. The most common malignancies treated with allogeneic HCT in 2020 were acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndromes (MDS), while autologous HCT was most frequently used in multiple myeloma (MM), non-Hodgkin lymphoma (NHL), and Hodgkin lymphoma (HL)[9].

- Hematopoietic cells can come from peripheral blood, bone marrow, or umbilical cord blood (UCB). Although an HLA-matched sibling is the preferred donor source for allogeneic HCT, only about 30% of patients have such a donor available[4]. While there is a high likelihood of most HCT candidates being able to find a suitable (HLA-matched or minimally mismatched) adult donor, the likelihood varies significantly between racial and ethnic groups. Whites of European descent have the highest probability of finding an optimal donor, at 75%, and blacks of South or Central American descent have the lowest probability, at 16%[4]. UBC is an important stem cell source for non-White patients who are underrepresented in international adult donor registries.
- Some advantages of using UCB grafts include rapid cell procurement, no harm to mothers and donors, low immunogenicity and less stringent HLA-matching requirements, decreased chronic GvHD, and low relapse rate in minimal residual disease (MRD)[5]. A limitation of UCB transplantation is the limited numbers of hematopoietic cells in each unit, and multiple units are typically required. Additionally, UCB is associated with delayed engraftment, higher risk for graft failure, higher rates of infectious complications, and higher costs. UCB transplantation is generally reserved for patients without an HLA-matched donor[13], however UCB only accounts for approximately 3% of the market share for donor sources.
- Approval for Omisirge® was based on one randomized, open-label, Phase 3 clinical trial: *P0501* (NCT02730299).
    - Study Duration: 42 days, median follow-up of 10 months post transplant
    - Patient population: Patients (N=125) ages 12 to 65 years old with high-risk hematologic malignancies who were candidates for myeloablative allo-HSCT, and had no readily available matched sibling or matched unrelated adult donor.
        - Key exclusions: HLA-matched donor able to donate, prior allo-HSCT
    - Intervention: Patients were randomly assigned to receive: omidubicel (n = 62) or standard umbilical cord blood transplant (UCBT) (n = 63)
    - Primary endpoint: Time to neutrophil engraftment

- Secondary endpoints: Proportion of patients achieving platelet engraftment by Day 42; proportion of patients with Grade 2 or 3 bacterial or invasive fungal infections within the first 100 days after transplant; number of days alive and out of hospital within the first 100 days after transplant.
- Results:
  - Primary Endpoint:

Efficacy Results in Patients Randomized to Receive omidubicel or UCB in Study P0501 (ITT Population)[1,6]

	Omidubicel N=62	**UCB** N=63	**Absolute Difference** (95% CI)	***P* value**
Median time to neutrophil recovery [a,b]	12 days (95% CI: 10-14 days)	22 days (95% CI: 19-25 days)	10 days (95% CI: 6-14 days)	<0.001
Incidence of Grade 2/3 bacterial or Grade 3 fungal infections through 100 days following transplantation	39%	60%	22% (95% CI: 4%-39%)	

[a] Time to neutrophil recovery was defined as the time from transplantation to the earliest of 3 consecutive measurements on different days with absolute neutrophil count greater than or equal to 0.5 Gi/L assessed with 42 days of follow-up.
[b] Median time to neutrophil recovery was estimated by the Kaplan-Meier estimator.
Abbreviation: CI: Confidence interval; UCB: umbilical cord blood

  - Secondary Endpoints:
    - Cumulative incidence of platelet engraftment by Day 42: 55% with omidubicel compared to 35% for standard UCB (P = 0.028).
    - Omidubicel reduced the incidence of Grade 2/3 bacterial or Grade 3 fungal infections (first 100 days) (difference, -22%; 95% CI 4% to 39%)
    - Days out of hospital in first 100 days post transplant: median of 61 days with omidubicel compared to a median of 48 days with UCB (P value for difference = 0.005)
    - Median time from transplant to discharge from the hospital: 27 days with omidubicel versus 35 days with UCB (P = 0.005).
  - Safety:
    - Incidence of aGVHD and cGVHD similar between both groups

- ❖ 11 deaths (17%) among the as-treated population omidubicel group vs 18 deaths (29%) among UCB group. Most common reasons for death included disease relapse and GVHD

REFERENCE/RESOURCES:

1. Omisirge® Package insert. Gamida Cell, Inc. Boston, MA. May 2023.
2. Omisirge® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed June 22, 2023
3. Omisirge® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed June 22, 2023
4. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. N Engl J Med. 2014;371(4):339-348. doi:10.1056/NEJMsa1311707
5. Zhu X, Tang B, Sun Z. Umbilical cord blood transplantation: Still growing and improving. Stem Cells Transl Med. 2021;10 Suppl 2(Suppl 2):S62-S74. doi:10.1002/sctm.20-0495
6. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. Blood 2021; 138 (16): 1429–1440. doi: https://doi.org/10.1182/blood.2021011719
7. Lin C, Scjwarzbach A, Sanz J, et al. Multicenter long-term follow-up of allogeneic hematopoietic cell transplantation with omidubicel: a pooled analysis of five prospective clinical trials [published online ahead of print, 2023 Feb 10]. Transplant Cell Ther. 2023;S2666-6367(23)01071-0. doi:10.1016/j.jtct.2023.01.031
8. Majhail NS, Miller B, Dean R, et al; Hospitalization and Healthcare Resource Use of Omidubicel Vs Cord Blood Transplantation for Hematological Malignancies in a Global Randomized Phase III Clinical Trial. Blood 2021; 138 (Supplement 1): 4036. doi: https://doi.org/10.1182/blood-2021-147480
9. Center for International Blood and Marrow Transplant, a contractor for the C.W. Bill Young Cell Transplantation Program operated through the U. S. Department of Health and Human Services Health Resources and Services Administration. Number of transplants by year: by cell source, disease category and donor type. Updated April 13, 2022. Accessed May 3, 2023. Available at: https://bloodstemcell.hrsa.gov/sites/default/files/bloodstemcell/data/transplant-activity/transplants-year-cell-source-disease-category-donor-type.xlsx
10. Ballen, K. (2017), Umbilical Cord Blood Transplantation: Challenges and Future Directions. STEM CELLS Translational Medicine, 6: 1312-1315. https://doi.org/10.1002/sctm.17-0069.

11. Majhail NS, Mothukuri JM, Brunstein CG, et al. Costs of Hematopoietic Cell Transplantation: Comparison of Umbilical Cord Blood and Matched Related Donor Transplantation and the Impact of Posttransplant Complications. American Society for Blood and Marrow Transplantation. 2009; 15(5):564-573. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S1083879109000548?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1083879109000548%3Fshowall%3Dtrue&referrer=https:%2F%2Fpubmed.ncbi.nlm.nih.gov%2F
12. Ballen KK, Joffe S, Brazauskas R, et al. Hospital Length of Stay in the First 100 Days after Allogeneic Hematopoietic Cell Transplantation for Acute Leukemia in Remission: Comparison among Alternative Graft Sources. Biology of Blood and Marrow Transplantation. 2014; 20(11)1819-1827. https://doi.org/10.1016/j.bbmt.2014.07.021.
13. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™": Hematopoietic Cell Transplantation (HCT), Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf
14. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™": Acute Myeloid Leukemia, Version 3.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
15. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™": Acute Lymphoblastic Leukemia, Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
16. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™": Myelodysplastic Syndromes, Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
17. Kanata AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. 2020; 26(7)1247-1256. DOI:https://doi.org/10.1016/j.bbmt.2020.03.002

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO015.0623	**BIOLOGICAL** **OPHTHALMIC VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS** See Appendix A for medications covered by policy
Effective Date: 8/1/2023  **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 01/18, 05/18, 10/18, 10/19, 10/20, 11/20, 04/21, 07/21, 04/22, 08/22, 11/22, 05/23 (JN) P&T Committee Meeting Date: 02/18, 12/18, 08/19, 12/19, 10/20 (off-cycle), 12/20, 06/21, 08/21, 06/22, 07/22, 08/22, 12/22, 06/23 Original Effective Date: 05/18 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For **initiation of therapy** with the requested medication (new start): Must have one of the following diagnoses and meet any required criteria:
    a. **Neovascular (wet) age-related macular degeneration (AMD):**
        i. For faricimab (Vabysmo®) and brolucizumab (Beovu®): Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
            1) bevacizumab
            2) aflibercept (Eylea®)
            3) ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®)
        ii. For ranibizumab (Lucentis®): Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
            1) bevacizumab

2) aflibercept (Eylea®)
3) ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®)

iii. For ranibizumab implant (Susvimo®):
1) Documentation that bevacizumab and aflibercept (Eylea®) have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient AND
2) Documentation of previous response to at least two intravitreal injections of ranibizumab (Lucentis®), ranibizumab-eqrn (Cimerli®), or ranibizumab-nuna (Byooviz®) AND
3) Documentation that increased risk of endophthalmitis associated with ranibizumab (Susvimo®) has been discussed with the patient

b. **Diabetic macular edema or Diabetic retinopathy:**
i. For faricimab (Vabysmo®) and brolucizumab (Beovu®):
Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
1) bevacizumab
2) aflibercept (Eylea®)
3) ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®)

ii. For ranibizumab (Lucentis®):
Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
1) bevacizumab
2) aflibercept (Eylea®)
3) ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®)

c. **Macular edema following retinal vein occlusion:**
i. For ranibizumab (Lucentis®):
Documentation that ALL the following agents have been ineffective, not tolerated, or contraindicated or rationale is provided why therapy is not appropriate for the patient:
1) bevacizumab
2) aflibercept (Eylea®)
3) ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®)

d. **Myopic Choroidal Neovascularization (mCNV):**
   i. For ranibizumab (Lucentis®):
   Documentation that ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®) has been ineffective, not tolerated, or contraindicated or rationale is provided why therapy with ranibizumab-nuna (Byooviz®) or ranibizumab-eqrn (Cimerli®) is not appropriate for the patient

2. For **patients established on therapy** with the requested agent (within the previous year): Documentation of positive response to therapy (such as stabilization or improvement in vision)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed and administered by an ophthalmologist or retinal specialist

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMITS:
Approval may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines and are subject to medical claims audits. (See Table 1 for dosing guidelines)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO015	BIOLOGICAL OPHTHALMIC VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) INHIBITORS See Appendix A for medications covered by policy

INTRODUCTION:
Brolucizumab (Beovu®), ranibizumab (Lucentis®), ranibizumab-eqrn (Cimerli®), aflibercept injection (Eylea®), ranibizumab-nuna (Byooviz®), ranibizumab (Susvimo®), and faricimab (Vabysmo®) are vascular endothelial growth factor (VEGF) inhibitors used for the treatment of a variety of ophthalmic conditions. These products are administered by intravitreal injection. Ranibizumab (Susvimo®) is an intravitreal injection that is injected via the Susvimo® ocular implant.

FDA APPROVED INDICATIONS:
Brolucizumab (Beovu®)
- Neovascular (Wet) Age-related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)

Ranibizumab (Lucentis®) and Ranibizumab-eqrn (Cimerli®)
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

Aflibercept (Eylea®)
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Retinopathy of Prematurity (ROP)

Ranibizumab – nuna (Byooviz®)
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Myopic Choroidal Neovascularization (mCNV)

Ranibizumab (Susvimo®)
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)

Faricimab (Vabysmo®)
- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Diabetic Macular Edema (DME)

POSITION STATEMENT:
- Age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME) are leading causes of blindness and severe visual impairment. Intravitreal injection of a VEGF inhibitor is an effective therapy and first line treatment for these conditions. VEGF inhibitors work to improve visual

acuity by reducing leakage from blood vessels, preventing proliferation of new abnormal vessels and decreasing swelling of the retina.

- Ranibizumab is a recombinant monoclonal antibody, ophthalmic VEGF Inhibitor. Ranibizumab has been approved by the FDA for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR) and Myopic Choroidal Neovascularization (mCNV).
- Aflibercept is a fully human recombinant fusion protein that inhibits VEGF. It is approved by FDA for AMD, RVO and DME.
- Pegaptanib is an aptamer, a pegylated modified oligonucleotide, which is a selective VEGF antagonist. It is FDA approved only for the treatment of AMD. Of note, pegaptanib (Macugen®) has discontinued marketing status per the FDA.
- Brolucizumab recombinant human vascular endothelial growth factor inhibitor. Brolucizumab-dbll is a humanized monoclonal single-chain Fv (scFv) antibody fragment
- Bevacizumab is the full-length monoclonal antibody from which ranibizumab is derived. It is FDA approved for intravenous treatment of various malignancies. However, it is also used off-label for AMD, DME, RVO and DR. While bevacizumab use is off-label it is listed in national treatment guidelines and is recognized by the Centers for Medicare and Medicaid Services as a safe and effective treatment option for wet AMD, DME, and RVO.
- Aflibercept, bevacizumab, pegaptanib and ranibizumab all work using the same mechanism of action; by binding to the receptor binding site of active forms of VEGF-A.
- Brolucizumab was compared to aflibercept in the HAWK and HARRIER trials for the treatment of wet AMD. Brolucizumab was non-inferior to aflibercept in mean best-corrected visual acuity (BCVA) change from baseline to Week 48. Brolucizumab showed greater reduction in central subfield thickness (CST), and fewer patients had intra-retinal (IRF) and/or sub-retinal fluid (SRF) compared to the aflibercept treated patient. Brolucizumab was also compared to aflibercept in the KESTREL and KITE trials for the treatment of DME. In both studies, BEOVU was non-inferior to aflibercept for the change in BCVA from baseline to Week 52.
- For treatment of wet AMD, there have been two (2) controlled trials which found that aflibercept was similar to bevacizumab in effectiveness. The NIH-sponsored Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration CATT study suggest that there were no major differences with respect to vision related outcomes between the therapies after one year of treatment. The American Academy of Ophthalmology (AAO) guidelines recommend aflibercept, bevacizumab or ranibizumab for the treatment of wet AMD. The AAO does not recommend the use of pegaptanib in the treatment of

as the other therapies have been shown to provide greater benefit with less toxicity.

- For treatment of DME there was a large 1-year study sponsored by the NIH that randomized 660 adults with diabetic macular edema to intravitreal aflibercept 2 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg every 4 weeks. In patients with mild initial visual acuity loss (visual acuity letter score 69-78), there were no significant differences in mean visual acuity at 1 year between the three groups. In patients with a visual acuity letter score <69, the mean improvement was significantly better with aflibercept (18.9 letters) than with ranibizumab (14.2) or bevacizumab (11.8). The American Academy of Ophthalmology guidelines support the use of aflibercept, bevacizumab or ranibizumab in the treatment of DME.
- Safety: There is low certainty in the evidence demonstrating differences in adverse events between intravitreal VEGF inhibitors. Bevacizumab must be compounded and repackaged and therefore there may be safety concerns of using this product. However, The American Society of Retina Specialists has published online safety information about compounding pharmacies to help retina specialists choose high-quality providers of bevacizumab. The FDA has Draft Guidance regarding drug compounding and repackaging of biologics to further standardize quality of bevacizumab. Furthermore, a 2015 study comparing injections of bevacizumab and injections of aflibercept, found that compounded bevacizumab was not linked to a higher risk of eye infection versus those treated with aflibercept. Rates of serious eye infection were 0.017 percent for compounded bevacizumab and 0.025 percent for aflibercept.
- Retina specialists are responsible for the quality and safety of any compounded drug that they administer to a patient. The AAO has the following recommendations for sourcing bevacizumab:
    - Select a compounding pharmacy accredited by the PCAB, which adheres to quality standards for aseptic compounding of sterile medications (USP <797>). Please note: PCAB does not track or keep record of specific medications that a pharmacy can compound.
    - Record the lot numbers of the medication in the patient's record and in a logbook or spreadsheet in case the numbers are needed for tracking later.
- For payment guidance for bevacizumab given via intravitreal injection see payment policy 97.0 Compound Drugs Administered in the Physician's Office

Table 1: Recommended Dosing Regimen

Drug	Indication	Dosing Regimen
Brolucizumab (Beovu®)	AMD	6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first three

Drug	Indication	Dosing Regimen
		doses, followed by 6 mg (0.05 mL) by intravitreal injection once every 8-12 weeks
	DME	6 mg (0.05 mL of 120 mg/mL solution) every six weeks (approximately every 39-45 days) for the first five doses, followed by one dose of 6 mg (0.05 mL of 120 mg/mL solution) by intravitreal injection every 8-12 week
Ranibizumab (Lucentis®) Ranibizumab-eqrn (Cimerli®)	AMD	0.5 mg (0.05 mL of a 10 mg/mL solution) once a month (about every 28 days) **Alternative dosing:** Once monthly injections for three months followed by 4-5 doses dispersed among the following nine months Or Treatment may be reduced to one injection every three months' after the first 4 injections if monthly injections are not feasible
	RVO	0.5 mg (0.05 mL of a 10 mg/mL solution) every 28 days
	DME or DR	0.3 mg (0.05 mL of 6 mg/ml solution) every 28 days
	mCNV	0.5 mg (0.05 mL of a 10 mg/mL ranibizumab solution) once a month for up to 3 months; may retreat if needed
Aflibercept (Eylea®)	AMD	2 mg (0.05 mL) once a month for three months then once every two months. Some patients may need every four weeks (monthly) dosing after the first 12 weeks (three months). Although not as effective as the recommended every eight week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy
	RVO	2 mg (0.05 mL) once a month
	DME or DR	2 mg (0.05 mL) once a month for five months then once every two months
	ROP	0.4mg (0.01 mL or 10 microliters). Treatment interval between doses in same eye should be at least 10 days
Ranibizumab (Susvimo®)	AMD	2 mg (0.02 mL of 100mg/mL solution) continuously delivered via the Susvimo® ocular implant with

Drug	Indication	Dosing Regimen
		refills administered every 24 weeks (approximately six months)
Ranibizumab-nuna (Byooviz®)	AMD	Once a month
	RVO	Once a month
	mCNV	Once a month
Faricimab (Vabysmo®)	AMD	6 mg (0.005 mL of 120 mg/mL solution) every four weeks for the first four doses. Additional efficacy was not demonstrated when dosed every four weeks compared to every eight weeks, some patients may need every four weeks (monthly) dosing after the first four doses.
	DME	1). 6 mg (0.05 mL of 120 mg/mL solution) administered every four weeks for at least four doses. If resolution of edema, can be dosed every four weeks or every eight weeks 2). 6 mg dose every eight weeks Additionally, efficacy was not demonstrated in most patients when dosed every four weeks compared to every eight weeks, some patients may need every four weeks dosing after the first doses.

Table 2. Indications

Drug	Neovascular (Wet) Age-related Macular Degeneration (AMD)	Macular Edema Following Retinal Vein Occlusion (RVO)	Diabetic Macular Edema (DME)	Diabetic Retinopathy (DR)	Myopic choroidal Neovascularization (mCNV)	Retinopathy of Prematurity (ROP)
Bevacizumab (Avastin®)	**X****	**X****	**X****	**X****		
Brolucizumab (Beovu®)	**X**		**X**			
Ranibizumab (Lucentis®)	**X**	**X**	**X**	**X**	**X**	
Ranibizumab-eqrn (Cimerli®)	**X**	**X**	**X**	**X**	**X**	
Ranibizumab-nuna (Byooviz®)	**X**	**X**			**X**	
Ranibizumab (Susvimo®)	**X**					

Aflibercept (Eylea®)	**X**	**X**	**X**	**X**		**X**
Pegaptanib (Macugen®)*	**X**					
Faricimab (Vabysmo®)	**X**		**X**			

*Discontinued marketing status as per the FDA; **Off-label FDA Uses

Table 3: List of Covered Diagnoses and Synonyms

Covered Diagnosis	Synonyms
Neovascular (wet) age-related macular degeneration	Exudative senile macular degeneration Age-related macular degeneration (ARMD) Choroidal neovascularization (CNV)
Diabetic Macular Edema and Diabetic Retinopathy	Diabetic macular edema (DME) associated with diabetic retinopathy DME due to Type 1 or Type 2 diabetic retinopathy DME due to nonproliferative or proliferative diabetic retinopathy (mild, moderate, or severe) Center involving diabetic macular edema Diabetic retinal edema Clinically significant diabetic macular edema (CSME)
Macular edema associated with Retinal Vein Occlusion	Macular edema associated with central retinal vein occlusion (CRVO) Macular edema associated with branch retinal vein occlusion (BRVO) Macular edema associated with tributary (branch) retinal vein occlusion
Myopic choroidal neovascularization	Choroidal neovascularization secondary to pathologic myopia (mCNV)
Retinopathy of prematurity	Retrolental firoplasia (RLF) Terry syndrome

REFERENCES:

1. Eylea package insert. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2023 Feb.

2. Lucentis package insert. South San Francisco, CA: Genentech Inc.; 2020 October.
3. Susvimo package insert. South San Francisco, CA: Genentech Inc.; 2022 April.
4. Vabysmo package insert. South San Francisco, CA: Genentech Inc.; 2022 February.
5. Cimerli package insert. Redwood City, CA: Coherus BioSciences, Inc.; 2022 August.
6. Bevacizumab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
7. Arroyo JG. Age-related macular degeneration: Treatment and prevention. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on November 29, 2017.)
8. American Academy of Ophthalmology-Preferred Practice Patterns (AAO-PPP) Retina/Vitreous Panel, Hoskins Center for Quality Eye Care. Age-Related Macular Degeneration PPP – Update 2015. Jan 2015.
9. American Academy of Ophthalmology-Preferred Practice Patterns (AAO-PPP) Retina/Vitreous Panel, Hoskins Center for Quality Eye Care. Diabetic Retinopathy PPP – Update 2016. Feb 2016.
10. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. The IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC. Ophthalmology. 2012;7:1399-1411.
11. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, Ying GS, Jaffe GJ, et al. Ranibizumab and Bevacizumab for Treatment of Neovascular Age-related Macular Degeneration: Two-Year Results. Ophthalmology; 2012;7:1388-98.
12. SD Solomon et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. Cochrane Database Syst Rev 2014 Aug 29; 8:CD005139.
13. The Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med 2015 Feb 18.
14. [Beovu®] package insert. East Hanover, NJ: Novartis Pharmaceutical Corporation. May 2021
15. Dugel PU, Koh A, Ogura Y, et al.: HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology. 2019; pii: S0161-6420(18)33018-5. 10.1016/j.ophtha.2019.04.017

16. FDA approved first biosimilar to treat macular degeneration disease and other eye conditions. U.S. Food & Drug Administration. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-biosimilar-treat-macular-degeneration-disease-and-other-eye-conditions. (Accessed on April 24, 2022).

APPENDIX A.

Brand Name	Generic Name	Q-Code/J-Code
Preferred Products – No Prior Authorization Required		
Byooviz®	ranibizumab-nuna injection	Q5124
Cimerli®	ranibizumab-eqrn vial	Q5128
Compounded Avastin®	bevacizumab	J7999
Eylea®	aflibercept injection / syringe	J0178
Non-Preferred Products – Prior Authorization/Step Therapy Required		
Beovu®	brolucizumab injectable	J0179
Lucentis®	ranibizumab injection	J2778
Susvimo®	ranibizumab injection and implant	J2779
Vabysmo®	faricimab	J2777

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH018.1023	**MISCELLANEOUS PRODUCTS** **ORAL RINSES** Products: Aquoral, Caphosol, Episil, Gelclair, Gelx, Mugard, Neutrasal
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 01/17, 07/17, 07/18, 07/19, 09/19, 08/20, 09/21, 09/22, 08/22 (MTW) P&T Committee Meeting Date: 02/17, 08/17, 08/18, 08/19, 10/19, 10/20, 10/21, 10/22, 10/23 Original Effective Date: 04/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
Must be in accordance with use authorized by the FDA. Covered uses are limited to:
- Mucositis/stomatitis secondary to chemotherapy or radiation
- Xerostomia secondary to chemotherapy or radiation
- Sjögren's syndrome

REQUIRED MEDICAL INFORMATION:
For mucositis/stomatitis secondary to chemotherapy or radiation
1. Diagnosis of mucositis/stomatitis secondary to chemotherapy or radiation

AND

2. Documented trial of TWO of the following:
    a. Over-the-counter oral anesthetics (such as OraGel®, Anbesol®)
    b. Prescription oral anesthetics (such as viscous lidocaine 2%)
    c. Saliva substitutes (such as Biotene®, Mouth Kote®)
    d. Magic mouthwash - a compounded product often containing viscous lidocaine, Maalox®, and diphenhydramine. Multiple formulations are compounded and these may contain different ingredients. Note: premeasured kits for these solutions are not available on formulary
3. For Aquoral®, Caphosol®, Episil®, Gelx®, Mugard®, Neutrasal®: Trial and failure, intolerance, or contraindication to Gelclair®

Reauthorization requires:
1. Documentation of continued need for therapy (such as continued chemotherapy and/or radiation)
2. Documentation of initial response to therapy (such as reduced signs and symptoms of mucositis, increased ability to tolerate food and beverages)

For xerostomia secondary to chemotherapy or radiation and Sjögren's syndrome
1. Diagnosis of one of the following: xerostomia secondary to chemotherapy, xerostomia secondary to radiation, or Sjögren's syndrome

AND
2. Documented trial to both of the following:
    a. TWO over the counter saliva substitutes (such as Biotene®, Mouth Kote®)
    b. Saliva stimulants (such as sugar free lozenges or chewing gum)

Reauthorization requires:
1. Documentation of continued need for therapy (e.g., continued chemotherapy and/or radiation)
2. Documentation of initial response to therapy (e.g., reduced signs and symptoms of xerostomia, increased ability to tolerate food and beverages)

EXCLUSION CRITERIA:
Other indications not outlined above

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
1. For mucositis/stomatitis and xerostomia secondary to chemotherapy or radiation initial authorization and reauthorization will be approved for six months.
2. For Sjögren's syndrome initial authorization and reauthorization may be reviewed annually to assess continued medical necessity and effectiveness of medication.

QUANTITY LIMIT:
Gelclair: Three single-use packets (45 mL) per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy

document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

The products on this policy are classified as medical devices, and therefore, do not have an active drug ingredient. These products have differing ingredients that produce a protective layer over the oral cavity. The products claim to form a barrier that can reduce pain and enable patients to eat and drink more easily. These products require a written prescription for dispensing.

FDA APPROVED INDICATIONS:

These products are approved by the FDA as medical devices and do not have approval as drug products.

- Aquoral®: Intended to provide relief from chronic and temporary xerostomia (dry mouth). which may be a result of disease such as Sjogren's, oral inflammation, medication, chemo or radiotherapy, stress, or aging. Aquoral® relieves symptoms of dry mouth such as difficulties in swallowing, speech, and changes in taste.
- Caphosol®:
    - Indicated for dryness of the mouth or throat (hyposalivation, xerostomia), regardless of the cause and regardless of whether the condition is temporary or permanent. Caphosol® is also indicated as an adjunct to standard oral care in treating the mucositis that may by caused by radiation or high dose chemotherapy.
    - May be used for relief of dryness of the oral mucosa when hyposalivation results from the following: surgery, radiotherapy near the salivary glands, chemotherapy; infection or dysfunction of the salivary glands; inflammation of the mouth or throat; fever; emotional factors such as fear or anxiety: obstruction of the salivary ducts: Sjogren's syndrome; and Bell's Palsy.

  - Also indicated for dryness of the oral mucosa due to drugs such as antihistamines or atropine or other anticholinergic agents that suppress salivary secretion.

- Episil®: Indicated for the management of pain and relief of pain, by adhering to the mucosal surface of the mouth, soothing oral lesions of various etiologies, including oral mucositis/stomatitis (may be caused by chemotherapy or radiotherapy).

- Gelclair®: Indicated for the management of pain and relief of pain, by adhering to the mucosal surface of the mouth, soothing oral lesions of various etiologies, including oral mucositis/stomatitis (caused by chemotherapy or radiotherapy), irritation due to oral surgery, and traumatic ulcers caused by braces or ill-fitting dentures, or disease. Also indicated for diffuse aphthous ulcers.

- Gelx®: Indicated for the management of pain and relief of pain, by adhering to the mucosal surface of the mouth, soothing oral lesions of various etiologies, including: oral mucositis/stomatitis (caused by chemotherapy or radiotherapy), irritation due to oral surgery, and traumatic ulcers caused by braces or ill-fitting dentures, or disease. Also indicated for diffuse aphthous ulcers.

- Mugard®: Indicated for the management of oral mucositis/stomatitis (that may be caused by radiotherapy and/or chemotherapy) and all types of oral wounds (mouth sores and injuries), including aphthous ulcers/canker sores and traumatic ulcers, such as those caused by oral surgery or ill-fitting dentures or braces.

- Neutrasal®:
  - (OTC) Neutrasal® is indicated for the dryness of the mouth (hyposalivation, xerostomia), dryness of the oral mucosa due to drugs such as antihistamines or atropine or other anticholinergic agents that suppress salivary secretion and may be used as part of an oral hygiene program for patients with dry mouth. Neutrasal® also provides intensive hygiene of the oral cavity.
  - (Rx): Neutrasal® is indicated as an adjunct to standard oral care in relieving the discomfort associated with oral mucositis that may be caused by radiation or high dose chemotherapy. Rx Neutrasal® may be used for relief of dryness of the oral mucosa when hyposalivation results from the following: surgery, radiotherapy near the salivary glands, chemotherapy, infection or dysfunction of the salivary glands; fever; emotional factors

such as fear or anxiety; obstruction of the salivary ducts; Sjogren's syndrome.

POSITION STATEMENT:
There is limited clinical evidence supporting the use of these types of products and no evidence to support the use of these agents over other standard of care regimens.

These products are approved medical devices. If approved, they may be processed at a pharmacy for the appropriate medical benefit cost-share and will apply to medical expenses.

European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment, and follow-up for oral and gastrointestinal mucositis
Oral mucositis is a common complication of head and neck radiation and high-dose chemotherapy (e.g., 5-FU, irinotecan, capecitabine). The pain severity can lead to requirement of enteral nutrition support as well as escalated doses of opioid analgesics. In addition, some of the newer oncology agents, such as tyrosine kinase inhibitors (TKIs) and mTOR inhibitors, have led to oral and gastrointestinal mucositis despite their targeted approach to therapy.

Prevention is a key component to reducing the severity of mucositis side effects. These include reducing the sources of trauma (ill-fitting prostheses), eliminating extreme temperature foods/beverages, proper oral hygiene, and regular checking of the oral mucosa. Oral rinses (alcohol-free) are recommended to be used at least four times a day for about one minute each time, after brushing teeth. Due to conflicting evidence, there is not a recommended oral rinse and the ESMO guidelines state that plain water can be used, although they prefer saline rinses for target therapies (e.g., TKIs and mTOR inhibitors).

For the treatment of oral mucositis, the guidelines focus on preventing infection with various antibacterial rinses. These guidelines do not mention the products outlined on this policy.

Additional organizations providing guidance on oral mucositis in cancer patients including the Multinational Association of Supportive Care in Cancer/ International Society of Oral Oncology (MASCC/ISOO) and National Comprehensive Cancer Network (NCCN) do not provide recommendations in regards to these agents due to lack of quality evidence.

The Sjögren's Foundation Clinical practice guidelines for oral management of Sjörgen disease: Dental caries prevention, recommend increasing saliva through gustatory, masticatory and pharmaceutical agents. Recommended pharmaceutical agents are saliva stimulants such as sugar free lozenges or chewing gum; pilocarpine; and cevimeline. The guidelines do not give any recommendations around saliva substitutes. The European League Against Rheumatism (EULAR) provides recommendations for treatment of oral dryness based upon severity of gland dysfunction. Saliva substitutes are only recommended for severe dysfunction and non-responders to other treatment options.

REFERENCE/RESOURCES:

1. Peterson DE, Boers-Doets CB, Bensadoun RJ et al. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2015; 26 (suppl 5): v139-v151.
2. Yarom N, Hovan A, Bossi P, et al. Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines-part 1: vitamins, minerals, and nutritional supplements. *Support Care Cancer*. 2019;27(10):3997-4010. Available from: https://pubmed.ncbi.nlm.nih.gov/31286229/. Accessed Sept 9, 2021.
3. Saunders DP, Epstein JB, Elad S, et al. Systematic review of antimicrobials, mucosal coating agents, anesthetics, and analgesics for the management of oral mucositis in cancer patients. *Support Care Cancer*. 2013;21(11):3191-3207. Available from: https://pubmed.ncbi.nlm.nih.gov/23832272/. Accessed Sept 9, 2021.
4. Bensinger W, Schubert M, Ang KK *at al*. NCCN task force report: prevention and management of mucositis in cancer care. *J Natl Compr Canc Netw.* 2008; 6 Suppl 1:S1.
5. Zero DT, Brennan MT, Daniels TE, *et al*. Clinical practice guidelines for oral management of sjögren disease: dental caries prevention. *J Am Dent Assoc* 2016;147:295–305. Available from: https://pubmed.ncbi.nlm.nih.gov/26762707/. Accessed Sept 9, 2021.
6. Ramos-Casals M, Brito-Zerón P, Bombardieri S On behalf of the EULAR-Sjögren Syndrome Task Force Group*, et al.* EULAR recommendations for theD management of Sjögren's syndrome with topical and systemic therapies. *Annals of the Rheumatic Diseases.* 2020;79:3-18.
7. Fortovia Therapeutics, Inc. GelClair. Available at http://www.gelclair.com (Accessed Sept 9, 2021)
8. EUSA Pharma. Caphosol. Available at https://eusapharma.com/our-focus/our-products (Accessed Sept 9, 2021)

9. Camurus AB. Episil. Available at https://www.episil.net/ (Accessed Sept 14, 2023)
10. USWM, LLC. Gelx. Available at https://gelxuk.com/hcp/what-is-gelx/ (Accessed Sept 9, 2021)
11. OraPharma. Neutrasal. Available at http://www.neutrasal.com/ (Accessed Sept 9, 2021)
12. U.S. Food & Drug Administration 510(k) Premarket Notification database. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm (Accessed Sept 18, 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND STEP THERAPY CRITERIA ORPTCEND077.0423	**ENDOCRINE & METABOLIC AGENTS** **OSTEOANABOLIC AGENTS** **Evenity®** (romosozumab-aqqg for subcutaneous injection)
Effective Date: 6/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 03/23 (KH) P&T Committee Meeting Date: 04/22, 04/23 Original Effective Date: 06/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit

REQUIRED MEDICAL INFORMATION:
For the treatment or prevention of osteoporosis

1. Must meet ONE of the following criteria (a-e):
    a. Patient has a history of multiple or severe vertebral fractures, or history of fragility fractures
    b. Patient has a spine or hip bone mineral density (BMD) T-score less than or equal to -3.0
    c. Patient has a spine or hip bone mineral density (BMD) T-score less than or equal to -2.5 to -3.0 and high risk for fracture, defined as one of the following:
        i. Age more than 80 years
        ii. Chronic glucocorticoid use
        iii. Documented increased fall risk
    d. Patient has a spine or hip BMD T-score less than or equal to -2.5 to -3.0 and one of the following:

i. Documented failure to anti-resorptive therapy (such as denosumab, bisphosphonates). Failure is defined as a new fracture or worsening BMD while adherent to therapy
ii. Documented contraindication or intolerance to therapy with **all** the following: 1. denosumab, 2. oral bisphosphonate (such as alendronate), and 3. IV bisphosphonate therapy (such as zoledronic acid)

e. Patient has a spine or hip BMD T-score between -1.0 and -2.5 and **BOTH** of the following:
   i. Fracture Risk Assessment (FRAX) probability score for hip fracture of at least 3% or, for other major osteoporosis fracture, of at least 20%
   ii. One of the following:
      1. Documented failure to anti-resorptive therapy (such as denosumab, bisphosphonates). Failure is defined as a new fracture or worsening BMD while adherent to therapy
      2. Documented contraindication or intolerance to therapy with **all** the following:
         a. Denosumab
         b. Oral bisphosphonate (such as alendronate)
         c. IV bisphosphonate therapy (such as zoledronic acid).

EXCLUSION CRITERIA:
For Evenity®: Myocardial infarction or stroke within the preceding year, hypocalcemia

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an endocrinologist or rheumatologist

COVERAGE DURATION:
May be approved for up to one year, ensuring the total duration of Evenity® therapy does not exceed one year of total therapy duration.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

PHARMACY PRIOR AUTHORIZATION POLICY AND STEP THERAPY CRITERIA ORPTCEND077	ENDOCRINE & METABOLIC AGENTS OSTEOANABOLIC AGENTS **Evenity®** (romosozumab-aqqg for subcutaneous injection)

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Evenity® (romosozumab) is a monoclonal antibody (IgG2) that increases bone formation and, to a lesser extent, decreases bone resorption by binding to and inhibiting sclerostin. Evenity® is an anabolic osteoporosis medication with a unique mechanism of action compared to current anabolic agents on the market, abaloparatide (Tymlos®) and teriparatide (Forteo®). Evenity® is administered subcutaneously every month for a total therapy duration of 12 months and should be administered by a health care professional. The bone-building effect of Evenity® is gradually lost with continuous treatment; therefore, therapy is given for only 12 months. It is then necessary to follow that course of Evenity® with an anti-remodeling agent such as a bisphosphonate or denosumab to maintain or improve the gains in bone mineral density and protection from fracture.

FDA APPROVED INDICATIONS:

Treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.

POSITION STATEMENT:

The 2020 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) osteoporosis guidelines recommend that all postmenopausal women over the age of 50 be screened for osteoporosis risk. Treatment is recommended if the individual has osteoporosis or has osteopenia. First line agents that are recommended include alendronate, risedronate, zoledronic acid, and denosumab. The guidelines additionally recommend medications based on fracture risk. For individuals who have low to moderate risk of fracture, alendronate and risedronate are recommended. For individuals with highest risk of fracture and unable to use oral therapy, abaloparatide, denosumab, romosozumab, teriparatide, and zoledronic acid are recommended. The AACE/ACE guidelines further state that ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy. Raloxifene is not recommended for use in the ACP guidelines.

Evenity®

- There is moderate quality evidence that romosozumab may reduce vertebral fractures risks based on two phase 3, double-blind, multicenter, randomized clinical trials, FRAME and ARCH, that showed statistically significant fewer occurrences of new vertebral fractures at either 12 or 24 months in postmenopausal women ages 55 to 90 years.
- The FRAME trial (Trial 1) demonstrated moderate quality evidence in romosozumab compared to placebo in postmenopausal women with bone mineral density (BMD) T-score less than or equal to -2.5 at the total hip or femoral neck. Romosozumab compared to placebo had statistically significantly lower new vertebral fractures at 12 months (0.5% vs 1.8%, respectively; 95% CI, 0.16 to 0.47; $p < 0.001$) and at 24 months with romosozumab or placebo therapy followed by denosumab (0.6% vs 2.5%, respectively; 95% CI, 0.16 to 0.40; $p < 0.001$). Most common adverse reactions (>5%) included arthralgia and headache. Two cases of osteonecrosis of the jaw occurred both happening 12 months after therapy of romosozumab with one case occurring after one dose of denosumab. In summary, the FRAME trial was a large-scale trial that showed romosozumab does have benefit after the one year of total therapy duration. Some limitations of the trial include high risk fracture patients were excluded and the study population was not representative of the US population with only 3% of patients being studied in North America and most patients (43%) studied in Central/Latin America.
- The ARCH trial (Trial 2) demonstrated moderate quality evidence in romosozumab compared to oral alendronate 70 mg weekly in postmenopausal women with bone mineral density (BMD) T-score less than or equal to -2.5 at the total hip or femoral neck and either one moderate or severe vertebral fracture or two mild vertebral fractures, or BMD T-score less than or equal to -2.0 at the hip or femoral neck and either two moderate or severe vertebral fractures or a history of a proximal femur fracture. Romosozumab significantly reduced the incidence of new vertebral fractures compared to alendronate at 24 months (6.2% vs. 11.9%, respectively; 95% CI, 0.40 to 0.66; $p < 0.001$). A serious safety concern that led to the placement of the boxed warning for cardiovascular events was 2.5% of serious cardiovascular events at month 12 occurred in the romosozumab followed by alendronate group compared to 1.9% serious cardiovascular events occurring in the alendronate alone group. Most common adverse reactions (>5%) in the ARCH trial included arthralgia and headache. One case of osteonecrosis of the jaw occurred in both groups as well as 2 events

of atypical femoral fracture in the romosozumab group and 4 cases of atypical femoral fracture in the alendronate group. The ARCH trial's strengths included a population that had a higher risk of fractures and did use an active comparator. Some limitations include not using an active comparator more appropriate for high-risk fractures, such as IV bisphosphonates (e.g., zoledronic acid) or denosumab, and only 2% of the study setting was in North America with 40% being in Central or Eastern Europe.

- Additionally, per the prescribing information, Evenity should have a limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered.
- Summary of Safety:
    - Boxed warning for major cardiac events (do not initiate in patients who have had a myocardial infarction or stroke within the preceding year)
    - Serious warnings and precautions include hypersensitivity reactions, hypocalcemia, osteonecrosis of the jaw, and atypical subtrochanteric and diaphyseal femoral fractures
    - No risk of osteosarcoma as seen in alternative anabolic agents include abaloparatide (Tymlos®) and teriparatide (Forteo®).
- Pharmacoeconomic Assessment:
    - Romosozumab total cost of therapy (one year) is a shorter duration of therapy and a lower cost of therapy when compared to the total cost of therapy (two years) for abaloparatide or teriparatide.
    - Romosozumab's total cost of therapy is significantly more compared to the yearly cost of therapy of denosumab or zoledronic acid. However, denosumab and zoledronic acid can be given indefinitely while romosozumab's max therapy duration is one year.
- Romosozumab provides efficacious therapy with a different mechanism of action than other anabolic agents, abaloparatide and teriparatide. However, there is insufficient data for long term safety and efficacy beyond 12 months of administration. Therefore, due to romosozumab requiring administration by a medical professional and to ensure appropriate use of this medication, romosozumab is covered under the medical benefit with prior authorization.

- FRAX score assessment tool can be found at FRAX WHO Fracture Risk Assessment Tool website. http://www.sheffield.ac.uk/FRAX/tool.jsp?country=9
- **Drug holidays** - recommendations from the American Association of Clinical Endocrinologists/American College of Endocrinology and the American Society for Bone and Mineral Research

- Bisphosphonates may retain residual benefit after discontinuation
- May consider a drug holiday from bisphosphonates after 5 years of therapy in low-risk patients, but continue treatment up to an additional 5 years if fracture risk remains high. For patients with very high risk of fracture, can consider a bisphosphonate holiday after 6 to 10 years of stability.
- **Drug holidays are NOT recommended for patients on therapies other than bisphosphonates (e.g., denosumab, raloxifene)**
- If a drug holiday is warranted, patients should be re-evaluated at least every 2-3 years, or sooner if clinically appropriate (e.g., new fracture, institution of steroid therapy)

Contraindications to oral bisphosphonate therapy:

- Esophageal abnormalities (e.g., stricture or achalasia) that delay esophageal emptying
- Hypersensitivity to bisphosphonates
- Hypocalcemia; correct prior to initiation of therapy
- Inability to stand or sit upright for 60 minutes after administration of oral tablets

Contraindications to IV bisphosphonate therapy:

- Hypocalcemia
- Creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment due to an increased risk of renal failure
- Hypersensitivity to bisphosphonates

REFERENCE/RESOURCES:

1. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2022.
2. Tymlos® package insert. Waltham, MA: Radius; 2022 Dec.
3. Forteo® package insert. Indianapolis, IN: Eli Lilly and Company; 2015 Feb.
4. Evenity® package insert. Thousand Oaks, CA: Amgen Inc; 2020 Apr.
5. Tymlos® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed March 4, 2023.
6. Tymlos® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed March 4, 2023.
7. Evenity® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed March 4, 2023.

8. Evenity® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed March 4, 2023.
9. Miller, Paul D., et al. "Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial." *Jama* 316.7 (2016): 722-733.
10. Cosman, Felicia, et al. "Eighteen months of treatment with subcutaneous abaloparatide followed by 6 months of treatment with alendronate in postmenopausal women with osteoporosis: results of the ACTIVExtend trial." *Mayo Clinic Proceedings*. Vol. 92. No. 2. Elsevier, 2017.
11. American Association of Clinical Endocrinologists (AACE) and American College Of Endocrinology (ACE). AACE/ACE Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis — 2020 Update. Available at https://pro.aace.com/sites/default/files/2020-05/Vol%2026%20Supplement%201%20(May%202020)%20GL-2019-0524_0.pdf (Accessed March 4, 2022)
12. Liel, Yair. Opinion piece of Teriparatide vs risedronate for osteoporosis. Lancet. Vol 391. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2818%2930754-2. (Accessed March 4, 2022).
13. Endocrine Society. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline J Clin Endocrinol Metab, May 2019, 104(5):1595–1622.
14. Kendler D, Marin F, Zerbini C, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): A multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2017 [Epub ahead of print].
15. Managing Patients on Long-Term Bisphosphonate Treatment: American Society for Bone and Mineral Research, 2015.
16. Oregon Health Authority. Drug class update with new drug evaluation: bone metabolism drugs. Available at https://www.orpdl.org/durm/meetings/meetingdocs/2019_09_26/drafts/BoneMetabolism_ClassUpdate.pdf (Accessed March 4, 2022).
17. Anabolic therapies for osteoporosis in postmenopausal women: effectiveness and value. Institute for Clinical and Economic Review. Available at https://icer-review.org/wp-content/uploads/2016/11/CTAF_Osteoporosis_Draft_Evidence_Report_050317.pdf (Accessed March 4, 2022).
18. Cosman F., Crittenden D.B, Adachi J.D., et al. “Romosozumab treatment in postmenopausal women with osteoporosis.” The New England Journal of Medicine. Vol. 375 (2016): 1532-1543.

19. Saag K.G, Peterson J., Brandi M.L., et al. “Romosozumab or alendronate for fracture prevention in women with osteoporosis. The New England Journal of Medicine. Vol. 377 (2017): 1417-1427.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCGEN008.0224	**GENITOURINARY AGENTS** **OXLUMO®** (lumasiran injection solution)
Effective Date: 4/1/2024	**Review/Revised Date**: 02/21, 07/21, 01/22, 01/23, 12/23 (MTW)
Original Effective Date: 04/21	**P&T Committee Meeting Date**: 02/21, 08/21, 02/22, 02/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For **initiation of therapy** (new starts), all the following criteria must be met:
    a. Patient has a diagnosis of primary hyperoxaluria type 1 (PH1), confirmed by one of the following:
        i. Genetic testing demonstrating mutation in the alanine: glyoxylate aminotransferase (AGXT) gene
        ii. Liver biopsy demonstrating significantly decreased or absent alanine: glyoxylate aminotransferase (AGT) enzyme activity
    b. Documentation of one of the following:
        i. Elevated urine oxalate (UOx) excretion as measured by body surface area-normalized daily UOx output greater than upper limit of normal (ULN)
        ii. Elevated UOx excretion as measured by UOx: creatinine ratio above age-specific upper limit of normal (ULN) OR
        iii. Elevated plasma oxalate (POx) concentration (POx concentration greater than ULN)
    c. Documentation of a trial of high fluid intake of at least three liters per meter-squared of Body Surface Area (BSA) per day and that high fluid intake will continue with therapy

   d. Concurrent use of pyridoxine or previous trial of at least three months with no significant improvement in urine oxalate concentration
   e. Documentation of current patient weight and dosing not exceeding FDA-recommended dosing
2. For patients **established on therapy** (within the previous year):
   a. Documentation of a clinically significant reduction in urine or plasma oxalate levels relative to pre-treatment baseline
   b. Patient continues with concurrent high fluid intake (at least three liters per meter-squared BSA per day) and pyridoxine (unless individual is a pyridoxine non-responder)
   c. Documentation of current patient weight and updated dosing not exceeding FDA-recommended dosing

EXCLUSION CRITERIA:
1. Patients with a history of liver transplant
2. Patients with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m2
3. Patients with secondary hyperoxaluria or genetic test positive for another form of primary hyperoxaluria such as type 2 and type 3 primary hyperoxaluria

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a nephrologist or urologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for 12 months

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCGEN008	GENITOURINARY AGENTS **OXLUMO®** (lumasiran injection solution)

INTRODUCTION:
Lumasiran reduces the amount of available glyoxylate, a substrate for oxalate production, by targeting hydroxyacid oxidase 1 (HAO1) messenger RNA in hepatocytes through RNA interference, subsequently decreasing glycolate oxidase enzyme levels.

FDA APPROVED INDICATIONS:
Treatment of primary hyperoxaluria type 1 (PH1) to lower urinary and plasma oxalate levels in pediatric and adult patients

POSITION STATEMENT:
- Primary hyperoxaluria type 1 (PH1) is a rare genetic, metabolic disorder characterized by the hepatic overproduction of oxalate. Oxalate, is poorly soluble and combines with calcium to form kidney and urinary stones. It is a progressive disease that can result in kidney dysfunction and ultimately End Stage Renal Disease (ESRD). As a patient's glomerular filtration rate (GFR) decreases throughout their lifetime, plasma oxalate levels will increase, and calcium oxalate will deposit into other areas of the body, such as the heart, bones, and retina. In the absence of effective treatment, ESRD and/or complications from systemic oxalosis can be fatal.
- There are other types of Primary hyperoxaluria, but PH1 is considered the most severe.
- Lumasiran is the first FDA approved therapy for the treatment of PH1.
- Other therapies include conservative treatment which includes increasing fluid intake to at least 3 L/m2 Body Surface Area (BSA) per day, alkalizing the urine, and trialing pyridoxine.
    - Between 30% and 50% of patients with PH1 may see a response to pyridoxine after three months of treatment.
    - Therapeutic doses of pyridoxine are 5 to 8 mg/kg/day up to a maximum dose of 20 mg/kg/day
- Alkalinizing the urine with potassium citrate can be used to reduce urinary calcium oxalate saturation by forming completes with calcium, which decreases stone formation. Other calcium oxalate crystallization inhibitors include neutral phosphate and magnesium oxide.
- Dialysis is typically started when a patients estimated glomerular filtration rate (eGFR) is between 20 and 30 mL/min/1.72 m2
- Liver transplantation is the only potentially curative option to normalize oxalate production. It has significant risks and limitations but transplantation of liver, kidney or combined liver transplantation can be considered for some patients.
- The efficacy of lumasiran was established based on two small studies, ILLUMINATE-A and ILLUMINATE-B.

- ILLUMINATE-A, was a randomized, double blind, placebo controlled study in 39 patients six years of age and older with PH1. Patients received three loading doses of 3 mg/kg lumasiran or placebo administered once monthly, followed by maintenance doses of 3 mg/kg lumasiran or placebo every three months. The primary endpoint was the percent reduction from baseline in 24-hour urinary oxalate excretion corrected for body surface area (BSA) averaged over months three through six.
    - The least squares (LS) mean percent change from baseline in 24-hour urinary oxalate in the lumasiran group was -65% vs. -12% in the placebo group (between-group LS mean difference of 53%, 95% CI: 45, 62; $p < 0.0001$).
    - By month six, 52% of patients treated with lumarisan achieved a normal 24-hour urinary oxalate corrected for BSA vs. 0% placebo-treated patients ($p = 0.001$).
- ILLUMINATE-B was a single-arm study in pediatric patients less than six years of age with PH1. The primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months three through six.
    - Patients treated with lumasiran achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 71% (95% CI: 65, 77).
- These two studies provide low quality of evidence that lumasiran significantly lowers urinary oxalate (a surrogate marker), compared to placebo, in adult and pediatric patients with PH1 with relatively preserved renal function. Long-term studies are needed to confirm that this therapy will lead to improved outcomes such as preservation of renal function or reduction in kidney stones. Additionally, data is needed for patient with more advanced renal impairment (these patients will be included in the planned ILLUMINATE-C trial).
- The recommended dosing regimen consists of loading doses followed by maintenance doses administered subcutaneously by a healthcare provider as shown in the table below. Dosing is based on actual body weight.

Body weight	**Loading Dose**	**Maintenance Dose (begin 1 month after the last loading dose)**
Less than 10 kg	6 mg/kg once monthly for three doses	3 mg/kg once monthly
10 kg to less than 20 kg	6 mg/kg once monthly for three doses	6 mg/kg once every three months (quarterly)
20 kg and above	3 mg/kg once monthly for three doses	3 mg/kg once every three months (quarterly)

REFERENCE/RESOURCES:

1. OXLUMO (lumasiran) [Package Insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. October 2022.
2. Oxlumo In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed January 5, 2023
3. Oxlumo In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed January 5, 2023
4. Alnylam Pharmaceuticals. A study of lumasiran in infants and young children with primary hyperoxaluria type 1 (ILLUMINATE-B). NLM Identifier: NCT 03905694. Last updated: December 9, 2020. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03905694?term=NCT03905694&draw=2&rank=1. Accessed: January 6, 2021.
5. Alnylam Pharmaceuticals. A study to evaluate lumasiran in children and adults in primary hyperoxaluria type 1 (ILLUMINATE-A). NLM Identifier: NCT 03681184. Last updated: November 17, 2020. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03681184?term=03681184&draw=2&rank=1. Accessed: January 6, 2021.
6. Cochat P, Rumsby G. Primary hyperoxaluria. N Engl J Med. 2013;369(7):649-658. doi:10.1056/NEJMra1301564
7. Cochat P, Basmaison O. Current approaches to the management of primary hyperoxaluria. Arch Dis Child. 2000;82(6):470-473. doi:10.1136/adc.82.6.470
8. Niaudet P. Primary hyperoxaluria. Last updated: December 10, 2020. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: January 5, 2021
9. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. Am J Nephrol. 2005 Mar-Apr;25(2):154-60.
10. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Prostate Cancer version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (Accessed 09 January 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR042.0623	**CARDIOVASCULAR AGENTS** **PCSK9 INHIBITORS** **Leqvio®** (inclisiran sodium syringe)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 06/22, 05/23 (JCN) P&T Committee Meeting Date: 04/22, 08/22, 06/23 Original Effective Date: 06/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization

1. One of the following:
    a. Trial and failure of at least eight weeks of therapy with a high-intensity statin therapy (atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily), defined as failure to achieve desired LDL-C lowering
    OR
    b. Documentation of statin intolerance, defined as one of the following:
        i. Rhabdomyolysis
        ii. Skeletal muscle related symptoms while on separate trials of at least two different statins, and resolution of symptoms after discontinuation
        iii. Elevated liver enzymes while on separate trials of at least two different statins with resolution after discontinuation
    OR
    c. The patient has an FDA labeled contraindication to a statin
2. Must meet listed criteria below for each specific diagnosis:
    a. For **familial hypercholesterolemia (FH),** one of the following must be met:

i. A "possible" diagnosis of FH via Simon Broome criteria or a "probable" diagnosis of FH via Dutch Lipid Clinic Network Criteria score of greater than or equal to 6 (see appendix)
OR
ii. Genetic mutation in one of the following genes: low-density lipoprotein receptors (LDLR), apolipoprotein B gene (APOB), or proprotein convertase subtilisin kexin type 9 (PCSK9), or ARH adaptor protein 1/LDLRAP1
OR
iii. LDL-C greater than 190 mg/dL (pretreatment or highest level while on treatment) and secondary causes have been ruled out. Secondary causes may include hypothyroidism, nephrosis, or extreme dietary patterns
OR
iv. Presence of xanthomas

b. For **ASCVD**, attestation of LDL-C greater than or equal to 70 mg/dL and history of clinical ASCVD, defined as one of the following:
i. Acute coronary syndromes
ii. History of myocardial infarction
iii. Stable/unstable angina
iv. Coronary or other arterial revascularization
v. Stroke or transient ischemic attack
vi. Peripheral artery disease presumed to be of atherosclerotic origin

For initial reauthorization: Provider attestation of response to therapy, defined as a decrease in LDL-C levels from pre-treatment levels.

EXCLUSION CRITERIA:
- Concomitant use with another PCSK9 inhibitor
- Non-familial hyperlipidemia/hypercholesterolemia
- Primary prevention of ASCVD

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization for one year. Reauthorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Inclisiran (Leqvio®) is a double-stranded small interfering RNA (siRNA) that inhibits proprotein convertase subtilisin kexin type 9 (PCSK9) synthesis. The inhibition of PCSK9 results in increased numbers of LDLR on the surface of hepatocytes. LDLRs clear LDL-cholesterol from the blood; therefore, PCSK9 inhibitors reduce serum levels of LDL-C.

FDA APPROVED INDICATIONS:

Leqvio®:

- Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- Adjunct to diet and maximally tolerated statin therapy for treatment of adults with clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.
- Limitations of use: the effect of inclisiran on cardiovascular morbidity and mortality has not been determined.

POSITION STATEMENT:

Inclisiran (Leqvio®) showed significant LDL-C lowering effects in clinical trials (39.7-51.3%) in addition to maximally tolerated statin therapy. Inclisiran was studied in three clinical phase 3 trials demonstrating that inclisiran compared to placebo as adjunct to maximally tolerated statin therapy reduces LDL-C in adults with HeFH (ORION-9 study) and in adults with ASCVD (ORION-10 and ORION-11). The cardiovascular outcomes trial for inclisiran, ORION-4, is not expected to be completed until 2026.

Familial hypercholesterolemia (FH) is typically diagnosed by either genetic testing or clinical presentation. A definitive diagnosis can be made with genetic mutations in any of the following genes: LDLR, APOB, or PCSK9. Clinical presentation involves many different patient factors. However, in the clinical trials for alirocumab, patients were diagnosed with definite FH using the Simon Broome criteria (see Appendix 2) or the World Health Organization/Dutch Lipid Network criteria (See Appendix 3). Severely elevated LDL-C levels and the presences or tendon xanthomas are typically diagnostic of FH.

REFERENCE/RESOURCES:

1. Leqvio Package insert. Novartis Pharmaceuticals Corporation. Dec. 2021.
2. Leqvio In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed February 21, 2022.
3. Leqvio In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed February 21, 2022.
4. 2018 AHA/ACC/AACVRP/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2019 Jun, 73 (24) e285-e350. Available at: https://www.jacc.org/doi/abs/10.1016/j.jacc.2018.11.003?_ga=2.130559624.666084477.1543267586-144035656.1543267586.
5. Ray, KK, Wright, RS, Kallend, D, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. The New England Journal of Medicine. 2020; 382:1501-1519. Available at: https://www.nejm.org/doi/10.1056/NEJMoa1912387?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0pubmed.
6. Rall, FJ, Kallend D, Ray, KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. The New England Journal of Medicine. 2020; 382: 1520-1530. Available at: https://www.nejm.org/doi/10.1056/NEJMoa1913805?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub 0pubmed.
7. High cholesterol. Institute for Clinical and Economic Review (ICER). Public Meeting February 2021. Available at: https://icer.org/assessment/high-cholesterol-2021/. Accessed on February 25, 2022.

Table 1. Cholesterol levels to be used as diagnostic criteria for the index individual levels either pre-treatment or highest on treatment

	Total cholesterol	LDL-C
Child/young person	> 6.7 mmol/L (260 mg/dL)	> 4.0 mmol/L (154 mg/dL)
Adults	> 7.5 mmol/L (290 mg/dL)	> 4.9 mmol/L (190 mg/dL)

APPENDIX 1: Simon Broome criteria for FH

Diagnose a person with <u>definite</u> familial hypercholesterolemia (FH) if they have:

- Cholesterol concentrations as defined in table 1 and tendon xanthomas, or evidence of these signs in first- or second-degree relative
  OR
- Deoxyribonucleic acid (DNA)-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Diagnose a person with <u>possible</u> FH if they have cholesterol concentrations as defined in table 1 and at least one of the following.

- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative.
- Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.

APPENDIX 2: World Health Organization (WHO)/Dutch Lipid Network criteria

Family history			
a	First degree relative known with premature (men<55 yrs, women <60yrs) coronary and vascular disease.		1
b	First degree relative known with LDL-cholesterol >95th percentile.		
	and/or		
a	First degree relative with tendon xanthomata and/or arcus cornealis.		2
b	Children below 18 yrs. with LDL-cholesterol >95th percentile.		
Clinical history			
a	Patient has premature (men<55 yrs, women <60yrs) CAD		2
b	Patient has premature (men<55 yrs, women <60yrs) cerebral or peripheral vascular disease.		1
Physical examination			
a	Tendon xanthomata		6
b	Arcus cornealis below the age of 45 yrs.		4
Laboratory analysis			
	mmol/l	mg/dl	
a	LDL-cholesterol >8.5	>330	8
b	LDL-cholesterol 6.5 - 8.4	250-329	5
c	LDL-cholesterol 5.0 - 6.4	190-249	3
d	LDL-cholesterol 4.0 - 4.9	155-189	1
	(HDL-cholesterol and triglycerides are normal)		
DNA-analysis			
a	Functional mutation low-density lipoprotein receptor gene present		8

Diagnosis of FH is:	
certain when	>8 points
probable when	6-8 points
possible when	3-5 points

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCINF038.1223	**ANTI-INFECTIVE AGENTS** **PREVYMIS®** (letermovir injectable)
Effective Date: 2/1/2024	**Review/Revised Date**: 02/18, 10/18, 10/19, 10/20, 07/21, 11/21, 11/22, 10/23, 12/23 (MTW)
Original Effective Date: 04/18	**P&T Committee Meeting Date**: 04/18, 12/18, 12/19, 12/20, 08/21, 12/21, 12/22, 10/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For **initiation of therapy** (new start) to prevent cytomegalovirus (CMV) infection and disease, both of the following must be met:

1. One of the following:
    a. Patient is using for prophylaxis of cytomegalovirus (CMV) infection after allogeneic hematopoietic stem cell transplant (HSCT) and all of the following:
        i. Patient is CMV seropositive
        ii. Attestation that therapy will be started within 28 days post-transplantation
        iii. One of the following:
            1) Member is within 100 days post-transplant
            2) Documentation is provided that patient is at high risk for late cytomegalovirus infection and disease and patient is within 200 days post-transplant
    b. Patient is using for prophylaxis of CMV disease after kidney transplant and all of the following:
        i. Patient is at high risk, defined as CMV seropositive Donor in a Recipient that is CMV seronegative (D+/R-)

   ii. Attestation that therapy will be started within seven (7) days post-transplantation
   iii. Member is within 200 days post transplant
2. Medical rationale provided for not using oral formulation (such as patient is unable to swallow)

For member **established on therapy** (within the previous year): Documentation of response to therapy and member is within 200 days post allogeneic or kidney transplant

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for 18 years and older.

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hematologist, oncologist, or infectious disease specialist.

COVERAGE DURATION:
Authorization will be approved for up to 200 days post-transplant

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Letermovir works by inhibiting the production of proper unit length genomes and interfering with virion maturation. It inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89), which is required for viral DNA processing and packaging.

FDA APPROVED INDICATIONS:

- Prophylaxis of cytomegalovirus (CMV) in seropositive adult patients who received an allogeneic hematopoietic stem cell transplant (HSCT)
- Prophylaxis of cytomegalovirus (CMV) disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])

POSITION STATEMENT:
Current therapy for CMV in patients with allogeneic stem cell transplant is either prophylactic or preemptive. Prophylaxis involves administering medication to prevent infection for at-risk patients while preemptive therapy involves routine screening to detect early infection and administering medications early to avoid disease progression. The Center for Disease Control (CDC), Infectious Disease Society of America (IDSA) American Society for Bone Marrow Transplant (ASBMT), and National Cancer Network (NCCN) all support the use of surveillance with pre-emptive therapy.

In allogeneic HCT recipients, NCCN recommends surveillance for at least 3 to 6 months after transplant in CMV IgG seropositive cases. For primary prophylaxis in seropositive patients, NCCN recommends to consider therapy with letermovir. For preemption, NCCN recommends routine CMV surveillance with weekly monitoring by Polymerase Chain Reaction (PCR). If CMV reactivation is detected, it is recommended to initiate therapy with oral valganciclovir or IV ganciclovir. Oral valganciclovir therapy is most commonly used, however some centers prefer ganciclovir. IV foscarnet and IV cidofovir may be used for cases of ganciclovir-resistant CMV or when ganciclovir is not tolerated (e.g. myelosuppression). NCCN notes that higher risk transplant subgroups may exist and require different management strategies. For CMV-seronegative HSCT recipients of seropositive donor cells (i.e., D-positive or R-negative), the Center for Disease Control (CDC) preferentially recommends for a preemptive approach against early CMV (i.e., <100 days after HSCT) over prophylaxis because of the low attack rate of active CMV infection if screened or filtered blood product support is used. Per package insert, letermovir may be continued through 100 days post-HSCT for CMV prophylaxis, and through 200 days in patients with increased risk of late CMV infection. Examples of risk factors for late CMV infection include: HLA-related (sibling) donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, B or DR; haploidentical donor; unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, B, C and DRB1; use of umbilical cord blood as stem cell source; use of ex vivo T-cell-depleted grafts; receipt of anti-thymocyte globulin; receipt of alemtuzumab; use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day. Letermovir may by continued through 200 days post-kidney transplant for CMV prophylaxis.

Acyclovir or valacyclovir can be used for prophylaxis but require careful virus monitoring and preemptive antiviral therapy for CMV infection according to the Infectious Disease Society of America (IDSA) and American Society for Bone Marrow Transplant (ASBMT). However, NCCN does not recommend either acyclovir or valacyclovir due to limited efficacy. Primary prophylaxis with ganciclovir is not recommended in guidelines as toxicity (such as bone marrow suppression) outweigh efficacy in HSCT patients.

In a double-blind, phase three study (N=565), patients were randomized to receive either letermovir or placebo for 14 weeks for post-HSCT. Fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection by week 24 after transplantation (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], P<0.001). Clinically significant CMV infection was defined as CMV disease or viremia leading to preemptive therapy. Amongst those who developed clinically significant CMV infection, most had CMV viremia rather than CMV disease. CMV viremia resulting in preemptive therapy occurred in 52 of 325 patients receiving letermovir (16.0%) and 68 of 170 patients receiving placebo (40.0%). CMV disease was roughly equivalent in both groups and occurred in 5 of 325 patients receiving letermovir (1.5 %) and 3 of 170 patients receiving placebo (1.8 %). All-cause mortality at week 24 was lower in the letermovir group compared to placebo (9.8% vs 15.9% respectively) but at 48 weeks after transplantation not significant (20.9% among letermovir recipients and 25.5% among placebo recipients [P=0.12]).

The 2019 American Society of Transplantation guidelines for CMV in solid organ transplant recipients recommends valganciclovir, IV ganciclovir, and high dose valacyclovir for CMV prophylaxis in solid organ transplant patients. Valganciclovir was noted to be the preferred agent due to improved bioavailability and lower pill burden. Use of acyclovir is not recommended for CMV prophylaxis. An extended duration of 200 days versus 100 days is recommended due to post prophylaxis delayed-onset CMV disease. At the time of publication, letermovir was not approved for use in kidney transplant recipients but is mentioned as a possible future therapy.

In a double-blind, phase three study (N=589), patients were randomized to receive either letermovir or valganciclovir for 28 weeks for post-kidney transplant. Letermovir group was noninferior to valganciclovir group for prevention of CMV disease through week 52 after transplant (30 of 289 patients [10.4%] vs. 35 of 297 [11.8%], 95% CI, −6.5% to 3.8%). CMV disease was confirmed by an independent masked adjudication committee, through post-transplant week 52 (prespecified noninferiority margin, 10%). Development of confirmed CMV occurred in 0 of 289 patients receiving letermovir (0.0%) and 5 of 297 patients receiving placebo (1.7%), [95% CI, −3.4% to 0.1%].

According to ASBMT, risk factors for CMV infection or disease include GVHD requiring high dose of steroids, prolonged immunosuppression, T cell depletion, and certain donor sources.

Dosing

- The recommended dose is 480 mg orally or intravenously once daily. Dosing should be adjusted when co-administered with cyclosporine. Letermovir injection should be used only in patients unable to take oral therapy and patients should be switched to oral letermovir as soon as they are able to take oral medications. Tablet and injection formulations may be used interchangeably, and no dose adjustment is necessary when switching formulations.
- For use after HSCT: Initiate letermovir between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT. In patients at risk for late CMV infection and disease, letermovir may be continued through Day 200 post-HSCT.
- For use after kidney transplant: Initiate letermovir between Day 0 and Day 7 post-transplant and continue through Day 200 post-transplant.

REFERENCE/RESOURCES:

1. [Prevymis®] package insert. Whitehouse Station, NJ: Merck; August 2023.
2. [Prevymis®] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed November 2, 2022.
3. [Prevymis®] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed November 2, 2022.
4. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients: A Randomized Clinical Trial. JAMA. 2023;330(1):33-42.
5. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. N Engl J Med. 2017 Dec 21;377(25):2433-2444.
6. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009 Oct;15(10):1143-238. doi: 10.1016/j.bbmt.2009.06.019. Erratum in: Biol Blood Marrow Transplant. 2010 Feb;16(2):294. Boeckh, Michael A [corrected to Boeckh, Michael J]. PMID: 19747629; PMCID: PMC3103296.

7. Boeckh M, Ljungman P. How we treat cytomegalovirus in hematopoietic cell transplant recipients. Blood. 2009 Jun 4;113(23):5711-9.
8. National Comprehensive Cancer Network® (NCCN), "Prevention and Treatment of Cancer-Related Infections," Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf
9. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3—Prevention of Cytomegalovirus Infection and Disease After Hematopoietic Cell Transplantation. Transplantation and Cellular Therapy. 2021 Sept;27 (9):707-719.
10. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33:e13512. https://doi.org/10.1111/ctr.13512

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM027.1223	**HEMATOLOGICAL AGENTS** **PROPHYLACTIC HEREDITARY ANGIOEDEMA THERAPY** **Cinryze®** (C1 Esterase Inhibitor injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 06/10, 06/11, 12/11, 04/12, 10/12, 12/12, 10/13, 10/14, 10/15, 10/16, 10/17, 09/18, 11/18, 10/19, 10/20, 01/21, 07/21, 10/21, 11/22, 11/22 (DJW)
Original Effective Date: 06/09	**P&T Committee Meeting Date**: 04/09, 06/10, 06/11, 04/12, 12/11, 10/12, 12/12, 10/13, 10/14, 10/15, 10/16, 10/17, 10/18, 12/18, 12/19, 12/20, 02/21, 08/21, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. **For initiation of therapy (new starts)**, all of the following criteria (a-d) must be met:
    a. Documented history of one of the following clinical criteria:
        i. Recurrent, self-limiting, non-inflammatory subcutaneous angioedema without urticaria, or
        ii. Recurrent, self-remitting abdominal pain without clear organic etiology, or
        iii. Recurrent laryngeal edema
    b. Documentation of greater than or equal to two HAE attacks per month on average for the past three months despite removal of triggers (such as estrogen containing oral contraceptive, angiotensin converting enzyme inhibitors) unless medically necessary,
    c. One of the following:
        i. For HAE Type I and Type II, documentation of the following (per laboratory standard):
            1) Serum C4 level is below the lower limit of normal, and
            2) One of the following:

a) C1-inhibitor (C1-INH) protein level less than 50 percent of the lower limit of normal, or
b) C1-INH protein function less than 50 percent of the lower limit of normal

ii. For HAE with normal C1-INH or HAE Type III, one of the following:
1) Confirmed Factor 12 (FXII), ANGPT1, PLG, or KNG1 gene mutation, or
2) Positive family history for HAE and attacks that lack response with high dose antihistamines or corticosteroids.

d. Documentation of trial and failure or contraindication to Haegarda®.

2. **For patients established on therapy** (within the previous year)**:** Documentation must be provided showing benefit of therapy with reduction of frequency and severity of HAE attack episodes by at least 50% from baseline.

EXCLUSION CRITERIA:
Combination prophylaxis therapy with Cinryze®, Haegarda®, Takhzyro®, or Orladeyo®

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an immunologist or an allergist.

COVERAGE DURATION:
Initial authorization will be approved for three months. Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM027	HEMATOLOGICAL AGENTS PROPHYLACTIC HEREDITARY ANGIOEDEMA THERAPY **Cinryze®** (C1 Esterase Inhibitor injection)

INTRODUCTION:

Hereditary angioedema is a rare, genetic, and potentially life-threatening disorder associated with recurrent attacks of severe swelling in various parts of the body, including the throat. Medications for hereditary angioedema (HAE) can be categorized into on-demand therapies taken during an acute attack and therapies for prophylaxis of attacks. International guidelines and consensus documents recommend that all attacks be considered for treatment and that long-term prophylaxis be considered in all patients for whom on-demand therapy is insufficient to minimize effects of the disease.

FDA APPROVED INDICATIONS:

Cinryze® is indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (six years old and above) with Hereditary Angioedema (HAE).

Table 1. Additional Drug Information

Drug	HCPCS Code	Use	Formulation	Availability	Dose
Cinryze (C1 Esterase Inhibitor)	J0598	Prophylaxis	IV	500 units/vial	1000 units every 3-4 days; up to 2500 units BIW

POSITION STATEMENT:

- HAE is a condition characterized by acute attacks of sudden edema formation in the skin or in the walls of the upper respiratory tract or gastrointestinal tract. Management of patients with C1 inhibitor deficiency should cover their long-term, short-term and acute needs
    - Cases of laryngeal edema can rapidly become life threatening. The most frequent cause of death is airway obstruction secondary to laryngeal edema.
    - Cases of gastrointestinal attacks have been misdiagnosed and have led to unnecessary surgeries.
    - The clinical course, triggers, and frequency of attacks can be difficult to predict.
    - The approach to treatment has two main goals: (1) prevent acute attacks of hereditary angioedema from developing and (2) rapidly treat acute angioedema attacks if they do occur.
    - HAE can be characterized into several subtypes. Type I and II (also called HAE-C1INH) is characterized by C1INH deficiencies/dysfunction and is associated with abnormal C1INH and complement protein levels. Type III (also called HAE-nC1) is characterized by normal

C1INH and complement studies but may be associated with factor XII mutations. The average age of onset is 26.8 years for HAE-nC1 whereas the mean age of onset for HAE-C1INH is 12 years.

- Diagnosis of HAE requires laboratory confirmation
    - Laboratory tests should be performed in an accredited laboratory registered with a suitable quality assurance scheme.
    - Serum C4 level is a good screening test for C1 INH deficiency as serum C4 is invariably low in untreated HAE (C4 < 30% of mean normal level). It has been shown that for untreated C1 INH deficiency low C4 has 100% sensitivity, 100% negative predictive value and is thus an effective screening test.
    - The diagnosis of type I HAE (85% of cases) is made by measuring low amounts of C1 inhibitor protein. If C1 inhibitor value appears normal or raised (and C4 is low), a test of C1 inhibitor function should be carried out as an absence of function suggests a type II defect.
    - Complement studies are not a reliable tool for diagnosis of HAE in infants less than 1 year of age due to high variability of levels.
    - Complement studies for diagnosis must be performed when the patient is not receiving C1INH concentrate, because it will alter results. If it has been initiated, it should be discontinued for one week before diagnostic complement studies are obtained. Patients receiving androgens will often still have low C4 and C1INH levels, but if complement results are normal, androgens should be withheld for a week and testing repeated.
    - There are no routine laboratory tests to confirm diagnosis of HAE-nC1, though genetic testing may be helpful in confirming this diagnosis. The most common mutation linked to HAE-nC1 involves the F12 gene which can be detected by commercially available PCR assay.
- Cinryze® is made from human blood and may carry the risk of transmission of infectious agents (e.g. viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent). Serious arterial and venous thromboembolic events have also been reported with IV formulation.
- Cinryze® is a protein designed to replace the missing C1 esterase inhibitor in HAE patients.

REFERENCE/RESOURCES:

1. Cinryze® Package Insert. Exton, PA: ViroPharma Incorporated; 2021 Jan.
2. Zuraw BL, Bernstein JA, Lang DM et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol.* 2013;131(6):1491.

3. Lang DM, Aberer W, Bernstein JA et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109(6):395
4. Magerl M, Germenis AE, Mass C et al. Hereditary Angioedema with Normal C1 Inhibitor. *Immunol Allergy Clin N Am*. 2017;37(3)571-584
5. Bowen T, Cicardi M, Farkas H, et al. 2010 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Allergy, Asthma, and Clinical Immunology.* 2010; 6:24
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.

APPENDIX 1: Complement Studies

HAE Type	C4 (10-40mg/dL)*	C1INH Protein (21-39mg/dL)	C1 Function (greater or equal to 68%)**	C1q (5.0-8.6mg/dL)
Type I	Low	Low	Low	Normal
Type II	Low	Normal or Elevated	Low	Normal
HAE-nC1 (Type III	Normal	Normal		Normal

*The normal range for C4 is extremely wide and may be reported as a concentration, absolute level, or percentage of normal. If the C4 level is presented in mg without a percent, 25 mg would be considered a normal level (100 percent), and levels less than 10 mg are strongly suggestive of C1INH deficiency (pathologic), while levels between 10 and 15 mg are possibly pathologic, and levels greater than 15 mg are not pathologic.
** 41-67% value is equivocal; less than or equal to 40% is abnormal

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC105.0224	**ANTINEOPLASTIC AGENTS** **PROVENGE®** (sipuleucel-T for intravenous infusion)
Effective Date: 4/1/2024	**Review/Revised Date**: 01/19, 01/20, 12/20, 01/22, 01/23, 01/24 (CJD)
Original Effective Date: 04/19	**P&T Committee Meeting Date**: 02/19, 02/20, 02/21, 02/22, 02/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 3	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION: N/A

EXCLUSION CRITERIA: NA

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved for three complete doses administered at approximately two-week intervals (six weeks) for one course of therapy per lifetime.

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC105	ANTINEOPLASTIC AGENTS PROVENGE® (sipuleucel-T for intravenous infusion)

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Sipuleucel-T consists of autologous peripheral blood mononuclear cells that have been activated with a recombinant human protein consisting of prostatic acid phosphatase (PAP) an antigen expressed in prostate cancer, linked to granulocyte-macrophage colony stimulating factor (PAP-GM-CSF).
The patient's peripheral blood mononuclear cells are obtained via a leukapheresis procedure three days' prior the infusion. Each dose of sipuleucel-T contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, suspended in 250 ml of Lactated Ringer's Injection, USP. The recommended single course of therapy is three doses infused at approximately two week intervals. In controlled clinical trials, the median dosing interval between infusions was two weeks (range one to 15 weeks); the maximum dosing interval has not been established. Patients have only received one single course of three dose therapy per lifetime.

FDA APPROVED INDICATIONS:

Treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

POSITION STATEMENT:

Concomitant use of chemotherapy and immunosuppressive medications with sipuleucel-T has not been studied. Previous treatment with chemotherapy does not preclude patients from receiving sipuleucel-T. Androgen deprivation modalities may be continued during treatment with sipuleucel-T. Sipuleucel-T is intended solely for autologous use.

National Comprehensive Cancer Network (NCCN) Guidelines for prostate cancer indicate that sipuleucel-T is a category 1 recommendation for the treatment of asymptomatic or minimally symptomatic castration-resistant prostate cancer that is positive for metastases, in patients with good performance status, life expectancy >6 months, and no liver metastases. This has not been studied in patients with visceral metastases.[6]

REFERENCE/RESOURCES:

1. Provenge® Package Insert. Seattle, WA: Dendreon Corporation; 2021 Dec.
2. Higano CS, Schellhammer PF, Small EJ, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy. *Cancer*. 2009; 115:3670-3679.
3. Kantoff P, Higano CS, Berger ER, et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *The New England Journal of Medicine*. 2010; 363: 411-422.
4. Petrylak DP, Dawson NA, Gardner T et al. Persistence of immunotherapy survival effects of sipuleucel-T and relationship to post randomization docetaxel use in phase III studies. *J Clin Oncol.* 2010; 28:15s (suppl; abstr 4551).
5. Small EJ, Schellhammer PF, Higano CS et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic asymptomatic hormone refractory prostate cancer. *J Clin Oncol.* 2006; 24:3089-3094.
6. National Comprehensive Cancer Network (NCCN). NCCN Guidelines for Prostate Cancer version 4.201.https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf (Accessed 08 January 2020).
7. Cookson M, Roth B, Dahm P. Castration-Resistant Prostate Cancer: AUA Guideline. American urological Association (AUA) Guideline 2018.
8. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Autologous Cellular Immunotherapy Treatment (110.22). Available at https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=344&ncdver=1&bc=AAAAgAAAAAAA& (Accessed 09 January 2022).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR022.0623	**CARDIOVASCULAR AGENTS** **PULMONARY HYPERTENSION** See Table 1 for Applicable Medications
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/02, 06/03, 06/04, 06/05, 04/06, 02/07, 02/08, 04/08, 10/09, 02/10, 06/10, 12/10, 04/11, 02/12, 10/12, 10/13, 02/14, 04/14, 10/14, 12/14 , 10/15, 01/16 , 05/16 , 08/16 , 09/17, 08/18, 08/19, 01/20, 09/20, 05/21, 05/22, 04/23 (MTW) P&T Committee Meeting Date: 08/02, 06/03, 06/04, 06/05, 04/06, 02/07, 02/08, 04/08, 10/09, 02/10, 06/10, 12/10, 04/11, 02/12, 10/12, 10/13, 02/14, 04/14, 10/14, 12/14, 02/16, 06/16, 10/16, 10/17, 09/18 (cv), 10/19, 02/20, 10/20, 06/21, 06/22, 06/23 Original Effective Date: 08/02 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
1. Pulmonary Arterial Hypertension
2. Pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) for Tyvaso® only

REQUIRED MEDICAL INFORMATION:
The following criteria must be documented:
1. Diagnosis of Pulmonary Hypertension (PH) confirmed by right heart catheterization as defined by:
    a. Mean pulmonary artery pressure (mPAP) greater than or equal to 20 mmHg at rest
    AND
    b. Pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) less than or equal to 15 mmHg
    AND
    c. Pulmonary vascular resistance (PVR) greater than 3 Wood units (WU)
    AND
2. Patient has one of the following:
    a. Documented World Health Organization (WHO) Group 1 classification (PAH) and a WHO/New York Heart Association (NYHA) functional class status as outlined below:

i. Flolan®, Veletri®, Tyvaso® and Ventavis®: Class III or IV
ii. Remodulin®, Uptravi® and Revatio® injection: Class II, III, or IV

b. For Tyvaso® only, WHO Group 3 classification PH-ILD

Reauthorization: Documentation of response to therapy, such as lack of disease progression or improvement in WHO functional class

EXCLUSION CRITERIA:
Heart failure caused by reduced left ventricular ejection fraction for epoprostenol (Flolan®, Veletri®)

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by or in consultation with a pulmonologist or cardiologist

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Pulmonary arterial hypertension (PAH) is a chronic life-threatening disorder with several treatment options available. There are several medication classes available for the treatment of this disease, with differing mechanisms of action. A definitive diagnosis of PAH is important for determining the most appropriate therapy for this disease.

FDA-APPROVED INDICATIONS:

Flolan® (epoprostenol for infusion): treatment of PAH (WHO Group 1) in adults to improve exercise capacity.

- Trials establishing effectiveness included predominantly (97%) patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).

Veletri® (epoprostenol for infusion): treatment of PAH (WHO Group 1) in adults to improve exercise ability.

- Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Remodulin® (treprostinil for infusion):

- Treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise.
    - Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%)
- In patients with PAH requiring transition from epoprostenol, Remodulin is indicated to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

Tyvaso® (treprostinil for inhalation):

- Treatment of PAH (WHO Group 1) in adults to improve exercise ability
    - Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).The effects diminish over the minimum recommended dosing interval of four hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration
- Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability.
    - The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%)

Ventavis® (Iloprost for inhalation): treatment of PAH (WHO Group 1) in adults to a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.

- Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%)

Revatio® (Sildenafil for injection):

- Treatment of PAH (WHO Group 1) in adults to improve exercise ability and delay clinical worsening. The delay of clinical worsening was demonstrated when sildenafil was added to epoprostenol infusion therapy.
- Treatment of PAH (WHO group 1) in pediatric patients 1 to 17 years old to improve exercise ability and, in pediatric patients to young to perform standardized exercise testing, pulmonary hemodynamics thought to underly improvements in exercise. Uptravi® (selexipag for infusion): treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.
- Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms and etiologies of idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%) or PAH associated with congenital heart disease with repaired shunts (10%).

POSITION STATEMENT:

A right heart catheterization (RHC) is required to confirm diagnosis of PAH which is defined as mPAP greater or equal to 20 mmHg, PCWP/LVEDP less than or equal to 15 mmHg, and PVR greater than 3 WU. The recent 2022 ESC/ERC Guidelines came out with a revised hemodynamic definition and suggest that PAH may be diagnosed in patients with mPAP greater than 20 mmHg and PVR greater than 2 WU[12]. Of note, the efficacy of drugs approved for PAH has only been demonstrated in patients with mPAP greater than or equal to 25 mmHg and PVR greater than 3 WU. PCWP is the pulmonary capillary wedge pressure, also called pulmonary arterial wedge pressure (PAWP). PVR is pulmonary vascular resistance, measured Wood unit, is calculated using the following formula: PVR = (mPAP – PAWP) / CO. CO is cardiac output which is measured during RHC, and it is preferable to use CO estimated by thermodilution rather than estimation via Fick principle where accuracy depends on correct estimation of oxygen consumption. CHEST 2018 and ESC/ERS 2022 Guidelines suggest acute vasoreactivity testing during RHC to identify candidates for high-dose calcium channel blocker (CCB), only in patients with idiopathic, heritable, or drug-induced PAH. A high-dose CCB trial of up to three to four months is suggested for vaso-reactive patients without right-sided heart failure, prior to starting PAH-targeted therapy. After diagnosis, patients are classified based on symptomology. The World Health Organization functional class (WHO-FC) is one

of the most highly used classification systems to help predict survival and direct therapy options.

Treatment-naïve PAH patients without symptoms (WHO FC I) are considered to have relatively low risk of mortality within one year. However, due to the progressive nature of PAH, patients should be closely monitored for symptoms including worsened dyspnea on exertion, fatigue, lower extremity edema, angina, and/or syncope. Treatment-naïve PAH patients with WHO-FC II to IV should be initiated on PAH-targeted medication(s). Combination therapy (employed sequentially or initially) may be used to delay PAH disease progression and improve functional capacity. Due to the progressive nature of the disease, the benefit of combination therapy may outweigh risks. For treatment-naïve WHO-FC II and III patients, initial combination of ambrisentan and tadalafil has been recommended to improve 6-minute walk distance (6MWD), based on limited evidence. Monotherapy may be considered if tolerance for combination therapy is a concern. For treatment-naïve patients with WHO-FC II or WHO-FC III patients without evidence of rapid disease progression (such as enlargement and/or decreased function of right ventricle on ECHO), monotherapy with an endothelin receptor antagonist (bosentan, ambrisentan, or macitentan), a phosphodiesterase type 5 inhibitor (sildenafil or tadalafil), riociguat, or an oral prostacyclin receptor agonist may be considered.

The 2022 ESC/ERS Guidelines published a new recommendation to assess risk at the time of diagnosis using a three-strata model (low, intermediate, and high risk), considering all available data, including hemodynamics. For patients with PAH, they recommend having a treatment goal of achieving and maintaining a low-risk profile on optimized medical therapy. Development of a treatment plan is then made based off the patient's risk. According to these guidelines, patients assigned low or intermediate risk should receive combination oral therapy with an endothelin receptor antagonist and a phosphodiesterase 5 inhibitor, and high risk patients should be placed on this same therapy with the addition of a parenteral prostacyclin analogue. Of note, all drug approvals are based in part on WHO functional class and these risk assessment models have not been used as an outcome to assess treatment in any PAH trial.

Phosphodiesterase type 5 (PDE-5) inhibitors and riociguat target the same chemical pathway (nitric oxide-mediated) and concomitant use is contraindicated. Oral treprostinil has an approved indication for monotherapy in WHO-FC II-III patients, but it did not improve 6MWD at 16 weeks when added to an endothelin receptor antagonist (ERA) and/or a PDE5 inhibitor in FREEDOM-C and FREEDOM C-2.5,6 In GRIPHON7, the primary composite endpoint of death from any cause or a complication related to PAH was lower in patients on selexipag, as a monotherapy

or add-on therapy to ERA and/or PDE5 inhibitor, compared to placebo at 26 weeks and was found to be statistically significant (99% CI 0.46 to 0.78, p<0.001).

WHO-FC III patients with evidence of rapid disease progression or poor prognosis, a parenteral prostacyclin (IV epoprostenol, IV treprostinil, or SC treprostinil) may be considered. If patient is not a candidate for parenteral therapy, then an inhaled or oral prostacyclin pathway targeted therapy should be initiated (inhaled treprostinil, oral selexipag). For WHO-FC IV, parenteral prostacyclin initiation is recommended but if patient is not a candidate for parenteral therapy, then consider combination of inhaled prostacyclin with an oral PDE5 inhibitor and an endothelin receptor antagonist. For treatment-experienced patients who have not achieved adequate response to initial therapy, add on additional PAH therapy from another class.[2,3,4]

In patients with pulmonary hypertension (PH) due to left heart disease (LHD), epoprostenol is contraindicated due to association of increased mortality rates reported in the FIRST trial.[5] ERA use in patients with PH due to LHD should be avoided. A large study with bosentan, ENABLE, failed to show benefit and reported increased risk of early heart failure (HF) exacerbations due to fluid retention. Studies with other ERAs also indicated an upward trend in HF exacerbation and increased mortality[8]. More recently, a clinical trial explored the use of riociguat for treatment of PH due to idiopathic interstitial pneumonia. Patients experienced worsening of interstitial lung disease and more deaths occurred in the riociguat group, therefore FDA updated riociguat's contraindication to include idiopathic interstitial pneumonia[9].

The FDA approval of treprostinil oral inhalation (Tyvaso®) for pulmonary hypertension associated with interstitial lung disease (WHO group 3 – PA due to lung disease) to improve exercise ability was based off a single randomized control trial of 326 patients. The majority of the trial patients had idiopathic interstitial pneumonia (including idiopathic pulmonary fibrosis), combined pulmonary fibrosis and emphysema (CPFE) or connective tissue disease. Tyvaso® resulted in an improvement (mean difference of 31 meters) in the 6-Minute Walk Distance (6MWD) test compared to placebo after 16 weeks. The mean baseline 6MWD was 260 meters. Individuals with a 6MWD less than 100 meters were excluded from the trial. Approximately 25% of patients were on background therapy of pirfenidone or nintedanib.

REFERENCE/RESOURCES:

1. Relevant package inserts
2. Klinger J, Elliott G, Levine D, *et al.* Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel

Report: Endorsed by: Pulmonary Hypertension Association (PHA). *CHEST.* 2019; 155(3):565-586

3. Galie N, Corris PA, Frost A. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D60-72.
4. Galie N, Humbert M, Vachiery JL *et al*. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
5. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest. 2012; 142(6):1383
6. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest. 2013; 144(3): 952
7. Sitbon O, Channick R, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med. 2015; 373(26): 2522-33
8. Adir Y and Amir O. Pulmonary Hypertnesion Associated with Left Heart Disease. *Semin Respir Crit Care Med.* 2013; 34:665-680
9. Nathan SD, Behr J, Collard HR, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomized, placebo-controlled phase 2b study. Lancet Respir Med. 2019; http://dx.doi.org/10.1016/S2213-2600(19)30250-4
10. Waxman A, Restrepo-Jaramillo R, Thenappan T *et al*. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. *N Engl J Med*. 2021 Jan 28;384(4):325-334.
11. Simonneau G, Montani D, Celermajer DS, *et al*. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913
13. Humbert M, Kovacs G, Hoeper M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. European Respiratory Journal. 2023; (1) 2200879; DOI: 10.1183/13993003.00879-2022.Opotowsky AR, Hess E, Maron B. Thermodilution vs Estimated Fick Cardiac Output Measurement in Clinical Practice. JAMA Cardiol. 2017; 2(10):1090-1099

TABLE 1

Brand Name	Generic Name
Flolan®	epoprostenol for infusion
Remodulin®	treprostinil for infusion
Revatio®	sildenafil for injection
Tyvaso®	treprostinil for inhalation
Uptravi®	selexipag for infusion
Veletri®	epoprostenol for infusion
Ventavis®	Iloprost for inhalation

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU041.0823	**NEUROMUSCULAR DRUGS** **QALSODY®** (tofersen injection)
Effective Date: 10/01/2023	Review/Revised Date:
	P&T Committee Meeting Date: 08/23
	Original Effective Date: 10/23
	Approved by: Oregon Region Pharmacy and Therapeutics Committee
Robert Gluckman, M.D. **Chief Medical Officer**	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy, all the following criteria must be met:
    a. Documentation of diagnosis of amyotrophic lateral sclerosis (ALS) with mutation in the superoxide dismutase 1 (SOD1) gene
    b. Documentation of baseline ALS Functional Rating Scale-Revised (ALSFRS-R)
    c. Forced vital capacity (FVC) greater than or equal to 50% of predicted (taken within the past three months)
    d. Documentation of weakness attributable to ALS

2. For patients established on therapy, all the following criteria must be met:
    a. Documentation of a clinical benefit from therapy such as stabilization of disease or slowing of disease progression from pre-treatment baseline ALSFRS-R scores

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:

Patient age within FDA approved label

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist with expertise in ALS

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Tofersen is an antisense oligonucleotide (ASO) that binds specific RNA produced from mutated SOD1 genes to stop toxic SOD1 proteins from being made. Accumulation of toxic SOD1 protein can lead to loss of motor neurons resulting in progressive loss of muscle mass, strength, function, and death. To date, there are no treatments available that specifically target the underlying pathophysiology of SOD1-ALS.

FDA APPROVED INDICATIONS:
Treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (SOD1) gene.

This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain (NfL) observed in patients treated with Qalsody. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

POSITION STATEMENT:
Tofersen is the first drug approved for adult patients with ALS who have a mutation in the superoxide dismutase 1 (SOD1) gene. About 2% of ALS cases are associated with mutations in the SOD1 gene, with an estimated ~300-500 people in the US affected.[6]

Tofersen received an accelerated approval. Accelerated approval was based on a reduction in plasma neurofilament light (NfL), a biomarker of nerve injury and neurodegeneration that the FDA believes is reasonably likely to predict a clinical benefit in SOD1-ALS. This is the first time a biomarker has been used as a surrogate endpoint in ALS. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).[7]
ALS Functional Rating Scale (ALSFRS-R) is a tool used by clinicians to assess disease progression in ALS patients. It assesses bulbar, fine motor, gross motor and respiratory function. On a scale from 0 to 48, higher scores indicate better function. A minimally clinically important difference (MCID) threshold has not been established for this measure primarily due to its ordinal nature. Change in ALSFRS-R scores typically follow a nonlinear curve, where a 1-point change is not consistent across the scale. Though it is noted that even a small drop in an individual's ALSFRS-R can significantly inhibit functional abilities.[9] Kaufmann et al evaluated whether the ALSFRS-R predicts survival time in an ALS clinic population. They found that a single point drop in ALSFRS-R may equate to a 7% increase in risk of death or tracheostomy.[8]
Neurofilaments (NfL) are axonal cytoskeletal proteins found in the cerebrospinal fluid (CSF) and blood in a wide range of central nervous system disorders. In the setting of ALS, studies have associated NfL levels with the rate of both disability, measured by the decline in the ALSFRS-R, and with overall survival. Elevated NfL levels have been linked to increased rate of disease progression.[9]

***VALOR (NCT02623699)*[4]**
- The approval of tofersen was based on one phase 3 trial that suggests that tofersen, compared to placebo, may slow disease progression in adults with ALS who have a mutation in the superoxide dismutase 1 (SOD1) gene.
- Tofersen failed to demonstrate statistically significant results on the primary endpoint, change from baseline in the ALS Functional Rating Scale–Revised (ALSFRS-R) score. However, secondary endpoints, change from baseline in plasma neurofilament and CSF SOD1 protein, were statistically significant in favor of tofersen.
- Key inclusion criteria included adults with weakness attributable to ALS; confirmed SOD1 mutation; riluzole and edaravone were allowed to be continued if patient was established on drug at baseline; for fast progressors, SVC ≥65% of

predicted value as adjusted for sex, age, and height (from the sitting position); for non-fast progressors, SVC ≥50% of predicted value as adjusted for sex, age, and height (from the sitting position).

DRUG INFORMATION[1]

- Dosage and Administration:
  - 100mg intrathecally every 28-days following three loading doses administered at 14-day intervals
- Safety:
  - Warnings & Precautions: Myelitis/radiculitis, papilledema, elevated intracranial pressure, aseptic meningitis
  - The most common adverse reactions (≥ 10% of patients treated with tofersen and greater than placebo) were pain, fatigue, arthralgia, CSF white blood cell increased, and myalgia.

REFERENCE/RESOURCES:

1. Qalsody® prescribing information. Biogen Inc; Cambridge, MA. April 2023.
2. Qalsody® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed June 21, 2023.
3. Qalsody® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed June 21, 2023.
4. Miller T, et al. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N Engl J Med. 2022;387(12):1099–1110.
5. Institute for Clinical and Economic Review. Amyotrophic Lateral Sclerosis (ALS). September 13, 2022. Available at: https://icer.org/wp-content/uploads/2022/09/ICER_ALS-Policy-Recommendations_9132022.pdf. Accessed July 10, 2023.
6. Brown CA, et al. Estimated Prevalence and Incidence of Amyotrophic Lateral Sclerosis and SOD1 and c9orf72 Genetic Variants. Neuroepidemiology. 2021;55(5):342-353.
7. Center for Drug Evaluation and Research. Integrated Review. Qalsody (tofersen). NDA 215887. April 24, 2023.
8. P. Kaufmann, G. Levy, J. L.P. Thompson, M. L. DelBene, V. Battista, P. H. Gordon, L. P. Rowland, B. Levin, H. Mitsumoto. The ALSFRSr predicts survival time in an ALS clinic population. Neurology Jan 2005, 64 (1) 38-43.
9. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Final Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Tofersen/Biogen. March 22, 2023.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU022.0823	**NEUROMUSCULAR DRUGS** **RADICAVA®** (edaravone solution for injection) **RADICAVA ORS®** (edaravone oral suspension)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/17, 09/17, 07/18, 07/19, 06/20, 07/21, 02/22 07/22, 07/23 (JN) P&T Committee Meeting Date: 09/17, 10/17, 08/18, 08//19, 08/20, 08/21, 04/22, 08/23 Original Effective Date: 09/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy, all the following criteria (a-d) must be met:
    a. Documentation of definite or probable amyotrophic lateral sclerosis (ALS) within the previous two years per the El Escorial (Airlie House) Criteria
    b. Documentation of baseline ALS Functional Rating Scale-Revised (ALSFRS-R) with at least two points in each individual item (See Appendix 1)
    c. Forced vital capacity (FVC) of at least 80% (taken within the past three months)
    d. Dosing is in accordance with the FDA approved labeling
2. For patients established on therapy:
    a. Documentation of a clinical benefit from therapy such as stabilization of disease or slowing of disease progression from pre-treatment baseline ALSFRS-R scores. Edaravone may not be covered for patients

experiencing rapid deterioration while on therapy due to lack of clinical benefit in this patient population.

b. Documentation that patient is not dependent on invasive ventilation or tracheostomy
c. Dosing is in accordance with the FDA approved labeling

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, a neurologist with expertise in ALS.

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
Radicava ORS®: 50 mL per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Radicava® **(**edaravone) is a free radical and peroxynitrite scavenger that prevents oxidative damage to cell. Oxidative stress is considered to play a role in the onset as well as progression of amyotrophic lateral sclerosis (ALS) and edaravone may protect neuronal cells from oxidative stress. However, the exact mechanism by which it slows the decline of physical function in patients with ALS is unknown.

FDA APPROVED INDICATIONS:
Treatment of amyotrophic lateral sclerosis (ALS).

POSITION STATEMENT:

- The FDA's approval of edaravone was based on one small phase 3 placebo controlled trial in 137 Japanese patients with ALS. In this trial edaravone showed a smaller decline in ALSFRS-R score after 24 weeks compared with placebo [-5.01 ± 0.64 vs placebo -7.50 ± 0.66 (95% CI, 0.99 – 3.98, p = 0.0013]
- This trial had strict inclusion criteria based on Post hoc analysis of a subgroup of patients from a previous trial in a broader ALS population
    - Key inclusion criteria for this trial: age 20−75 years, definite or probable ALS according to the revised El Escorial criteria, ALS of grade 1 or 2 in the Japan ALS Severity Classification, Scores of at least 2 points on all 12 items of the (ALSFRS-R), Forced vital capacity of 80% or more, disease duration of 2 years or less, and a decrease of 1−4 points in the ALSFRS-R score during a 12-week observation period before randomization
        - Patients with Japanese ALS severity classification of class 5 were not included in the trial (only class/grade 1 or 2). Japanese ALS severity class 5 is using a tracheostomy tube, tube feeding, or tracheostomy positive pressure ventilation.
    - Key exclusion criteria for the trial: 3 or less on ALSFRS-R for dyspnea, orthopnea, or respiratory insufficiency
- Based on this trial, there is moderate quality evidence that edaravone may slow functional decline compared to placebo but only in a specific patient population with early, progressive disease, that has maintained function.
- Two prior clinical studies in a broader population of ALS patients (one with a wider inclusion criterion, and one with patients with more advanced disease) failed to reach statistical significance on their primary endpoints compared to placebo. Therefore, there is currently no evidence indicating that edaravone may be effective in slowing disease progression in a larger population of ALS patients who do not meet specific criteria.
- Riluzole is the second medication the FDA approved for the treatment of ALS and current standard of therapy along with supportive care. It has a relatively safe adverse effect profile and has been shown to prolong survival by about two months in patients with ALS. In the approval trial patients taking riluzole could continue receiving it throughout the study as long as the regimen remained unchanged and 91% of patients in the trial were on riluzole.

- Sodium phenylbutyrate/taurursodiol is the third drug approved for ALS. The exact mechanism of action is unknown; however, it is thought to target endoplasmic reticulum stress and mitochondrial dysfunction resulting in reduced neuronal death. The CENTAUR trial demonstrated a statistically significant treatment benefit, as measured by a slowing in decline on the ALSFRS-R, for sodium phenylbutyrate/taurursodiol compared to placebo. In post hoc long-term analyses, survival benefit was observed for those patients who were originally randomized to sodium phenylbutyrate/taurursodiol compared to those originally randomized to placebo.
- El Escorial (Airlie House) Criteria is used to help with diagnosis of ALS. It requires evidence of upper motor neuron degeneration by clinical, electrophysiological, or neuropathologic examination and lower motor neuron degeneration by clinical examination as well as progressive spread of symptoms.

REFERENCE/RESOURCES:

1. Edaravone (Radicava®) package insert. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc.; December 2022.
2. Edaravone (Radicava®) In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed July 06, 2023.
3. Edaravone (Radicava®) In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed July 06, 2023.
4. Writing group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017. 16(7):505-12.
5. Abe K, Itoyama, Sobue G, et al. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amylotroph Lateral Scler Frontotemporal Degener. 2014; 15: 610–617.
6. Miller RG, Jackson CE, Kasarskis EJ. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Neurology. 2009; 73(15): 1227-33. (Reaffirmed 2020)
7. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. J Neurol Sci. 1999. 169:13-21.
8. American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Retrieved from

https://www.aan.com/Guidelines/home/GuidelineDetail/370 . Accessed February 28, 2022.

9. Miller R, Mitchell J, Lyon M, et al. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Amyotroph Lateral Scler Other Motor Neuron Disord. 2003; 4(3): 191-206.
10. Castrillow-Viguera C, Grasso DL, Simpson E, et al. Clinical significance in the change of decline in ALSFRS-R. Amyotroph Lateral Scler. 2010; 11(1-2): 178-80.
11. Pattee G, Suarez Zambrano G, Zhang J, Nelson S, Apple S. Post hoc analysis of edaravone study 19: efficacy in bulbar onset ALS patients with and without reduced pulmonary function. Presented at: 2020 MDA Clinical & Scientific Conference. Abstract 53.

Appendix 1: The ALS Functional Rating Scale — Revised (ALSFRS-R)

1) Speech: Score_____

- □ Normal speech processes **(4 points)**
- □ Detectable speech disturbance **(3 points)**
- □ Intelligible with repeating **(2 points)**
- □ Speech combined with non-vocal communication **(1 point)**
- □ Loss of useful speech **(0 points)**

2) Salivation: Score_____

- □ Normal **(4 points)**
- □ Slight but definite excess of saliva in mouth; may have nighttime drooling **(3 points)**
- □ Moderately excessive saliva; may have minimal drooling **(2 points)**
- □ Marked excess of saliva with some drooling **(1 point)**
- □ Marked drooling; requires constant tissue or handkerchief **(0 points)**

3) Swallowing: Score_____

- □ Normal eating habits **(4 points)**
- □ Early eating problems — occasional choking **(3 points)**
- □ Dietary consistency changes **(2 points)**
- □ Needs supplemental tube feeding **(1 point)**
- □ NPO (exclusively parenteral or enteral feeding) **(0 points)**

4) Handwriting: Score_____

- □ Normal **(4 points)**
- □ Slow or sloppy: all words are legible **(3 points)**
- □ Not all words are legible **(2 points)**
- □ Able to grip pen but unable to write **(1 point)**
- □ Unable to grip pen **(0 points)**

5) Cutting food and handling utensils: Score_____

a). Cutting food and handling utensils **(patients without gastrostomy)**

- □ Normal **(4 points)**
- □ Somewhat slow and clumsy, but no help needed **(3 points)**
- □ Can cut most foods, although clumsy and slow; some help needed **(2 points)**
- □ Food must be cut by someone, but can still feed slowly **(1 point)**
- □ Needs to be fed **(0 points)**

b). Cutting food and handling utensils (**alternate scale for patients with gastrostomy)**

- Normal **(4 points)**
- Clumsy but able to perform all manipulations independently **(3 points)**
- Some help needed with closures and fasteners **(2 points)**
- Provides minimal assistance to caregiver **(1 point)**
- Unable to perform any aspect of task **(0 points)**

6) Dressing and hygiene: Score_____

- Normal function **(4 points)**
- Independent and complete self-care with effort or decreased efficiency **(3 points)**
- Intermittent assistance or substitute methods **(2 points)**
- Needs attendant for self-care **(1 point)**
- Total dependence **(0 points)**

7) Turning in bed and adjusting bed clothes: Score_____

- Normal **(4 points)**
- Somewhat slow and clumsy, but no help needed **(3 points)**
- Can turn alone or adjust sheets, but with great difficulty **(2 points)**
- Can initiate, but not turn or adjust sheets alone **(1 point)**
- Helpless **(0 points)**

8) Walking: Score_____

- Normal **(4 points)**
- Early ambulation difficulties **(3 points)**
- Walks with assistance **(2 points)**
- Non-ambulatory functional movement **(1 point)**
- No purposeful leg movement **(0 points)**

9) Climbing stairs: Score_____

- Normal **(4 points)**
- Slow **(3 points)**
- Mild unsteadiness or fatigue **(2 points)**
- Needs assistance **(1 point)**
- Cannot do **(0 points)**

10) Dyspnea: Score_____

- None **(4 points)**

□ Occurs when walking **(3 points)**
□ Occurs with one or more of the following: eating, bathing, dressing (ADL) **(2 points)**
□ Occurs at rest, difficulty breathing when either sitting or lying **(1 point)**
□ Significant difficulty, considering using mechanical respiratory support **(0 points)**

11) Orthopnea: Score_____

□ None **(4 points)**
□ Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows **(3 points)**
□ Needs extra pillows in order to sleep **(2 points)**
□ Can only sleep sitting up **(1 point)**
□ Unable to sleep **(0 points)**

12) Respiratory insufficiency: Score_____

□ None **(4 points)**
□ Intermittent use of BiPAP **(3 points)**
□ Continuous use of BiPAP during the night **(2 points)**
□ Continuous use of BiPAP during the night and day **(1 point)**
□ Invasive mechanical ventilation by intubation or tracheostomy **(0 points)**

Total score: _____

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM020.1223	**HEMATOLOGICAL AGENTS** **REBLOZYL®** (luspatercept-aamt injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 05/20, 11/20, 10/21, 10/22, 11/23 (JCN)
Original Effective Date: 04/20	**P&T Committee Meeting Date**: 02/20, 06/20, 12/20, 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 10	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy (new starts) for **beta-thalassemia**, all the following must be met (supporting documentation required):

1. Diagnosis of beta-thalassemia confirmed by hemoglobin analysis such as high performance liquid chromatography (HPLC) or genetic testing
2. Symptomatic anemia defined as a pretreatment or pretransfusion Hgb level less than or equal to 11 grams per deciliter
3. Patient is transfusion-dependent, defined as receiving at least 6-20 units RBC transfusions every 24 weeks

For patients that are established on therapy for beta-thalassemia beyond nine weeks, ongoing documentation of patient response to therapy must include maintenance of reduced transfusion levels

For initiation of therapy (new starts) for **myelodysplastic syndrome (MDS)**, all the following must be met (supporting documentation required):

1. Symptomatic anemia defined as a pretreatment or pretransfusion Hgb level less than or equal to 11 grams per deciliter
2. A score of very low to intermediate risk based on the Revised International Prognostic Scoring System
3. Patient requires RBC transfusions of at least two units every eight weeks
4. Meets one of the following (a or b):
    a. Ring sideroblasts greater than or equal to 15% or ring sideroblasts greater than or equal to 5% and less than 15% with a SF3B1 mutation
    b. Both of the following:
        i. Ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation)
        ii. Endogenous erythropoietin level less than 500 mU/mL

For patients that are established on therapy for MDS, all the following must be met: Documentation that patient was able to achieve transfusion independence for at least eight weeks during previous treatment period

Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
At least 18 years of age

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a hematologist/oncologist

COVERAGE DURATION:
Beta-thalassemia: For initiation of therapy, authorization will be for nine weeks. For continuation of therapy, authorization will be for one year.

MDS-RS: For initiation of therapy authorization will be for six months. For continuation of therapy will be for one year

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive

Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Luspatercept-aamt is a recombinant fusion protein that binds to several endogenous TGF-β super family ligands, thereby weakening abnormal Smad2/3 signaling. Inhibition of TGF-β leads to increased differentiation and proliferation of erythroid precursors.

FDA APPROVED INDICATIONS:

- Treatment of anemia in adults with β-thalassemia requiring regular RBC transfusions
- Treatment of anemia failing an erythropoiesis stimulating agent and requiring two or more red blood cell units over eight weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).
- Treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.

POSITION STATEMENT:

Beta-thalassemia

Beta-thalassemia is a rare genetic blood disorder characterized by partial or complete deficiency of beta globin chain synthesis, leading to reduced red blood cell (RBC) production. The reduced amount (beta+) or absence (beta0) of beta globin chains result in an unbalanced excess of alpha globin chains, which leads to a cascade of events through the generation of ROS. ROS activates apoptotic pathways, hemolysis of mature red blood cells and degradation of immature erythroid precursors in the bone marrow (also known as ineffective erythropoiesis).

Beta-thalassemia is relatively rare in the United States, but it is one of the most common autosomal recessive disorders in the world. Incidence of symptomatic cases is estimated to be approximately one in 100,000 individuals worldwide. The condition is particularly prevalent in the Mediterranean, Middle East, Africa, central

Asia, India, Southern China and in South America. High gene frequency of beta-thalassemia in these regions is most likely related to the selective pressure from *Plasmodium falciparum* malaria.

Clinical presentation of β-thalassemia manifests usually within the first two (2) years of life and requires RBC transfusions once diagnosed. If patients are left untreated or poorly transfused, the clinical picture is characterized by growth retardation, pallor, jaundice, leg ulcers and skeletal changes from expansion of the bone marrow.
Current treatment relies on regular RBC transfusions and iron chelation therapy. However, long-term transfusion therapy can lead to cardiovascular, liver, and endocrine complications from iron overload.

Luspatercept-aamt represents the first FDA approved therapy for this condition.

Summary of Clinical Trials:
BELIEVE Trial (unpublished; Clinical Trials.gov Identifier: NCT02604433)

- Study Design: R, DB, PC, Phase 3
- Study Duration: 48 weeks
- Patient population (N=336)
    - Inclusion criteria: Adult patients with beta thalassemia requiring regular blood transfusions (6-20 units every 24 weeks prior to randomization with no greater than 35-day transfusion-free period at that time)
    - Exclusion criteria: Patients with diagnosis of hemoglobin S/β-thalassemia or alpha-thalassemia, DVT or stroke requiring medical intervention ≤24 weeks prior to randomization, chronic anticoagulation, platelet count <100 x 10^9/L, poorly controlled diabetes, use of ESA, ≤24 weeks prior to randomization, hydroxyurea treatment ≤24 weeks prior to randomization, pregnant or lactating females, uncontrolled hypertension, major organ damage, history of malignancy
- Intervention: Luspatercept 1 mg/kg subcutaneously once every 21 days plus best supportive care vs. Normal saline solution and best supportive care
- Primary endpoint: Proportion of subjects with ≥33% reduction from baseline in RBC transfusion burden with a reduction of at least two units from Week 13 to Week 24 compared to Week 12 prior to randomization
- Secondary endpoint:
    - Proportion of subjects with ≥33% reduction from baseline in RBC transfusion burden during weeks 37 to 48
    - ≥50% reduction from baseline in RBC transfusion burden during weeks 13 to 24

- ≥50% reduction from baseline in RBC transfusion burden during weeks 37 to 48
- Mean change from baseline in RBC transfusion burden during weeks 13 to 24

Efficacy Results:

		Luspatercept (n=224)	Placebo (n=112)	Odds Ratio (CI)	P value
Primary Endpoint	≥33% reduction in blood transfusion in Week 13-24	21.4% (n=48)	4.5% (n=5)	5.79 (2.24-14.97)	<0.0001
Secondary Endpoints	≥33% reduction in blood transfusion in Week 37-48	19.6%	3.6%	6.44 (2.27-18.26)	<0.0001
	≥50% reduction in blood transfusion in Week 13-24	7.6%	1.8%	4.55 (1.03-20.11)	0.0303
	≥50% reduction in blood transfusion in Week 37-48	10.3%	0.9%	11.92 (1.65-86.29)	0.0017

- Mean change in transfusion burden from baseline to weeks 13-24: -1.35 RBC units/12 weeks (95% CI -1.77 to -0.93; P<0.001)

Safety Results:

Adverse Event	Luspatercept	Placebo
Bone pain	19.7%	8.3%
Arthralgia	19.3%	11.9%
Cough	14.3%	11%
Dizziness	11.2%	4.6%
Hypertension	1.8%	0%
Thromboembolic events	3.6%	0.9%

- GRADE evidence rating: C
  - Strengths: Multicenter study from 15 countries, double-blinded, randomized, placebo-controlled
  - Limitations: Uncertain if threshold of 33% reduction of transfusion burden is associated with long-term benefit

Piga A et al (PubMed ID: 30617198)

- Study Design: OL, NR, UC, Phase 2
- Study Duration: 24 weeks initial stage; 5-year extension stage (currently ongoing)
- Patient population (N=64)
  - Inclusion criteria: Adult patients ≥18 years with documented diagnosis of β-thalassemia and classified as either non-transfusion dependent (<4 units RBC every eight weeks) or transfusion dependent (≥4 units RBC every eight weeks)
  - Exclusion criteria: Folate deficiency, symptomatic splenomegaly, history of thromboembolic events, any clinically significant major organ disease that is inadequately controlled
- Intervention:

  - Initial stage: Luspatercept 0.2 to 1.25 mg/kg once every 21 days received in dose escalation stages (0.2, 0.4, 0.6, 0.8, 1.0, 1.25 mg/kg)
  - Expansion stage: Luspatercept 0.8 mg/kg with dose titration up to 1.25 mg/kg allowed after completion of 2 treatment cycles
- Primary endpoint:
  - Hgb increase from baseline of ≥1.5 g/dL for ≥2 weeks (in the absence of RBC transfusions) for non-transfusion dependent patients
  - Reduction in RBC transfusion burden of ≥20% over a 12-week interval for transfusion-dependent patients
- Secondary endpoint:
  - Hgb increase of ≥1.5 g/dL from baseline for ≥12 consecutive weeks for non-transfusion dependent patients
  - Reduction in RBC transfusion burden of ≥33% or ≥50% in transfusion-dependent patients
  - Time to and duration of erythroid response
  - Changes in liver iron concentration (LIC) measured using MRI

Efficacy Results:

Non-transfusion dependent patients (n=31)		95% CI
Mean Hgb increase ≥1.5 g/dL for 14 days	18 (58%)	39.1-75.5
Transfusion-dependent patients (n=32)		
Transfusion burden reduction		
≥20%	26 (81%)	63.6-92.8
≥33%	23 (72%)	53.3-86.3
≥50%	20 (63%)	43.7-78.9

Safety Results:

Adverse Event	**Grade 1-2**	**Grade 3**
Bone pain	33%	5%
Headache	25%	2%
Myalgia	20%	0%
Arthralgia	19%	0%
Musculoskeletal pain	16%	0%
Back pain	11%	0%
Injection site pain	11%	0%

- GRADE evidence rating: D
  - Strengths: Inclusion of transfusion-dependent and non-transfusion dependent patients, a priori power analysis conducted for expansion cohort
  - Limitations: Open-label, single group study without control group for comparison; small population size (n=64) treated at various doses

Myelodysplastic syndrome (MDS)

MDS refers to a group of hematopoietic stem/progenitor cell (HSPC) disorders characterized by poor marrow cell function. This syndrome leads to ineffective

hematopoiesis, cytopenias, and carries a risk of transformation to acute myeloid leukemia.[11,12]

Treatment of MDS is based on disease type and risk score:[12]

- Disease-typing is based on WHO criteria and takes into account: number of dysplastic cell lineages, number of cytopenias, proportion of early red blood cells (RBCs) that are ring sideroblasts, proportion of blast cells in blood and bone marrow, and genetic abnormalities.
    - These criteria identify 6 distinct types of MDS: with multi-lineage dysplasia (MDS-MLD), with single lineage dysplasia (MDS-SLD), with ring sideroblasts (MDS-RS), with excess blasts (MDS-EB), with isolated del(5q), and unclassifiable (MDS-U).[13,14]
- MDS risk scoring is done using the Revised International Prognostic Scoring System (IPSS-R).[12] This score takes into account: genetics, percentage medullary blasts, hemoglobin, platelets, and ANC. The score predicts median survival, and time to disease progression to AML.[15] Patients with MDS are classified into five risk groups based on this risk score (very low, low, intermediate, high, very high).[12,15]
    - High to very-high risk MDS requires intensive therapy with allogenic hematopoietic stem cell transplant, immune-modulating therapies, or enrollment in clinical trials
    - Very low to intermediate risk MDS is often treated with a disease management strategy rather than intensive therapy with a curative goal; focus on preventing bleeds/infections and treating anemia.[12]
- Granulocyte colony-stimulating factors, lenalidomide, and immunomodulating therapies are alternatives following ESA failure, but only offer approximately 20-30% response rates, and can cause a range of serious adverse events.[17]
- Many patients with MDS become dependent on red blood cell transfusions despite these treatment modalities.[12]
- The National Comprehensive Cancer Network[15] recommendations for luspatercept include:
    - Treatment of lower risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts ≥15% (or ring sideroblasts ≥5% with an SF3B1 mutation) as a single agent [category 1]
    - Treatment of lower risk disease associated with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities with ring sideroblasts <15% (or ring sideroblasts <5% with an SF3B1 mutation) with serum erythropoietin ≤500 mU/mL as a single agent or following no response to an erythropoiesis-stimulating agent (ESA) alone (despite adequate iron stores) [category 2A]

- Erythropoiesis-stimulating agents (ESA) are the preferred treatment when ring sideroblasts <15% and serum erythropoietin ≤500 mU/mL

Revised international prognostic scoring system (IPSS-R) for myelodysplastic syndromes prognostic risk categories and scores[17]

Risk Category	Risk Scores
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

The pivotal trial used for the FDA approval was a double-blind, placebo-controlled phase 3 randomized clinical trial. Eligible patients were adults very low to intermediate risk MDS-RS requiring RBC transfusions (at least 2 units per 8 weeks) and had failed or were unlikely to respond to ESAs (owing to an endogenous erythropoietin level of >200 IU/L).

- Intervention: Patients were randomized in a 2:1 ratio to luspatercept or placebo SQ every 3 weeks for 24 weeks. Luspatercept was dosed initially at 1 mg/kg but could be titrated to 1.33 mg/kg and then 1.75 mg/kg.
- Primary outcome: transfusion independence for at least eight weeks during the study period
- Key secondary endpoint: transfusion independence for at least 12 weeks.
- Results: A total of 229 patients were enrolled in the trial
    - Significantly more patients in the luspatercept met the primary outcome than in the placebo group (38 vs 13%; p<0.001).
    - More patients in the luspatercept group met the key secondary endpoint (28 vs 8%; p<0.001).
- Safety: The most common adverse events (luspatercept vs placebo) were fatigue (27 vs 13%), diarrhea (22 vs 9%), asthenia (20 vs 12%), nausea (20 vs 8%), dizziness (20 vs 5%), and back pain.
    - 31% of patients receiving luspatercept and 30% of patients receiving placebo experienced a serious adverse event.[18]

Luspatercept was studied in ESA- naïve patients with very low to intermediate risk MDS in the COMMANDS trial of 356 patients randomized 1:1 to luspatercept or epoetin alfa. Key eligibility criteria included adult patients who were ESA-naïve with endogenous serum EPO levels of < 500 U/L and who required regular RBC transfusions (2–6 packed red blood cell units per 8 weeks for ≥8 weeks). Patients were stratified by baseline red blood cell transfusion burden (<4 units per 8 weeks vs

≥4 units per 8 weeks), endogenous serum erythropoietin concentration (≤200 U/L vs >200 to <500 U/L), and ring sideroblast status (positive vs negative)[1,16].

- Primary endpoint: proportion of patients who experienced both red blood cell transfusion independence (defined as the absence of any RBC transfusion during any consecutive 12-week period) and an associated concurrent mean improvement in hemoglobin by at least 1.5 g/dL for any consecutive 12 week period during Weeks 1-24
- Results: 86 (59%) of 147 patients in the luspatercept group and 48 (31%) of 154 patients in the epoetin alfa group reached the primary endpoint (common risk difference on response rate 26.6; 95% CI 15.8–37.4; p<0·0001)

REFERENCE/RESOURCES:

1. Reblozyl (luspatercept-aamt) prescribing information. Summit: Celgene Corporation; 2023 August.
2. Luspatercept. In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed November 8, 2023.
3. Fibach E, Rachmilewitz EA. Pathophysiology and treatment of patients with beta-thalassemia—an update. *F1000Res*. 2017;6:2156.
4. Galanello R, Origa R. Beta-thalassemia. *Orphanet J Rare Dis*. 2010;5:11.
5. Vichinsky E, Levine L, Bhatia S et al. Standard of care guidelines for thalassemia. 2012; https://thalassemia.com/documents/SOCGuidelines2012.pdf (accessed 2019 Nov 29).
6. ClinicalTrials.gov. An efficacy and safety study of luspatercept (ACE-536) versus placebo in adults who require regular red blood cell transfusions due to beta (β) thalassemia (BELIEVE). https://clinicaltrials.gov/ct2/show/NCT02604433 (accessed 2019 Nov 29).
7. Sun D, Abraham I. Cost of allogeneic blood transfusion. *World J Hematol*. 2012;1(3):8-13.
8. Weiss M, Parisi Jun M, Sheth S. Clinical and economic burden of regularly transfused adult patients with β-thalassemia in the United States: a retrospective cohort study using payer claims. *Am J Hematol*. 2019;94(5):E129-132.
9. Piga A, Perotta S, Gamberini MR et al. Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia. *Blood*. 2019;133(12):1279-89.
10. Cappellini MD, Viprakasit V, Taher A et al. The BELIEVE trial: results of a phase 3, randomized, double-blind, place-controlled study of luspatercept in adult beta-thalassemia patients who require regular red blood cell (RBC) transfusions. Presented at the 60th Annual Meeting of the American Society of

Hematology (ASH); December 1-4, 2018; San Diego, CA. (accessed 2019 Nov 29).
11. Kubasch AS and Platzbecker U. Setting fire to ESA and EMA resistance: New targeted treatment options in lower risk myelodysplastic syndromes. International journal of molecular sciences, 2019.
12. Hellström-Lindberg E, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin+ granulocyte colony-stimulating factor: significant effects on quality of life. British journal of haematology, 2003.
13. Fenaux P, et al. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. *Blood*, 2019.
14. Fenaux P, et al. Luspatercept in Patients with Lower-Risk Myelodysplastic Syndromes. *New Engl J Med*, 2020.
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, version 3.2023.
16. Platzbecker U, Della Porta MG, Santini V, *et al*. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet. 2023 Jul 29;402(10399):373-385.
17. Greenberg PL, Tuechler H, Schanz J, *et al*. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012 Sep 20;120(12):2454-65. doi: 10.1182/blood-2012-03-420489.
18. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. Hemasphere. 2022 Jul 29;6(8):e732.
19. Association of Public Health Laboratories (U.S.);Centers for Disease Control and Prevention (U.S.). Hemoglobinopathies: current practices for screening, confirmation and follow-up. December 2015. Available from https://stacks.cdc.gov/view/cdc/42387 (accessed November 10, 2023).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH045.1023	**MISCELLANEOUS PRODUCTS** **RETHYMIC®** (allogenic processed thymus tissue-agdc implant)
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 09/23 (JN) P&T Committee Meeting Date: 06/22, 10/23 Original Effective Date: 08/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For authorization of a one-time implant, all the following must be met:

1. Diagnosis of congenital athymia confirmed by all the following criteria:
    a. Absence of genetic markers of severe combined immunodeficiency (SCID)
    b. Flow cytometry, defined as one of the following:
        i. Less than 50 naïve T cells/mm3 in the peripheral blood
        ii. Less than 5% of total T cells being naïve in phenotype
    c. One of the following:
        i. Genetic defect associated with congenital athymia [such as 22q11.2 deletion syndrome, forkhead box protein N1 (FOXN1) deficiency]
        ii. CHARGE syndrome
2. Documentation that infection control measures, including immunoprophylaxis, will be maintained until thymic function is established (immune reconstitution sufficient to protect from infection is unlikely to develop until 6-12 months after treatment)

3. Attestation from provider of absence of comorbidities, in the opinion of the treating clinician, that are reasonably likely to result in severe complications, including death, from administration of allogeneic processed thymus tissue
4. Dose will not exceed 42 slices

EXCLUSION CRITERIA:

- Patients with severe combined immunodeficiency (SCID)
- Patients with heart surgery anticipated within four weeks prior to, or three months after, treatment
- Patients with pre-existing cytomegalovirus (CMV) infection or human immunodeficiency virus (HIV) infection
- Repeat administration of allogenic processed thymus tissue implant or previous history of thymus transplant
- Patients over 18 years of age

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a pediatric immunologist.

COVERAGE DURATION:
Authorization will be for one dose per lifetime. Repeat administration will not be covered.

QUANTITY LIMIT:
42 slices (~55,000 mm^2)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Rethymic® is the first and only FDA-approved treatment indicated for immune reconstitution in pediatric patients with congenital athymia (a condition that is typically fatal within the first 2-3 years of life). Rethymic® is a one-time regenerative tissue-based therapy that would be implanted with an inpatient surgical procedure, similar to other gene therapy such as CAR-T. Proposed mechanism of action of Rethymic® involves the migration of recipient T-cell progenitors from the bone marrow to the implanted Rethymic® slices, where they develop into naïve immunocompetent recipient T-cells. Evidence of thymic function can be observed with the development of naïve T-cells in the peripheral blood; this is unlikely to be observed prior to 6-12 months after

FDA APPROVED INDICATIONS:
Allogenic processed thymus tissue is indicated for immune reconstitution in pediatric patients with congenital athymia

- Limitations of Use: Allogenic processed thymus tissue is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

POSITION STATEMENT:
Congenital athymia arises in children born without a thymus and cause severe immunodeficiency. Most children die within a few years of birth due to infections or autoimmune symptoms. It is associated with other issues including congenital heart and kidney disease, endocrine abnormalities (such as thyroid problems and growth hormone deficiency), gastrointestinal problems, hearing loss, seizures, skeletal abnormalities, minor facial differences and learning and behavioral differences.[4,5] Congenital athymia affects both males and females. The exact incidence and prevalence of this disorder is unknown.[5]

Per the Rate Disease Database, the following conditions can result in congenital athymia:[5]

- Complete DiGeorge syndrome, also known as complete DiGeorge anomaly (cDGA) 22q11.2 deletion syndrome
- CHARGE syndrome
    - CHARGE is an acronym that stands for [C]oloboma, congenital [H]eart defects, choanal [A]tresia, growth [R]etardation, [G]enital hypoplasia and [E]ar anomalies or deafness.
- infant of diabetic mother
- FOXN1 gene deficiency
- TBX1 gene mutation
- TBX2 gene mutation

- PAX1 gene deficiency
- SEMA3E gene mutation

Of note, congenital athymic secondary to being an infant of a diabetic mother is not stated specifically in the above policy criteria as most infants with congenital athymia have chromosome 22q11.2 deletion syndrome or CHARGE syndrome. The above clinical criteria is anticipated to capture a large subset of patients for this rare disease. Clinical judgement will be utilized when assessing patients with congenital athymic secondary to being an infant with a diabetic mother.
Additionally, of note, congenital athymia can be found in a very small number of infants with no identifiable genetic mutations or syndromes.[5]
Physicians may use flow cytometry to diagnose congenital athymia. Very low T cell numbers shortly after birth are a sign of congenital athymia. Of note, diagnosis of congenital athymia cannot be made with a chest x-ray or computerized tomography scan, or by visualization during heart surgery because the thymus can be small or found in a different part of the body such as in the neck in the case of ectopic thymus.[4-5]

There are no other FDA-approved treatments for congenital athymia. Treatment with hematopoietic stem cell transplantation (HSCT) for athymia has been an option, although long-term survival after such transplants is low. Only available treatment for patients is supportive care which can include calcineurin inhibitors, intravenous immunoglobulin (IVIg), and prophylactic antibiotics.

Rethymic® received FDA approval based on efficacy evaluated in 10 prospective, single-center, open-label studies that enrolled a total of 105 patients, including 95 patients in the primary efficacy analysis. Patients were included in the clinical trial if they had congenital athymia, defined as any of the following: cDGA (including 22q11.2dx, CHARGE syndrome, other generic defects associated with congenital athymia, and diabetic embryopathy) in which patients had athymia plus either a congenital heart defect or hypocalcemia/hypoparathyroidism or FOXN1 deficiency. The diagnosis of congenital athymia was based on flow cytometry documenting fewer than 50 naïve T cells/mm3 (CD45RA+, CD62L+) in the peripheral blood or less than 5% of total T cells being naïve in phenotype in 91/95 patients (range 0-98 naïve T cells/mm3). The primary endpoint was Kaplan Meier estimated survival at one year post administration of Rethymic® with the clinical trials demonstrating Kaplan-Meier estimated survival rates of 77% (95% CI [0.670, 0.841]) at one year and 76% (95% CI [0.658, 0.832]) at two years. Additionally, for patients who were alive at one year after treatment with Rethymic®, the survival rate was 94% at a median follow-up of 10.7 years.[6]

REFERENCE/RESOURCES:

1. Rethymic Package insert. Cambridge, MA. Enzyvant Therapeutics, Inc. July 1, 2023.
2. Rethymic In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed Sept., 2023.
3. Rethymic In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed Sept., 2023.
4. IPD Analytics Payer & Provider Insights. NEW DRUG REVIEW: Rethymic (allogeneic processed thymus tissue–agdc). Available at www.ipdanalytics.com (Accessed May 13, 2022) 5. Congenital athymia.
5. Rare Disease Database – NORD. Available at: https://rarediseases.org/rare-diseases/complete-digeorge-syndrome/. Accessed on May 9, 2022.
6. Markert ML, Gupton SE, and McCarthry EA. Experience with cultured thymus tissue in 105 children. The Journal of Allergy and Clinical Immunology. 149 (2); 747-757. August 04, 2021. Available at: https://www.jacionline.org/article/S0091-6749(21)01056-3/fulltext. Accessed on May 10, 2022.
7. Thymus tissue transplantation – Medical Policy. Anthem BlueCross. March 25, 2022. Available at: https://www.anthem.com/dam/medpolicies/abc/active/policies/mp_pw_e001585.html. Accessed on May 10, 2022.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCONC058B.0224	**ANTINEOPLASTIC AGENTS** **RITUXIMAB** See Appendix A for medications covered by policy
Effective Date: 4/1/2024	**Review/Revised Date**: 08/06, 04/07, 12/08, 02/09, 12/09, 04/10, 06/11, 02/13, 06/13, 02/14, 02/15, 06/15, 07/15, 01/16, 12/16, 01/18, 04/18, 08/18, 01/19, 03/19, 09/19, 12/19, 01/20, 12/20, 04/21, 07/21, 01/22. 04/22, 01/23, 05/23, 01/24 (JN)
Original Effective Date: 08/06	**P&T Committee Meeting Date**: 08/06, 04/07, 12/08, 02/09, 12/09, 04/10, 06/11, 02/13 , 06/13, 02/14, 02/15, 06/15, 07/15, 02/16, 02/17, 02/18, 06/18, 10/18, 02/19, 04/19, 10/19, 12/19, 02/20, 06/20, 02/21, 04/21, 08/21, 02/22, 04/22, 02/23, 06/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 13	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit, some medically- accepted indications (as outlined in the Required Medical Information section).

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), both of the following criteria must be met:
    a. For **non-preferred rituximab** products: Documented trial and failure, intolerance, or contraindication to the use of both of the preferred biosimilar medications: Ruxience® (rituximab-pvvr) and Truxima® (rituximab-abbs). See Appendix A for preferred and non-preferred rituximab products
    b. Requests for rituximab may be approved for the following indications when the criteria below are met:
        i. For **Oncologic Diagnoses:** Use must be for a FDA approved indication or indication supported by National Comprehensive Cancer Network (NCCN) guidelines with recommendation 2A or higher
        ii. For **Rheumatoid Arthritis:**
            - Documentation of trial, failure, intolerance, or contraindication to at least one of the following targeted

immune modulators: etanercept, adalimumab, or infliximab **AND**

- Documentation that rituximab will be used concurrently with methotrexate. If intolerance or contraindication to methotrexate, then in combination with another disease-modifying antirheumatic drug (DMARD) (for example, leflunomide, sulfasalazine, hydroxychloroquine), unless medical rationale is provided to support monotherapy.

iii. For **Vasculitis,** including antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis [Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)] and refractory polyarteritis nodosa (resistant to cyclophosphamide):
- Documentation that rituximab will be given in combination with glucocorticoids, **AND**
- Documentation of severe disease (for example, critical organ system involvement)

iv. For **Immune Thrombocytopenia (ITP):**
- Documentation of trial, failure, intolerance, or contraindication to systemic corticosteroid therapy, **AND**
- Documentation of active bleeding, or high-risk of bleeding, or a platelet count less than 30,000 cells per microliter

v. For **Relapsing and Remitting Multiple Sclerosis (RRMS):** One of the following:
- Documentation of trial, failure, or intolerance, to at least two disease modifying therapies indicated for RRMS, OR
- Documentation that patient has highly active or aggressive disease

vi. For **Refractory Myasthenia Gravis:**
- Documentation that patient has severely impaired function due to myasthenia gravis, **AND**
- Documented trial, failure, intolerance, or contraindication to at least two of the following conventional therapies:
  - Acetylcholinesterase inhibitors (for example, pyridostigmine)
  - Corticosteroids (for example, prednisone, methylprednisolone)
  - Immunosuppressive agents (for example, azathioprine, cyclosporine, mycophenolate)
  - Plasma exchange

vii. For **Autoimmune Hemolytic Anemia (AIHA):**

- Diagnosis of warm AIHA and documentation of trial, failure, intolerance, or contraindication to glucocorticoids,
  OR
- Diagnosis of cold AIHA or cold agglutinin disease

viii. Confirmed diagnosis of **Neuromyelitis Optica (NMO)**
ix. Confirmed diagnosis of **Moderate to Severe Pemphigus Vulgaris (PV)**

2. For **patients established on therapy** with the requested product (within the previous year): Documentation of adequate response to the medication must be provided.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a specialist for the respective indication such as: an oncologist, hematologist, rheumatologist, neurologist (in the case of RRMS, NMO), dermatologist (in the case of PV), or nephrologist (in the case of renal disease).

COVERAGE DURATION:
For oncologic diagnoses: Authorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes

For non-oncologic diagnoses: Initial authorization will be approved for six months and reauthorization will be approved until no longer eligible with the plan, subject to formulary and. or benefit changes

---

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCONC058B	ANTINEOPLASTIC AGENTS RITUXIMAB See Appendix A for medications covered by policy

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Rituximab binds to the CD20 antigen on B-lymphocytes and the Fc portion recruits immune functions to mediate B-cell lysis. Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

Rituximab has a boxed warning for severe mucocutaneous reactions, hepatitis B (HBV) reactivation, and progressive multifocal leukoencephalopathy (PML). Intravenous rituximab also has a boxed warning for fatal-infusion related reactions within 24 hours of administration. The majority of these reactions occur with the first infusion.

FDA APPROVED INDICATIONS:
Rituximab and biosimilars, injection for intravenous use
- Non-Hodgkin's Lymphoma (NHL)
    - Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
    - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
    - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
    - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia (CLL): in combination with fludarabine and cyclophosphamide (FC) for the treatment of patients with previously untreated and previously treated CD20-positive CLL
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult and pediatric patients two years of age and older in combination with glucocorticoids (Rituxan®, Ruxience®, Truxima® only for adult and pediatric patients; Riabni® for adult patients only)
- Rheumatoid Arthritis (RA): (Moderate to Severe), in combination with methotrexate, in patients who had an inadequate response to one or more tumor-necrosis-factor (TNF) antagonist therapies

Rituxan® only
- Moderate to severe Pemphigus Vulgaris (PV) in adult patients

- Mature B-cell NHL and mature B-cell acute leukemia (B-AL): previously untreated, advanced stage, CD20-positive, diffuse large B-cell lymphoma (DLBCL), Burkitt-like lymphoma (BLL) or mature B-cell acute leukemia (B-AL) in combination with chemotherapy in pediatric patients age 6 months and older

  Limitations of use: Rituxan® is not recommended for use in patients with severe, active infection.

Rituxan Hycela® (rituximab and hyaluronidase) injection

- Follicular Lymphoma
  - Relapsed or refractory, follicular lymphoma as a single agent
  - Previously untreated follicular lymphoma in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
  - Non-progressing (including stable disease), follicular lymphoma as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
- Diffuse Large B-cell Lymphoma
  - Previously untreated diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens
- Chronic Lymphocytic Leukemia
  - Previously untreated and previously treated CLL in combination with fludarabine and cyclophosphamide (FC)

  Limitations of Use:
  - Initiate treatment only after patients have received at least one full dose of a rituximab product by intravenous infusion.
  - Not indicated for the treatment of non-malignant conditions.

POSITION STATEMENT:

Information to date suggests that patients with **rheumatoid arthritis** (RA) who receive rituximab have an increased risk of progressive multifocal leukoencephalopathy (PML). Physicians should consider the risk of PML in any patient treated with rituximab who presents with new onset neurologic manifestations. Consultation with a neurologist, brain magnetic resonance imaging (MRI) scan, and lumbar puncture should be considered as clinically indicated. The American College of Rheumatology guidelines, updated in 2021, recommend rituximab for use in certain populations including patients who were previously

treated for lymphoproliferative disorders such as B-cell chronic lymphocytic leukemia, non-Hodgkin lymphoma, hairy cell leukemia.

Vasculitis is a term for a general condition that causes inflammation of blood vessels that can lead to occlusion or rupture of the vessels. This can have devastating effects to organ systems, including ischemia or hemorrhage. The cause is unknown in most cases, but certain infections [human immunodeficiency virus (HIV), Hepatitis B] and autoimmune conditions (e.g., rheumatoid arthritis) can be considered risk factors. Diagnosis is typically done through biopsy, angiography, and other blood tests.

Granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis, is an uncommon subset of vasculitis that is characterized by inflammation of blood vessels that primarily affect the upper airways, lungs, and kidneys. Typically, symptoms start in the sinuses and can progress rapidly to organ systems like the kidneys, ultimately causing organ failure or dysfunction (e.g., glomerulonephritis). Microscopic polyangiitis (MPA) is another uncommon form of vasculitis that primarily affects small to medium sized blood vessels in the kidneys, lung, nerves, skin, and joints. Symptoms are related to the affected organ system (e.g., muscle/joint pain, or dermatologic rash). Both GPA and MPA are commonly associated with antineutrophil cytoplasmic autoantibody (ANCA), approximately 80 to 90% of patients are found to have ANCA. Although GPA and MPA are distinct entities within ANCA-associated vasculitis, they have been classified together due to their overlapping manifestations and it can be extremely difficult to differentiate between the two diseases. Experts commonly recognize ANCA antigen types for myeloperoxidase (anti-MPO) or proteinase 3 (anti-PR3), rather than by disease type (GPA or MPA). [12, 13, 14, 28, 29]

The 2022 European League Against Rheumatism (EULAR) update for management of ANCA-associated vasculitis (AAV) was developed in collaboration with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) and the European Vasculitis Association (EUVAS)[15]:

- For remission-induction and major relapse of new-onset organ-threatening or life-threatening AAV, it is recommended to treat with high-dose glucocorticoid therapy in combination with **rituximab** or cyclophosphamide for GPA and MPA (Grade A recommendation)
    - Two randomized controlled trials investigated the use of rituximab in AAV, the RAVE and RITUXVAS trials in patients with GPA and MPA.
    - In both studies, patients received high-dose glucocorticoids with rituximab 375 mg/m^2 weekly
    - Rituximab was non-inferior to cyclophosphamide in both trials

    - Rituximab appeared more effective for relapsing disease in RAVE trial, therefore it is preferred over cyclophosphamide for relapsing disease per EULAR/ERA-DTA recommendations
- Glucocorticoid plus rituximab or cyclophosphamide combination therapy is also recommended with a lower grade of evidence for eosinophilic granulomatosis with polyangiitis (EGPA) which is also known as Churg-Strauss syndrome.
- For remission-induction in non-organ-threatening disease in AAV, EULAR recommends combination of glucocorticoid and either methotrexate or mycophenolate mofetil. .
- Maintenance of remission is achieved by use of low-dose glucocorticoids plus either azathioprine, rituximab, methotrexate, or mycophenolate mofetil (listed in order of the strength of voting by the expert panel who developed the EULAR/ERA-DTA recommendations).
    - Leflunomide is no longer considered first-line therapy for remission maintenance due to more adverse effects compared to the immunosuppressants listed above
- For patients with recurrent infections, rituximab is associated with hypoimmunoglobulinemia, therefore it is recommended to test serum immunoglobulin levels prior to course of rituximab

The use of rituximab for polyarteritis nodosa (PAN) is supported by its efficacy in ANCA-associated vasculitis. PAN is a systemic vasculitis that is treated with glucocorticoids and cyclophosphamide in severe cases. Case reports has shown successful treatment by rituximab for life-threatening polyarteritis nodosa that did not respond to glucocorticoids and cyclophosphamide.

Immune thrombocytopenia (ITP) is also known as immune thrombocytopenic purpura or idiopathic thrombocytopenic purpura. This is an autoimmune disease characterized by immunologic destruction of otherwise normal platelets and is typically caused by an unknown trigger. First line treatment is typically with corticosteroids when the platelet count is $< 30x10^9$/L. Immune globulin (IgG) can be considered for add-on therapy (one-time dose) when a rapid increase in platelet count is needed. Second-line treatments include splenectomy, TPO-receptor agonists (e.g., eltrombopag, romiplostim), and rituximab. Splenectomy is the only treatment that provides sustained remission off all treatments at one year and beyond in a high proportion of ITP patients.

Per the American Academy of Neurology, determining initial treatment **for relapsing remitting multiply sclerosis (RRMS)** should encompass consideration of safety, route of administration, lifestyle, cost, efficacy, common adverse effects (AEs), and tolerability. Rituximab has been used off-label to treat RRMS for many years. A 2021 systematic Cochrane review assessed the beneficial and adverse effects of

rituximab as ‘first choice’ and as ‘switching’ therapy for adults with MS. In reviewing rituximab as a first choice agent for RRMS, one non-randomized study compared rituximab with interferon beta or glatiramer acetate, dimethyl fumarate, natalizumab, or fingolimod in active relapsing MS at 24 months' follow-up. Rituximab likely results in a large reduction in relapses compared with interferon beta or glatiramer acetate (hazard ratio (HR) 0.14, 95% confidence interval (CI) 0.05 to 0.39; 335 participants; moderate-certainty evidence). Rituximab may reduce relapses compared with dimethyl fumarate (HR 0.29, 95% CI 0.08 to 1.00; 206 participants; low-certainty evidence) and natalizumab (HR 0.24, 95% CI 0.06 to 1.00; 170 participants; low-certainty evidence). It may make little or no difference on relapse compared with fingolimod (HR 0.26, 95% CI 0.04 to 1.69; 137 participants; very low-certainty evidence). In those patients that were switching therapy, one RCT compared rituximab with placebo in relapsing MS at 12 months’ follow-up. Rituximab may decrease recurrence of relapses compared with placebo (OR 0.38, 95% CI 0.16 to 0.93; 104 participants; low-certainty evidence). The authors concluded, for preventing relapses in relapsing MS, rituximab as 'first choice' and as 'switching' may compare favorably with a wide range of approved DMTs. A comprehensive review on the treatment of multiple sclerosis by Gholamzad et al. 2019 suggested that rituximab for RRMS patients who did not respond to first- and second-line therapies and in cases where RRMS is stabilized after natalizumab treatment and is a candidate for a RRMS therapy with less PML risk.

Pemphigus vulgaris (PV) is an acquired autoimmune disease in which immunoglobulin (IgG) antibodies target desmosomal proteins to produce intraepithelial, mucocutaneous blistering. Rituxan in combination with short-term prednisone was compared to prednisone monotherapy (1:1) as first-line treatment in 90 newly diagnosed adult patients with moderate to severe pemphigus (74 PV). This was a randomized, open-label, controlled study. 66 of the patients with PV had severe disease, defined by Harman’s criteria. Study treatment included an initial IV infusion of 1 gram of rituximab in combination with a short-term regimen of oral prednisone 0.5mg/kg/day tapered over 3 months for moderate disease and 1mg/kg/day for severe disease tapered over 6 months. All patients received a second IV infusion of 1g on day 15. Maintenance infusions of 500 mg were administered at months 12 and 18. In the prednisone arm, patients received 1 mg/kg/day of oral prednisone tapered over 12 months for moderate disease and 1.5 mg/kg/day oral prednisone tapered over 18 months for severe disease. The primary endpoint was complete remission at month 24 without the use of prednisone therapy for two months or more. Rituximab plus prednisone had an 89% response rate and 90% response rate among the 38 PV patients compared to a 34% response rate among prednisone monotherapy (28% of 36 PV patients).

Autoimmune hemolytic anemia (AIHA) is a group of disorders characterized by a malfunction of the immune system that produces autoantibodies, which attack red blood cells as if they were substances foreign to the body. There are no randomized, controlled prospective trials to compare relative effectiveness of the different treatment options.

- There are two main types of AIHA: Warm AIHA where the autoantibodies attach to and destroy red blood cells (RBC) at normal body temperature and cold AIHA (cold agglutinin disease) where the autoantibodies (IgM) become most active and attack RBC only at temperatures well below normal body temperature.
- Treatment strategy in warm AIHA includes reduction in autoantibody production (e.g., glucocorticoids, rituximab) and reduction in autoantibody effectiveness (e.g., splenectomy)
    - First-line option is glucocorticoids at an initial dose of 1 to 1.5 mg/kg per day of prednisone or its equivalent in adults.
    - Second-line options include splenectomy or rituximab, although splenectomy is more likely to achieve long-term cure.
    - Third-line options include immunosuppressive or cytotoxic agents
- Treatment strategy in cold AIHA (cold agglutinin disease [CAD]) include minimizing cold-induced symptoms, maintaining an acceptable hemoglobin level, and addressing underlying disorders. Glucocorticoids and splenectomy are not effective therapy in CAD. Rituximab-containing regimens are usually recommended as first-line.

Neuromyelitis optica (NMO), previously known as Devic disease, is an autoimmune inflammatory disorder that typically affects the optic nerves and spinal cord.[32] Prophylactic treatment of NMO recurrence must be immediately performed when NMO is identified because the progression of NMO disability is related to the severity of attacks.

The pathogenesis of NMO is related to the presence of aquaporin-4 autoantibody, thus, rituximab has been often utilized as treatment given its activity against CD20. The depletion of CD20 provides a theoretical basis for treatment of autoimmune diseases, in which B cells and autoantibodies play a key role; for example, AQP4-Ab is associated with NMO. A meta-analysis of 26 studies with 577 participants was conducted to evaluate rituximab efficacy in terms of safety and tolerance and assessed the treatment efficacies based on relapse rates and disability. Antibodies against aquaporin-4 autoantibody were recorded in 435 of 577 (75.39%) patients with NMO. Rituximab therapy resulted in a mean − 1.56 (95% CI, − 1.82 to − 1.29) reduction in the mean ARR ratio and a mean − 1.16 (95% CI, − 1.36 to − 0.96) reduction in the mean EDSS score. A total of 330 of 528 patients (62.9%) reached

the relapse-free state. A total of 95 of 577 (16.46%) patients had adverse reactions.[33]

REFERENCE/RESOURCES:

1. Rituxan In: DRUGDEX® System [Internet database]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc.; Updated periodically. Accessed January 4, 2024.
2. Rituxan® package insert. South San Francisco, CA: Genentech; 2023 June.
3. Rituxan Hycela® package insert. South San Francisco, CA: Genentech; 2012 Nov.
4. Truxima® package insert. North Wales, PA: Teva Pharmaceuticals; 2023 Nov.
5. Ruxience® package insert. New York, NY: Pfizer; 2021 Nov.
6. Riabni® package insert. Thousand Oaks, CA: Amgen, Inc; 2020 Dec.
7. National Comprehensive Cancer Network. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. NCCN Guidelines Version 1.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf . Accessed January 6, 2022.
8. National Comprehensive Cancer Network. B-Cell Lymphomas. NCCN Guidelines Version 5.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 6, 2022.
9. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res*. 2021;73(7):924-939.
10. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. *Arthritis Care Res.* 2021; 73(8):1088-1105.
11. Langford CA. Update on the treatment of granulomatosis with polyangiitis (Wegener's). Curr Treat Options Cardiovasc Med. 2012;14(2):164-76.
12. Mukhtyar C, Guillevin L, Cid MC et al. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis*. 2009;68(3):310-7.
13. Villa-Forte A, European League Against Rheumatism, European Vasculitis Study Group. European League Against Rheumatism/European Vasculitis Study Group recommendations for the management of vasculitis. *Curr Opin Rheumatol*. 2010;22(1):49-53.
14. Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. *Drug Design, Development and Therapy*. 2017; 11: 2891-2904

15. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for management of ANCA-associated vasculitis. *Ann Rheum Dis.* 2016; 75(9): 1583-94
16. Seri Y, Shoda H, Hanata N, et al. A case of refractory polyarteritis nodosa successfully treated with rituximab. *Mod Rheumatol*. 2017; 27(4): 696-698
17. Ribeiro E, Cressend T, Duffau P, et al. Rituximab Efficacy during a Refractory Polyarteritis Nodosa Flare. *Case Rep Med.* 2009; doi: 10.1155/2009/738293. Epub 2010 Mar 14.
18. Neunert C, Terrell DR, Arnold DM *et al*. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.Erratum in: *Blood Adv*. 2020;4(2):252.
19. Lucchini E, Zaja F, Bussel J. Rituximab in treatment of immune thrombocytopenia: what is the role of this agent in 2019. *Haematologica*. 2019; 104(6): 1124-1135.
20. Filippini G, Kruja J, Del Giovane C. Rituximab for people with multiple sclerosis. Cochrane Database of Systematic Reviews 2021, Issue 11. Art. No.: CD013874. DOI: 10.1002/14651858.CD013874.pub2. Accessed 08 January 2022.
21. Rae-Grant A, Day GS, Marrie, RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. *Neurology*. Apr 2018, 90 (17) 777-88; DOI: 10.1212/WNL.0000000000005347
22. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis-Executive Summary. *Neurology*. 2021; 96: 114-122. doi:10.1212/WNL.0000000000011124
23. Ghloamzad M, Ebtekar M, Ardestani MS, et al. A comprehensive review on the treatment approaches of multiple sclerosis: currently and in the future. *Inflammation Research.* 2019; 68:25-38
24. Narayanaswami P, Sanders DB, Wolfe G et al. International consensus guidance for management of myasthenia gravis-2020 Update. Neurology. 2016 Jul 26; 87(4): 419-25.
25. Harman KE, Brown D, Exton LS, et al. British association of dermatologists' guidelines for the management of pemphigus vulgaris 2017. *Br J Dermatol*. 2017 Nov; 177(5):1170-1202.
26. Merck Manual. Autoimmune Hemolytic Anemia. https://www.merckmanuals.com/home/blood-disorders/anemia/autoimmune-hemolytic-anemia (Accessed January 9, 2022).
27. Brugnara C, Brodsky R. Warm autoimmune hemolytic anemia in adults (last updated November 30, 2021). In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019.
28. Mayo Clinic. Glomerulonephritis. https://www.mayoclinic.org/diseases-conditions/glomerulonephritis/symptoms-causes/syc-20355705 (Accessed January 9, 2022).

29. Mayo Clinic. Vasculitis. Available at https://www.mayoclinic.org/diseases-conditions/vasculitis/symptoms-causes/syc-20363435 (Accessed January 9, 2022).
30. 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.
31. Michalak SS, Olewicz-Gawlik A, Rupa-Matysek J, Wolny-Rokicka E, Nowakowska E, Gil L. Autoimmune hemolytic anemia: current knowledge and perspectives. Immun Ageing. 2020 Nov 20;17(1):38.
32. Pittock SJ, Berthele A, Fujihara K et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. *N. Engl. J. Med.* 2019; 381:614-625.
33. Gao F, Chai B, Gu C et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis. *BMC Neurology*. 2019; 19:36.
34. Trebst C, Jarius S, Berthele A, et al. Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS*). J Neurol*. 2014;261(1):1–16.
35. Kimbrough DJ, Fujihara K, Jacob A, et al. Treatment of Neuromyelitis Optica: Review and Recommendations. *Mult Scler Relat Disord*. 2012;1(4):180–187.
36. Sellner J, Boggild M, Clanet M et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *European Journal of Neurology*. 2010; 17:1019-1032.
37. Stellmann JP, Krumbholz M, Friede T et al. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. *J Neurol Neurosurg Psychiatry*. 2017; 88(8): 639-647.
38. Scott TF, Frohman EM, De Seze J. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011; 77: 2128-34.
39. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. JAMA Neurol. 2014 Jan 20.
40. Wingerchuk DM, Banwell B, Bennet JL et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2).
41. Tahara M, Oeda T, Okada K, Kiriyama T, Ochi K, Maruyama H, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2020 Apr;19(4):298-306. doi: 10.1016/S1474-4422(20)30066-1. Epub 2020 Mar 18. PMID: 32199095.

42. Murrell DF, Pena S, Joly P, et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. *Journal of the American Academy of Dermatology*, 2020-03-01; 82(3): 575-585e1.

APPENDIX A.

Brand Name	Generic Name	HCPCS Code
Preferred Products		
Ruxience®	rituximab-pvvr	Q5119
Truxima®	rituximab-abbs	Q5115
Non-preferred Products		
Riabni®	rituximab-arrx	Q5123
Rituxan®	rituximab infusion	J9312
Rituxan Hycela®	rituximab & hyaluronidase infusion	J9311

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM033.1223	**HEMATOLOGICAL AGENTS** **RYPLAZIM®** (plasminogen, human-tvmh vial)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/22, 11/23 (CJD)
Original Effective Date: 08/22	**P&T Committee Meeting Date**: 06/22, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:
1. Diagnosis of plasminogen deficiency type 1 confirmed by one of the following:
    a. Genetic testing (biallelic pathogenic variants in PLG gene), or
    b. Confirmed hypoplasminogenemia (reduced plasminogen protein levels and functional activity)
2. Documentation of plasminogen activity level of 45% or lower of laboratory standard within the previous six months
3. Documentation of clinical signs and symptoms of the disease (such as ligneous conjunctivitis, gingivitis, tonsillitis, abnormal wound healing)

For initial reauthorization, the following criteria must be met:
1. Documented positive response to therapy, defined as improvement in lesion number/size or improved function from baseline

For subsequent reauthorization, the following criteria must be met:
1. Documentation of no new or recurring lesions

2. Documentation that trough plasminogen activity levels are maintained at least 10% above baseline trough levels (indicating absence of anti-plasminogen antibodies)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a geneticist, hematologist, pulmonologist, ophthalmologist, and/or pediatric subspecialist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for six months.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Ryplazim® is the first FDA approved therapy for plasminogen deficiency (PLGD) type 1 (hypoplasminogenemia). Ryplazim® works by temporarily increasing plasminogen level in the blood.

FDA APPROVED INDICATIONS:
Ryplazim® is indicated for the treatment of patients with PLGD type 1 (hypoplasminogenemia).

POSITION STATEMENT:

Per the Genetic and Rare Disease Information Center, "type 1 plasminogen deficiency (PLGD) is a genetic condition associated with inflamed growths on the mucous membranes, the moist tissues that line body openings such as the eye, mouth, nasopharynx, trachea, and female genital tract. The growths may be triggered by local injury and/or infection and often recur after removal. The growths are caused by the deposition of fibrin (a protein involved in blood clotting) and by inflammation. Type 1 plasminogen deficiency is caused by genetic changes in the PLG gene. It is inherited in an autosomal recessive pattern."[5]

- In the United States there may be between 300 to 3,000 estimated people with type 1 PLGD.
- Symptoms can vary in area impacted and severity. The most common signs/symptoms include eye disease/abnormal vision and gingivitis/gingival overgrowth.
- Other abnormalities may include: reproductive system (fallopian tube/ovary/cervicitis), central nervous system (hydrocephalus, Dandy-Walker malformation), middle ear, respiratory system, skin, duodenal ulcer, nephrolithiasis, periodontitis.
- It is anticipated that only one or two patients would be expected to require plasminogen therapy in a one million-member health plan.
- There is currently no screening test available for PLGD; molecular genetic testing can only confirm a diagnosis. However, testing for PLG gene is not commonly performed in clinical practice. Diagnosis therefore generally relies on clinical symptoms, family medical history, and confirmatory testing. PLGD is highly individualized, so while some infants and children may show early manifestations, others may not have symptoms until adulthood.
- There is currently no standardized treatment for individuals with PLGD due to the rarity of the disease.

Per the package insert, Ryplazim® administration should be assessed every 12 weeks and may be discontinued due to neutralizing antibodies.[1]

Ryplazim was FDA approved based on evidence from one single-arm, open-label, phase 2/3 unblinded clinical trial (*Shapiro et al.)* enrolling 15 adult and pediatric patients with plasminogen type 1. Patients were included (see clinical trial for all inclusion criteria) in the trial if they had a history of lesions and symptoms consistent with a diagnosis of congenital plasminogen deficiency and a plasminogen activity level of equal to or less than 45%. The primary endpoint was number and percentage of patients who achieved target trough plasminogen activity levels, defined as an increase of individual plasminogen activity trough level by at least an absolute 10% above baseline, for at least three measurements in 12 weeks. The effectiveness of plasminogen was demonstrated by at least 50% improvement of lesions in any of the 15 patients through the 48 weeks of treatment.

REFERENCE/RESOURCES:

1. Ryplazim Package insert. Prometic Biotherapeutics, Inc. Fort Lee, New Jersey. November 15, 2021.
2. Ryplazim In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed October 31, 2022.
3. Ryplazim In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed Otober 31, 2022.
4. Type 1 plasminogen deficiency. NIH Genetic and Rare Diseases Information Center (GARD). Available at: https://rarediseases.info.nih.gov/diseases/4380/type-1-plasminogen-deficiency. Accessed on May 8, 2022.
5. Shapiro A.D, Nakar C., Parker JM, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood (2018) 131 (12): 1301-1310. Available at: https://ashpublications.org/blood/article/131/12/1301/36615/Plasminogen-replacement-therapy-for-the-treatment . Accessed on April 24, 2022.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH040.1023	**MISCELLANEOUS PRODUCT** **SAPHNELO®** (anifrolumab-fnia vial)
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 09/22, 09/23 (KN) P&T Committee Meeting Date: 10/21, 10/22, 10/23 Original Effective Date: 01/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit

For Medicaid: Coverage is limited to a condition that has been designated a covered line-item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions, such as urticaria, falls under this benefit when it impacts the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
All of the following must be met:
Initial authorization:
1. Documented diagnosis of Systemic Lupus Erythematosus (SLE) with laboratory test results showing at least one of the following:

   a. Positive Antinuclear antibody (ANA)
   b. Positive anti-double-stranded DNA (anti-dsDNA) on two or more occasions, OR if tested by ELISA, an antibody level above laboratory reference range
   c. Positive anti-Smith (Anti-Sm)
   d. Positive anti-Ro/SSA and anti-La/SSB antibodies

AND

2. Documented failure of an adequate trial (such as inadequate control with ongoing disease activity and/or frequent flares), contraindication, or intolerance to at least one of the following:
   a. Oral corticosteroid(s)
   b. Azathioprine
   c. Methotrexate
   d. Mycophenolate mofetil
   e. Hydroxychloroquine
   f. Chloroquine
   g. Cyclophosphamide

AND

3. Documentation that patient will continue to receive standard therapy (such as, corticosteroids, hydroxychloroquine, mycophenolate, azathioprine, methotrexate)

<u>Reauthorization:</u>

1. Documentation of positive clinical response to anifrolumab (such as, improvement in functional impairment, decrease of corticosteroid dose, decrease in pain medications, decrease in the number of exacerbations since prior to start of anifrolumab)
2. Patient currently receiving standard therapy for SLE

EXCLUSION CRITERIA:

Anifrolumab will not be approved if any of the following are present:

1. Severe active lupus nephritis
2. Severe active central nervous system lupus
3. Current use of other biologic immunomodulators
4. Concurrent use of voclosporin (Lupkynis®) or belimumab (Benlysta®)

AGE RESTRICTIONS:

May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:

Must be prescribed by, or in consultation with, a rheumatologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for 12 months.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Anifrolumab is a human immunoglobulin G1 kappa (IgG1k) monoclonal antibody that binds to subunit 1 of the type 1 interferon receptor (IFNAR) and inhibits type 1 IFN signaling. Anifrolumab also induces internalization of IFNAR1 and reduces the levels of cell surface IFNAR1. Increased IFNAR signaling has been associated with SLE and correlates with disease activity and severity.

Anifrolumab is available as an intravenous infusion in patients aged 18 years and older who are receiving standard therapy for SLE. Anifrolumab should not be used as monotherapy.

FDA APPROVED INDICATIONS:
- Treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy

Limitations of Use:
- Saphnelo has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus

POSITION STATEMENT:
Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease that presents with a wide range of symptoms including fatigue, joint pain, skin rash,

and swelling in the face and/or feet. SLE has a variable prognosis that depends on the disease severity and type of organ involvement. Current guideline for SLE is the European League Against Rheumatism (EULAR) which was last published in 2019. It does not include the newest agent, anifrolumab.

- Hydroxychloroquine is recommended for all patients with SLE
- Glucocorticoids can be used to provide rapid relief of symptoms.
- Immunosuppressive drugs (methotrexate, azathioprine, and mycophenolate mofetil) can facilitate glucocorticoid tapering and may prevent disease flares
- Cyclophosphamide can be used for severe organ-threatening or life-threatening SLE as well as rescue therapy in patients not responding to immunosuppressives
- Add-on treatment with belimumab can be considered in patients with inadequate response to standard of care

The efficacy and safety of anifrolumab was established in two randomized, double-blind, placebo-controlled trials, with a third trial that did not show benefit over placebo.

In the MUSE study, patients were required to meet the American College of Rheumatology (ACR) criteria for SLE and have autoantibody-positive with moderately to severe active SLE (defined by Systemic Lupus Erythematosus Disease Activity Score [SLEDAI], British Isles Lupus Assessment Group Index [BILAG] and Physicians Global Assessment [PGA]). All patients must also have been receiving a stable, standard regimen for SLE (i.e. corticosteroids, immunosuppressives, or antimalarials). Patients were randomized to receive anifrolumab IV 300mg, anifrolumab 1000mg, or placebo every four weeks. The primary endpoint was a composite of the SLE Responder Index (SRI-4) at week 24 with a sustained reduction in oral corticosteroids from week 12 through week 24. The primary endpoint with anifrolumab 300mg versus anifrolumab 1000mg versus placebo was 34.3% vs 28.8% vs 14.6%, respectively ($p = 0.014$ for placebo compared with anifrolumab 300mg, $p = 0.062$ for placebo compared with anifrolumab 1000mg).

- SRI-4 response is defined as:
    - at least a 4-point reduction in SLEDAI-2K
    - less than one new BILAG-2004 A or less than two new BILAG-2004 B organ domain scores
    - less than 0.3 point increase in PGA from baseline
    - no use of restricted medications beyond protocol-allowed thresholds
    - no discontinuation of investigational product.
- SLEDAI-2K captures the patient's persistent, active disease, BILAG-2004 assigns each domain a score from A through E, with an "A" score representing disease activity sufficient to require high-dose steroids, immunosuppressants, or

anticoagulation. A “B” score represents moderate disease activity requiring low dose corticosteroids, topical steroids or immunosuppressives, anti-malarial, or non-steroidal anti-inflammatory drugs. Scores C through E indicate mild to no disease activity.

- PGA is a general health assessment rated on a visual analog scale

In the TULIP1 study, patients were required to meet the American College of Rheumatology (ACR) criteria for SLE and have autoantibody-positive with moderately to severe active SLE. All patients were also required to be receiving a stable, standard regimen for SLE (i.e. corticosteroids, immunosuppressives, or antimalarials). Patients were randomized to receive anifrolumab IV 150mg, anifrolumab 300mg, or placebo every four weeks. The primary endpoint was the SLE responder index-4 (SRI-4) response at week 52. The primary endpoint with anifrolumab versus placebo was 40% vs 36%, respectively (p = 0.412) and the primary endpoint was not met. However, secondary endpoints, including the British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response, sustained oral corticosteroid dose reduction, and organ specific measures of skin and joint responses, suggested the possibility of clinical benefit of anifrolumab.

- BICLA was defined as:
    - reduction in any moderate-to-severe baseline disease activity
    - no worsening in any of the nine organ systems in the BILAG index
    - no worsening in the SLEDAI-2K
    - no increase of 0.3 points or more in the PGA
    - no discontinuation in the trial intervention
    - no use of medications restricted by the protocol)

The TULIP2 study was almost identical to the TULIP1 study, with an exception in the intervention and the primary endpoint. Patients were randomized to receive anifrolumab IV 150mg or placebo every four weeks and the primary endpoint of the study was a BICLA response at week 52. The primary endpoint with anifrolumab versus placebo was 47.8% vs 31.5%, respectively (p = 0.001). BICLA response can register both particle and complete improvement within an organ system. In contrast, the SRI requires complete resolution within a particular item to register change and cannot capture partial improvements.

Overall, the three trials showed similar benefits in favor of anifrolumab for BICLA response, the CLASI, glucocorticoid reduction, and flare reduction, whereas SRI(4) response were similar only in the MUSE trial and the TULIP2 trial.

There has been no direct comparison of anifrolumab to newer agents, such as belimumab.

Anifrolumab has not been studied and is not recommended in severe active lupus nephritis, severe active central nervous system lupus, or in combination with other biologics.

REFERENCE/RESOURCES:

1. Saphnelo®. [package isnert]. Wilmington, DE: AstraZeneca, Inc.; 2021.
2. Saphnelo® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September, 2022
3. 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. doi:10.1136/annrheumdis-2019-215089
4. Izmirly PM, Parton H, Wang L, et al. Prevalence of systemic lupus erythematosus in the United States: estimates from a meta-analysis of the Centers for Disease Control and Prevention National Lupus Registries. *Arthritis Rheumatol*. 2021;73(6):991-996. doi:10.1002/art.41632
5. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis Rheumatol*. 2017;69(2):376-386. doi:10.1002/art.39962
6. Furie R, Morand E, Bruce I, et al. Type 1 interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomized, controlled, phase 3 trial. *Lancet Rheumatol.* 2019;1:e208-19. doi: 10.1016/S2665-9913(19)30076-1
7. Morand EF, Furie R, Tanaka Y, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med*. 2020;382(3):211-221. doi:10.1056/NEJMoa1912196
8. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT01438489, A Study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus; October, 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT01438489. Accessed September 5, 2021.
9. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02446912, Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus; December, 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT02446912. Accessed September 5,

2021.
10. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 -. Identifier NCT02446899, Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus; April 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02446899. Accessed September 5, 2021.
11. Evidence Report on Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value, Institute for Clinical and Economic Review (ICER). Publication date: March 12, 2021. Available at: https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Final-Evidence-Report_041621.pdf

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP031.0623	**TOPICAL PRODUCTS** **SCENESSE®** (afamelanotide implant)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 6/20, 11/20, 05/21, 04/22 (snm), 05/23 (KN) P&T Committee Meeting Date: 06/20, 12/20, 06/21, 06/22, 06/23 Original Effective Date: 08/20 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initial authorization, all the following criteria must be met:
    a. Confirmed diagnosis of erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP) by one of the following:
        i. Gene sequencing showing an FECH, CLPX, or ALAS2 mutation
        ii. Elevated total erythrocyte protoporphyrin greater than 80 mcg/dL AND erythrocyte fractionation shows more than 50% metal-free vs. zinc protoporphyrin
    b. Documentation of characteristic symptoms of EPP/XLP phototoxicity (such as intolerance to light with symptoms including itching, burning, pain, erythema, or scarring of the skin on contact with sunlight)
    c. Documentation that sun avoidance and use of sunscreen and protective clothing have proven inadequate in controlling EPP/ XLP-associated painful skin reactions
    d. Documentation that the condition is having a significant impact on quality of life (QOL)

2. For reauthorization: documentation of a positive response to therapy by of one of the following:
    a. Decreased severity and number of phototoxic reactions
    b. Increased duration of sun exposure
    c. Increased quality of life
3. For request of more than three implants per year: medical justification must be provided addressing why member needs coverage for more than six months out of the year (afamelanotide is typically given during periods of high sunlight exposure, such as from spring to autumn)

EXCLUSION CRITERIA:

1. Current Bowen's disease, basal cell carcinoma, or squamous cell carcinoma
2. Personal history of melanoma or dysplastic nevus syndrome
3. Erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP) with significant hepatic involvement

AGE RESTRICTIONS:

Approved for 18 years of age or older

PRESCRIBER RESTRICTIONS:

Must be prescribed by, or in consultation with a dermatologist or porphyria specialist

COVERAGE DURATION:

Initial and reauthorization will be approved for six months for three implants (Medical justification is required for requests beyond three implants for seasonal coverage)

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Scenesse® is a melanocortin-1 receptor agonist that increases the levels of eumelanin in the skin, shielding against UV radiation (UVR) and visible light, including sunlight. Scenesse® is the first FDA-approved therapy for patients with a history of phototoxic reactions from erythropoietic protoporphyria (EPP).

FDA APPROVED INDICATIONS:
To increase pain free light exposure in adult patients with a history of phototoxic reactions from erythropoietic protoporphyria (EPP).

POSITION STATEMENT:

- Erythropoietic protoporphyria (EPP) is a type of porphyria. Porphyrias are caused by an abnormality in the heme production process.
- In EPP a mutation in the FECH gene results in the accumulation of protoporphyrin, initially in the bone marrow, and then in red blood cells, blood plasma, skin, and eventually liver. The buildup of protoporphyrin causes extreme sensitivity to sunlight (nonblistering cutaneous photosensitivity), and can lead to liver damage, abdominal pain, gallstones, and enlargement of the spleen. However, gallstones and liver damage do not occur very frequently. Patients are predisposed to vitamin D insufficiency because of sun avoidance, which may lead to osteoporosis.
- Management of photosensitivity is an essential therapeutic measure. Avoidance of sun exposure, even through window glass, is the most practical way of preventing photosensitivity reactions in EPP patients. The use of adequate clothing (hats, glasses, gloves) and sunscreen is also advisable. However, these compensatory behaviors greatly impair daily activities and quality of life. Oral beta-carotene may also be used by some patients to increase tolerance to sunlight.
- The approval of Scenesse® was based on two vehicle-controlled studies designed to assess exposure to direct sunlight on days with no phototoxic pain. The first study enrolled 93 patients and the second study enrolled 74 patients.
    - In study 1, the median total number of hours over 180 days spent in direct sunlight between 10 am and 6 pm on days with no pain was 64.1 hours for patients receiving Scenesse® and 40.5 hours for patients receiving vehicle.
    - In study 2, the median total number of hours over 270 days spent outdoors between 10 am and 3 pm on days with no pain for which “most of the day” was spent in direct sunlight was 6.0 hours for patients in the Scenesse® group and 0.75 hours for patients in the vehicle group.

  - Inclusion criteria: Age 18 and older; male or female subjects with characteristic symptoms of EPP phototoxicity and a biochemically-confirmed diagnosis of EPP
  - Exclusion criteria: EPP patients with significant hepatic involvement; personal history of melanoma or dysplastic nevus syndrome; current Bowen's disease, basal cell carcinoma, squamous cell carcinoma, or other malignant or premalignant skin lesions
- The most common adverse reactions (> 2%) with use were implant site reaction, nausea, oropharyngeal pain, cough, fatigue, dizziness, skin hyperpigmentation, somnolence, melanocytic nevus, respiratory tract infection, non-acute porphyria, and skin irritation.
- Concerns related to adverse effects: Increased skin pigmentation and darkening of preexisting nevi and ephelides may occur; full body skin examination (twice yearly) is recommended.
- Other warnings/precautions: Maintain sun and light protection measures during treatment to prevent phototoxic reactions related to erythropoietic protoporphyria.

REFERENCE/RESOURCES:

1. Scenesse package insert. Birmingham, AL: Clinuvel Inc. September 2021.
2. Afamelanotide acetate In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 29, 2022.
3. Afamelanotide acetate In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed April 29, 2022.
4. Langendonk JG, Balwani M, Anderson KE, et al. Afamelanotide for erythropoietic protoporphyria. *N Engl J Med*. 2015;373(1):48-59. doi: 10.1056/NEJMoa1411481.
5. Erythropoietic protoporphyria. National Institute of Health. https://rarediseases.info.nih.gov/diseases/4527/erythropoietic-protoporphyria. Last updated April 11, 2018. Accessed April 29, 2022.
6. Lecha M, Hervé P, Deybach JC. Erythropoietic protoporphyria. Orphanet J Rare Dis. 2009;4:19. https://doi.org/10.1186/1750-1172-4-19.
7. American Porphyria Foundation. Erythropoietic Protoporphyria (EPP) and X-Linked Protoporphyria (XLP). Bethesda, MD: American Porphyria Foundation; 2019. Available at: https://porphyriafoundation.org/for-patients/types-of-porphyria/EPP-XLP/?msclkid=2605911cc81611ec986894abeeef5b89 Accessed April 29, 2022.
8. Linenberger M, Fertrin KY. Updates on the diagnosis and management of the most common hereditary porphyrias: AIP and EPP. Hematology Am Soc Hematol Educ Program. 2020;2020(1):400-410.

doi:10.1182/hematology.2020000124

9. Erythropoietic protoporphyria. National Institute of Health. https://www1.rarediseasesnetwork.org/cms/porphyrias/Healthcare-Professionals/Disorder-Definitions. Accessed May 2, 2022.
10. Gou EW, Balwani M, Bissell DM, et al. Pitfalls in Erythrocyte Protoporphyrin Measurement for Diagnosis and Monitoring of Protoporphyrias. Clin Chem. 2015;61(12):1453-1456. doi:10.1373/clinchem.2015.245456

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCPSY004.0823	**PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENTS** **SKYSONA®** (elivaldogene autotemcel suspension for IV infusion)
Effective Date: 10/1/2023  **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/23 (KN) P&T Committee Meeting Date: 02/23, 08/23 Original Effective Date:04/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For authorization, ALL of the following must be met:
1. Patient has early active cerebral adrenoleukodystrophy (CALD) defined by ALL of the following:
    a. Elevated very-long-chain fatty acid (VLCFA) values
    b. Confirmed Adenosine Triphosphate (ATP)-binding cassette, subfamily D, member 1 (ABCD1) mutation
    c. Active central nervous system (CNS) disease established by central radiographic review of brain magnetic resonance imaging (MRI) demonstrating:
        i. Loes score between 0.5 and 9 (inclusive) on the 34-point scale
        ii. Gadolinium enhancement on MRI of demyelinating lesions
    d. Neurologic Function Score (NFS) of 1 or less
2. Documentation is provided indicating that patient has NONE of the following:

a. History of hematopoietic stem cell transplant (HSCT)
b. History of elivaldogene autotemcel treatment
c. HLA-matched willing sibling donor

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged 4-17 years

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a pediatric metabolic geneticist, neurologist, endocrinologist, hematologist, or oncologist

COVERAGE DURATION:
Authorization is limited to one treatment course per lifetime. Approval duration will be for 12 weeks

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Elivaldogene autotemcel (Skysona®) is a one-time gene therapy for the treatment of patients with cerebral adrenoleukodystrophy (CALD). Elivaldogene autotemcel works by delivering functional copies of the Adenosine Triphosphate (ATP)-binding cassette, subfamily D, member 1 (ABCD1) gene into a patient's own hematopoietic stem cells

FDA APPROVED INDICATIONS:
To slow the progression of neurologic dysfunction in boys 4-17 years old with early, active cerebral adrenoleukodystrophy (CALD)

POSITION STATEMENT:

- The current standard of care is allogeneic hematopoietic stem cell transplantation (HSCT) which carries risks including graft-versus-host disease, potential graft failure, and transplant-related morbidity and mortality. This risk is reduced (and chance of success increased) in patients with early stages of CALD and a matched sibling donor
- Safety and efficacy of elivaldogene autotemcel therapy has been evaluated in two ongoing clinical studies, ALD-102/LTF-304 and ALD-104
    - ALD-102 and ALD-104 differ regarding the myeloablative protocol with ALD-102 utilizing busulfan/cyclophosphamide and ALD-104 utilizing busulfan/fludarabine
    - ALD-102/LTF-304 (2 years/13 years): As of January 2020, 32 patients were enrolled in the study and had 30 months of follow-up. The primary efficacy endpoint of survival free of major functional disabilities (MFD) was met in 20 of the 23 evaluable patients who were then transitioned to LTF-304 for continued monitoring. Two patients were withdrawn and one patient died after rapid disease progression. Nine patients remained in ALD-102
    - LTF-304: As of November 2020, 26 evaluable patients (of the 27 enrolled) were alive and remained MFD-free at a median follow-up of 38.6 months. Fourteen of these patients had been enrolled in the study for over five years
    - Adverse Effects:
        - Boxed Warning for Hematologic Malignancy: As of the time of initial drug approval, three patients had been diagnosed with life-threatening myelodysplastic syndrome thought to have occurred due to the lentiviral vector, Lenti-D
        - Most common adverse effects: mucositis, nausea, vomiting, abdominal pain, diarrhea, decreased appetite, alopecia, headache, rash, pruritis
        - Most adverse effects consistent with mobilization, apheresis, and conditioning treatments
    - FDA advisory committee concluded elivaldogene autotemcel may provide a safer and more efficacious alternative treatment for patients with CALD without a matched sibling donor

REFERENCE/RESOURCES:

1. Eichler F, Duncan C, Musolino PL. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. *N Engl J Med* 2017;377:1630-8.
2. Eichler F, Duncan C, Orchard P, et al. Disease Stabilization Following Treatment with elivaldogene autotemcel (eli-cel, Lenti-D) Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy: Interim Results from Phase 2/3 (ALD-102) and Phase 3 (ALD-104) Studies (2064). *Neurology* 2021;96(15 Supplement)
3. Keam, SJ. Elivaldogene Autotemcel: First Approval. *Mol Diagn Ther* 2021;25:803-809.
4. Skysona® package insert. Somerville, MA. bluebird bio, inc. Sept 2022.
5. U.S. Food and Drug Administration Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. June 9, 2022. Accessed February 5, 2023. https://www.fda.gov/media/159132/download.
6. U.S. Food and Drug Administration Cellular, Tissue, and Gene Therapies Advisory Committee Summary Basis for Regulatory Action. June 9, 2022. https://www.fda.gov/media/162098/download

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO016.0623	**BIOLOGICAL** **SOLIRIS®** (eculizumab injection)
Effective Date: 8/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/09, 06/10, 06/11, 12/11, 02/12, 04/13, 10/13, 06/14, 12/14, 12/15, 10/16, 10/17, 04/18, 11/18, 08/19, 11/19, 10/20, 05/21, 07/21, 09/21, 05/22, 08/22, 04/23 (MTW) P&T Committee Meeting Date: 10/07, 04/09, 06/10, 06/11, 12/11, 02/12, 12/13, 12/14, 12/15, 12/16, 12/17, 06/18, 12/18, 10/19, 12/19, 12/20, 06/21, 08/21, 10/21, 06/22, 08/22, 06/23 Original Effective Date: 10/07 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet the indication-specific criteria below:
    a. For **Paroxysmal Nocturnal Hemoglobinuria (PNH),** all of the following must be met:
        i. Documented, confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by Flow Cytometric Immunophenotyping (FCMI) using at least two independent flow cytometry reagents on at least two cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glychophosphatidylinositol (GPI)-linked proteins (which may include CD59, CD55, CD14, CD15, CD16, CD24, CD45, and CD64),

        AND

        ii. Severe disease as indicated by at least one of the following:
            - Documented history of thrombosis, OR
            - Documentation of at least 10% PNH type III red cells AND at least one of the following:

- Transfusion dependence (e.g., hemoglobin less than 7 g/dL or symptomatic anemia with hemoglobin less than 9 g/dL)
- Disabling fatigue
- End-organ complications
- Frequent pain paroxysms (e.g., dysphagia or abdominal pain)
- Lactate dehydrogenase (LDH) levels greater than or equal to 1.5 times the upper limit of normal

- Trial and failure, intolerance, or contraindication to ravulizumab-cwvz (Ultomiris®)
- Dose and frequency is in accordance with FDA-approved labeling

iii. For **Complement-Mediated Hemolytic Uremic Syndrome (HUS)**, all of the following must be met:
- Diagnosis of non-infectious HUS, meaning HUS is not due to infection with Shiga toxin-producing Escherichia coli
- Clinical presentation that includes: microangiopathic hemolytic anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelets less than 150), and acute kidney injury (elevations in serum creatinine)
- Trial and failure, intolerance, or contraindication to ravulizumab-cwvz (Ultomiris®)
- Dose and frequency is in accordance with FDA-approved labeling

iv. For **Generalized Myasthenia Gravis (gMG)**, all of the following must be met:
- Anti-acetylcholine receptor (anti-AChR) antibody positive
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
- Myasthenia Gravis -Activities of Daily Living (MG-ADL) total score greater than five
- Failed treatment for at least one year with the following:
  - At least TWO immunosuppressive therapies (such as azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus, corticosteroids), OR
  - ONE immunosuppressive therapy and required at least four infusions/year of either intravenous immunoglobulin (IVIg) or plasma exchange (PE)

- Trial and failure, intolerance, or contraindication to ravulizumab- cwvz (Ultomiris®)
- Dose and frequency is in accordance with FDA-approved labeling

v. For **Neuromyelitis Optica Spectrum Disorder (NMOSD),** all the following must be met:
- Diagnosis of NMOSD as defined as the following:
  - Presence of at least one core clinical characteristic (optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions), AND
  - Anti-AQP4 antibody positive
- Documentation that other alternative diagnoses have been excluded, such as multiple sclerosis
- Trial and failure, intolerance (such as neutropenia, LFT elevation, hypogammaglobulinemia) or contraindication to rituximab AND satralizumab (Enspryng®)
- Documentation that medication will not be used in combination with complement inhibitor (e.g., ravulizumab-cwvz), anti-CD20-directed (e.g., rituximab), anti-CD19 directed (e.g., inebilizumab) or IL-6 inhibition pathway therapies (e.g., satralizumab)
- Dose and frequency is in accordance with FDA-approved labeling

b. For patients established on the requested medication within the previous year, must meet the indication-specific criteria below:

i. **For PNH:**
- Documentation of reduced LDH levels, reduced transfusion requirements, or improvement in PNH related symptoms
- Dose and frequency is in accordance with FDA-approved labeling

ii. For **HUS**:
- Documentation of improvement in at least two thrombotic microangiopathy endpoints, such as:
  - Maintenance of platelet counts, meaning improvements or reductions less than 25%
  - Reductions in LDH

- Reduction in number of needed plasmaphoresis or plasma infusion events
- Improvement in kidney function and reduction of dialysis

- Dose and frequency is in accordance with FDA-approved labeling

iii. For **gMG**:

- Initial reauthorization requires documentation of improvement in MG-ADL by at least two points from baseline.
- Dose and frequency is in accordance with FDA-approved labeling

iv. For NMOSD:

- Documentation of positive clinical response to therapy
- Documentation that medication will not be used in combination with complement inhibitor (e.g., ravulizumab-cwvz), anti-CD20-directed (e.g., rituximab), anti-CD19 directed (e.g., inebilizumab) or IL-6 inhibition pathway therapies (e.g., satralizumab)
- Dose and frequency is in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
Concurrent therapy with another FDA-approved product for PNH, meaning Ultomiris® or Empaveli®, unless in a four-week period of cross-titration between Soliris® and Empaveli®

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:

- PNH or HUS: Prescribed by an hematologist/oncologist or nephrologist
- gMG or NMOSD: Prescribed by a neurologist

COVERAGE DURATION:
Initial authorization will be approved for three months and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCBIO016	BIOLOGICAL **SOLIRIS®** (eculizumab injection)

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Soliris® (eculizumab) is a humanized monoclonal antibody indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). The medication specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9.

Soliris® inhibits terminal complement-mediated intravascular hemolysis in PNH patients and complement-mediated thrombotic microangiopathy in patients with aHUS.

The precise mechanism by which Soliris® exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

The precise mechanism by which Soliris® exerts its therapeutic effect in NMOSD is unknown, but is presumed to involve inhibition of aquaporin-4-antibody induced terminal complement C5b-9 deposition.

FDA APPROVED INDICATIONS:

Soliris® is indicated for

- The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis
- The treatment of patients with atypical hemolytic uremic syndrome (HUS) to inhibit complement-mediated thrombotic microangiopathy
- The treatment of patients with anti-acetylcholine receptor antibody positive generalized Myasthenia Gravis (gMG)
- The treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive

Limitation of Use: Soliris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

POSITION STATEMENT:

Paroxysmal Nocturnal Hemoglobinuria (PNH)

A phase III randomized, double-blind, placebo-controlled clinical trial compared eculizumab vs. placebo in 87 patients with documented PNH with >10% PNH cells and requiring four or more transfusions in previous 12 months. Results of the trial included:

- Stabilization of hemoglobin levels in the absence of transfusions in the eculizumab group vs.placebo (49% vs. 0%; p<0.001.)
- Reduction in median administration of packed red blood cells in the eculizumab group vs. placebo (0 vs. 10; p<0.001)
- Reduction in intravascular hemolysis as evidenced by reduced LDH levels
- Clinically significant improvements in quality of life

The FDA approval for ravulizumab (Ultomiris®) for use in the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) was based on two phase 3 open-label non-inferiority clinical trials.

- The 301 study looked at ravulizumab vs eculizumab in 246 adult patients with PNH naive to complement inhibitors.
    - The transfusion avoidance rate was 73.6% and 66.1% for ravulizumab vs eculizumab (difference of 6.8, 95% CI: -4.66, 18.14). LDH normalization occurred in 53.6% and 49.4% of ravulizumab and eculizumab patients, respectively (OR 1.19, 95% CI: 0.80, 1.77)
- The 302 study looked at ravulizumab vs eculizumab in 195 C5-inhibitor-experienced adult patients with PNH
    - The transfusion avoidance rate was 87.6% and 82.7% for ravulizumab and eculizumab (difference of 5.5, 95% CI: -4.3, 15.7). LDH percent change from baseline was -0.82% and 8.4% for ravulizumab vs eculizumab (difference of 9.2, 95% CI: -0.42, 18.8).

Based on these trials there is moderate quality of evidenced that ravulizumab is as effective and safe as eculizumab for the treatment of PNH in adult patients that are treatment naïve and those stable on eculizumab. Additionally ravulizumab has an advantage of a longer half-life than eculizumab.

Hemolytic uremic syndrome (HUS)

Hemolytic uremic syndrome (HUS) is defined by hemolytic anemia, thrombocytporenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA). Atypical HUS (aHUS) is a sub-type of HUS, caused by decreased regulation of the alternative complement pathway on cell surfaces due to a genetic cause. After a diagnosis of a TMA, clinical

diagnosis of aHUS requires thrombotic thrombocytopenic purpura (TTP) and Shiga toxin-producing *E. coli*-associated hemolytic uremic syndrome (STEC-HUS) to be ruled out. TTP is usually ruled out by an ADAMTS13 activity greater than 10%. aHUS is an extremely rare disease that, despite the administration of previous standard treatment with plasma therapy, often progresses to terminal chronic renal failure with a high associated rate of mortality. A Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference recommend all patients with a clinical diagnosis of aHUS be elgible for treatment with a complement inhibitor. At this time there are no direct comparisons between ravulizumab and eculizumab in the treatment of aHUS. Obtaining genetic or molecular studies should not delay treatment as early treatment can avoid irreversible kidney damage. Discontinuation of plasma therapy or complement inhibition may be possible if some patients with aHUS. The safety of Soliris therapy in patients with aHUS was evaluated in two prospective, single-arm studies (aHUS Studies 1 and 2) and one retrospective study (aHUS Study 3). The data were derived from 37 adult and adolescent patients.

Generalized Myasthenia Gravis (gMG)
Generalized Myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission. It is characterized by muscle weakness including ocular motor disturbances, oropharyngeal, respiratory, and limb muscle weakness. Symptoms can fluctuate and can become progressively severe. This disorder occurs when proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors and/or receptor-associated proteins) are attacked by antibody-mediated T-cells. The diagnosis of myasthenia gravis can be established by clinical and serologic testing.

The myasthenia gravis activities of daily living (MG-ADL) is a categorical scale that assesses the impact on daily function of eight signs or symptoms that are typically affected in gMG. Cumulative scores range from 0-24, with higher scores representing more severe disease. A 2-point decrease in the MG-ADL indicates clinical improvement. The MG-ADL correlates with the Quantitative Myasthenia Gravis (QMG) score, which is a 13-item direct physician assessment scoring system quantifying disease severity based on body function impairment. QMG cumulative scores range from 0-39, with higher scores representing more severe disease. A 2-3 point decrease in the QMG indicates clinical improvement.

Institute for Clinical and Economic Review conducted a systematic literature review and cost-effectiveness analysis to evaluate the health and economic outcomes of eculizumab for the treatment of myasthenia gravis. The report found that there is moderate certainty eculizumab has a small net health benefit over conventional therapy, with the possibility of a substantial net benefit. The report concluded that

eculizumab estimated cost effectiveness is well above usual thresholds for cost-effectiveness. Step therapy through efgartigimod was not encouraged at this time, but may be reasonable, as further evidence accumulates, based on price.

Ravulizumab (Ultomiris®), is a monoclonal antibody that inhibits terminal complement mediated intravascular hemolysis. It was engineered from eculizumab to have an extended half-life; its terminal half is approximately four times longer than that of eculizumab. Therefore, ravulizmab is dosed at a lower frequency than eculizumab. Ravulizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

- Prescribers must enroll in the program. Enrollment in the Ultomiris REMS program and additional information are available at www.ultomirisrems.com.
- The ALXN1210-MG-306 study evaluated the safety and efficacy of ravulizumab compared to placebo in patients (n=89) with gMG positive for anti-AChR antibodies. Treatment with ravulizmab demonstrated a statistically significant improvement in the MG-ADL (-1.6, confidence interval [CI] -2.6 to -0.7, $p < 0.001$) and Quantitative Myasthenia Gravis (QMG) total scores (-2.0, CI -3.2 to -0.8, $p < 0.001$) from baseline at Week 26 as compared to placebo. Notably, the least squares mean of the MG-ADL score improvement did not reach a clinically significant decrease of 2 or more.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune inflammatory disorder of the central nervous system. It is primarily characterized by recurrent optic neuritis and myelitis often resulting in poor recovery. Aquaporin-4 (AQP4) is a water channel protein that astrocytes in the central nervous system express. Preclinical data indicate that AQP4-IgG triggers the complement cascade, which leads to inflammation and the formation of the membrane attack complex. The membrane attack complex leads to astrocyte destruction and neuronal injury but is not seen in experimental models in the presence of a complement inhibitor. Diagnostic criteria for NMOSD require at least one core clinical characteristic (e.g., optic neuritis, acute myelitis, area postrema syndrome), a positive test for AQP4-immunoglobulin G (IgG), and exclusion of alternative diagnoses. Currently there are two other FDA approved drugs for NMOSD in adult patients who are anti-AQP4 antibody positive, inebilizumab (Uplizna®) and satralizumab (Enspryng®); however, immunosuppression therapy, such as rituximab, azathioprine and mycophenolate, have been commonly used for relapse prevention.

Eculizumab, a humanized monoclonal antibody, inhibits the terminal complement protein C5 and prevents its cleavage into C5a, which is proinflammatory, and C5b,

which coordinates the formation of membrane attack complex. It is estimated that 65 to 88% of patients with NMOSD are anti-AQP4 antibody positive.

The PREVENT Study evaluated the safety and efficacy of eculizumab compared to placebo in patients (n=143) with AQP4 auto antibody-positive. The primary efficacy end point in this time-to-event trial was the first adjudicated relapse. The time to the first adjudicated on-trial relapse was significantly longer in eculizumab-treated patients compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$). Eculizumab was generally well-tolerated with a safety profile similar to that seen in previous studies and real-world use.

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Immunize patients with a meningococcal vaccine at least two weeks prior to administering the first dose of Soliris, unless the risks of delaying Soliris therapy outweigh the risk of developing a meningococcal infection.
- Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.

Soliris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

- Member must be enrolled in Soliris® REMS (1-888-765-4747) prior to initiating treatment

REFERENCE/RESOURCES:

1. Soliris® (eculizumab) package insert. Cheshire, CT; Alexion Pharmaceuticals, Inc.; 2020 Nov..
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-2811.
3. Hillmen P, Young N, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2006;355:1233-43.
4. Hillmen P, Hall C, Marsh J, et al. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. *N Engl J Med* 2004;350:552-9.

5. Howard JF, Utsugiwasa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study*. Lancet Neurol* 2017; S1474-4422(17)30369-1.
6. Ultomiris® (ravulizumab-cwvz) package insert. Cheshire, CT; Alexion Pharmaceuticals, Inc.; April 2022.
7. Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. *Blood.* 2005;106(12):3699-709.
8. Pittock SJ, Berthele A, Fujihara K et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. *N. Engl. J. Med.* 2019;381:614-625.
9. Rathbone J, Kaltenthaler E, Richards A, et al. A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). *BMJ Open*. 2013;3(11):e003573.
10. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 2013 Sep 1;70(9):1110-7.
11. Gao F, Bingyan C, Gu C et al. Effectiveness of rituximab in neuromyelitis optica: a meta-analylsis. *BMC Neurology*. 2019; 19:36/
12. Sellner J, Boggild M, Clanet M et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. *European Journal of Neurology*. 2010; 17:1019-1032.
13. Stellmann JP, Krumbholz M, Friede T et al. Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response. *J Neurol Neurosurg Psychiatry*. 2017; 88(8): 639-647.
14. Trebst C, Jarius S, Berthele A et al. Update on the diagnosis and treatment of neuromyelitis optica: recommenations of the Neuromyelitis Optica Study Group (NEMOS). *J Neurol.* 2014; 261(1): 1-16.
15. Scott TF, Frohman EM, De Seze J. Evidence-based guideline: Clinical evaluation and treatment of transverse myelitis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2011; 77: 2128-34.
16. Mealy MA, Wingerchuk DM, Palace J, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. JAMA Neurol. 2014 Jan 20.
17. Wingerchuk DM, Banwell B, Bennet JL et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology.* 2015;85(2).
18. Goodship T, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving

Global Outcomes" (KDIGO) Controversies Conference. Kidney International. 2017; 91(3): 539-551.
19. National Organization for Rare Disorders (NORD). Atypical hemolytic uremic syndrome. Available from: https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/. Accessed May 4, 2021.
20. Eculizumab and efgartigimod for the treatment of myasthenia gravis: Effectiveness and value. Institute for Clinical and Economic review. October 2021. Available from: https://icer.org/wp-content/uploads/2021/03/ICER_Myasthenia-Gravis_Final-Report_102021-1.pdf
21. Lee JW, Fontbrune S, Lee WL, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naïve to complement inhibitors: the 301 study. Blood. 2018.
22. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2018.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND070.0423	**ENDOCRINE & METABOLIC DRUGS** **SOMATOSTATIN ANALOGS** **Sandostatin® LAR Depot** (octreotide injection) **Signifor® LAR** (pasireotide intramuscular suspension) **Somatuline® Depot** (lanreotide injection)
Effective Date: 6/1/2023  **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/21, 03/22, 02/23 (JH) P&T Committee Meeting Date: 06/21, 08/21, 04/22, 04/23 Original Effective Date: 09/21 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page: 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit. The following compendia supported indications may be approved subject to criteria: Acquired immunodeficiency syndrome (AIDS)-related diarrhea, chemotherapy-induced diarrhea, oncologic conditions.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet the indication specific criteria below:
    a. For **Acromegaly,** all of the following criteria are met:
        i. Confirmed diagnosis of acromegaly
        ii. Documentation that the patient has persistent disease (such as biochemical or clinical) following surgical resection or is not a candidate for surgical resection
        iii. For coverage of Signifor® LAR: documentation of trial and failure, intolerance or contraindication to octreotide injection therapy or lanreotide subcutaneous depot
    b. For **Cushing's disease**, Signifor® LAR may be covered if all the following criteria are met:

   i. Diagnosis of endogenous Cushing's disease
   ii. Documentation the patient has failed pituitary surgery or is not a candidate for surgery
c. For **Carcinoid Tumors or Carcinoid Syndromes**, Sandostatin® LAR or Somatuline® Depot may be covered when there is documentation of severe diarrhea or flushing
d. For **Vasoactive Intestinal Peptide Tumors,** Sandostatin® LAR or Somatuline® Depot may be covered when there is documentation of severe diarrrhea
e. For **Chemotherapy induced diarrhea**, Sandostatin® LAR may be covered if all the following criteria are met:
   i. Documentation that patient has severe diarrhea caused by chemotherapy
   ii. Documentation of an inadequate response or contraindication to loperamide
   iii. Documentation of good response and tolerability to short-acting octreotide
f. For **AIDS-related diarrhea**, Sandostatin® LAR may be covered if all the following criteria are met:
   i. Documentation that patient has severe diarrhea
   ii. Documentation of an inadequate response or contraindication to loperamide and diphenoxylate/atropine (Lomotil®)
   iii. Documentation of good response and tolerability to short-acting octreotide
g. For **oncologic diagnoses** use must be for a FDA approved indication or indication supported by National Comprehensive Cancer Network guidelines with recommendation 2A or higher

2. For patients established on the requested therapy within the previous year, must meet indication specific criteria below:
   a. For **acromegaly**: documentation of a positive clinical response to therapy such as reduction or normalization of IGF-1/GH level for same age and sex, reduction in tumor size
   b. For **Cushing's disease**: documentation of a positive clinical response to therapy such as clinically meaningful reduction and maintenance in late-night salivary cortisol or 24-hour urinary free cortisol levels, or improvement in signs or symptoms of the disease
   c. For **carcinoid tumors or carcinoid syndromes**: requires documentation of an improvement in the number of diarrhea and flushing episodes

d. For **vasoactive intestinal peptide tumors, chemotherapy-induced diarrhea, and AIDS-related diarrhea**: requires documentation of an improvement in the number of diarrhea episodes
e. For **oncologic diagnoses**: documentation of positive response to therapy

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

---

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS) or Drugdex and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Somatostatin and its analogues are inhibitors of growth hormone release and a variety of gastrointestinal process. Somatostatin is produced by paracrine cells that are scattered throughout the gastrointestinal tract and inhibits gastrointestinal endocrine secretion. Somatostatin is also found in various locations in the nervous system and exerts neural control over many physiological functions.

FDA APPROVED INDICATIONS:

Sandostatin LAR Depot® (10 mg, 20 mg and 30 mg): indicated in patients in whom initial treatment with Sandostatin Injection has been shown to be effective and tolerated

- Acromegaly: Long-term maintenance therapy in acromegalic 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 GH and IGF-1 levels to normal
- Carcinoid Tumors: Long-term treatment of the severe diarrhea and flushing episodes associated with metastatic carcinoid tumors
- Vasoactive Intestinal Peptide Tumors (VIPomas): Long-term treatment of the profuse watery diarrhea associated with VIP-secreting tumors
- For intramuscularly (IM) injection only and should be administered by a trained healthcare provider

Somatulin® Depot (60 mg, 90 mg and 120 mg):

- The long-term treatment of acromegalic patients who have had an inadequate response to or cannot be treated with surgery and/or radiotherapy.
- The treatment of adult patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.
- The treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analog rescue therapy
- For deep subcutaneous (SubQ) injection only and intended for administration by a healthcare provider

Signifor® LAR (10 mg, 20 mg, 30 mg, 40 mg, 60 mg)

- Cushing's disease for whom pituitary surgery is not an option or has not been curative
- Acromegaly in patients who have an inadequate response to surgery and/or for whom surgery is not an option

POSITION STATEMENT:

Acromegaly is a rare chronic disorder characterized by hypersecretion of growth hormone (GH), usually as a result of pituitary adenoma. The hypersecretion of GH leads to the production of excess IGF-1 which can lead to somatic overgrowth, multiple comorbidities, and premature mortality. The goal of treatment in acromegaly is to normalize growth hormone and serum insulin-like growth factor-I (IGF-I) levels to alleviate the signs and symptoms of acromegaly.

The Endocrine Society guidelines (2014) recommend surgery as first-line treatment for most patients. If patients have persistent disease following this surgery, a repeat

surgery should be considered. Pre-operative medical therapy with somatostatin receptor ligands (e.g., Signifor LAR®) should only be considered in patients with increased surgical risk such as severe pharyngeal thickness and sleep apnea, or high-output heart failure. If a patient continues to have persistent significant disease (e.g., elevated insulin-like growth factor (IGF)-1 or moderate-severe symptoms of GH excess), first line medical therapy is first generation somatostatin analogs (i.e., injectable octreotide or lanreotide). Second line therapy is often a switch to pegvisomant or pasireotide LAR depending on individual patient considerations. Pegvisomant added to first generation somatostatin analog may be consider when there is concern for tumor growth and impaired glucose metabolism. If a patient is experiencing only mild symptoms, a dopamine agonist (e.g., cabergoline) is recommended as the initial or adjuvant medical therapy in partial response.

Combination therapy with pasireotide and pegvisomant may also be an option for some patients. As with pasireotide monotherapy, hyperglycemia needs to consider and carefully monitored. Stereotactic radiosurgery or surgical intervention (reintervention) are recommended treatment options if biochemical control is not achieved after second line therapy.

Pasireotide (Signifor LAR®) can cause increases in blood glucose levels which can be severe. Fasting plasma glucose and hemoglobin A1c should be assessed prior to starting Signifor LAR®. Blood glucose monitoring should be done weekly for the first three months after starting Signifor LAR® and for the first six weeks after dose increases. Periodic monitoring as clinically appropriate should continue thereafter.

Cushing's disease is a rare disorder of chronic hypercortisolism due to a corticotropin-secreting pituitary adenoma. The disorder is associated with central obesity, osteoporosis, arterial hypertension, insulin resistance, glucose intolerance, diabetes mellitus, dyslipidemia, cardiovascular disease, and increased mortality. Treatment is geared towards reversing the clinical manifestations by reducing cortisol secretion to normal. According to the Endocrine Society clinical practice guidelines in 2015, the treatment of choice is surgical resection of causal lesion. Second line therapy includes medical therapy, bilateral adrenalectomy, and radiation therapy (for corticotrope tumors), which "must be individualized to each patient".

REFERENCE/RESOURCES:

1. Sandostatin® LAR Depot package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; Mar 2021.

2. Somatulin® Depot package insert. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc.; Jun 2019
3. Signifor® package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020 Jan.
4. Liddle, RA. Physiology of somatostatin and its analogues. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed on May 10, 2021.
5. Octreotide. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
6. Lanreotide. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
7. AACE Guidelines. The American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Acromegaly – 2011 Update. Endocr Pract. 2011;17(Supp 4):1-44.
8. Katznelson L, Laws ER, Melmed S *et al*. Acromegaly: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2014;99:3933–3951.
9. Newell-Price J, Pivonello R, Tabarin A, *et al*. Use of late-night salivary cortisol to monitor response to medical treatment in Cushing's disease. *Eur J Endocrinol*. 2020;182(2):207-217.
10. Amlashi FG, Swearingen B, Faje AT, *et al*. Accuracy of Late-Night Salivary Cortisol in Evaluating Postoperative Remission and Recurrence in Cushing's Disease. J Clin Endocrinol Metab. 2015 Oct;100(10):3770-7.
11. Fleseriu M, Biller BMK, Freda PU *et al*. A Pituitary Society update to acromegaly management guidelines. *Pituitary*. 2021 Feb;24(1):1-13.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP042.0623	**TOPICAL PRODUCTS** **SPEVIGO®** (spesolimab-sbzo vial)
Effective Date: 08/01/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date:05/23 (KN) P&T Committee Meeting Date: 12/22, 06/23 Original Effective Date: 02/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization, all of the following criteria must be met:

1. Diagnosis of generalized pustular psoriasis (GPP), confirmed by both of the following:
    a. Primary, sterile, macroscopically visible pustules on non-acral skin AND
    b. Pustulation is not restricted to psoriatic plaques
2. Presence of an acute flare of generalized pustular psoriasis of moderate to severe intensity, as defined by:
    a. Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 3 or greater AND
    b. The presence of new or worsening pustules AND
    c. Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub score of 2 or greater AND
    d. At least 5% of body surface area (BSA) with erythema and the presence of pustules
3. Dosing must be in accordance with FDA-approved labeling

Requests for one additional dose may be approved one week after initial dose for treatment of the same flare if the following criteria are met:

1. Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score of 2 or higher AND
2. Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub score of 2 or higher
3. Dosing must be in accordance with FDA-approved labeling

For reauthorization, all of the following criteria must be met:

1. All criteria for initial authorization must be met AND
2. Documentation of a clinical response to prior treatment with spesolimab, defined as achieving a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older.

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a dermatologist.

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for two weeks, limited to one 900 mg (2 vials) infusion

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION: Spesolimab-sbzo (Spevigo®) is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by

specifically binding to the IL36R. Binding of spesolimab-sbzo to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL-36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways.

The recommended dose in a single 900 mg intravenous infusion over 90 minutes. If GPP flare symptoms persist, an additional intravenous 900 mg dose (over 90 minutes) may be administered one week after the initial dose.

FDA APPROVED INDICATIONS:
Treatment of generalized pustular psoriasis (GPP) flares in adults.

POSITION STATEMENT:
Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening, form of psoriasis characterized by recurring flares of pustules, and can be accompanied by systemic symptoms such as fever and flushing[9]. GPP most commonly presents as acute generalized pustular psoriasis or generalized annular pustular psoriasis. Acute GPP causes a sudden onset of pustules surrounded by erythematous skin and is usually accompanied by systemic symptoms including high fever, neutrophil leukocytosis, and fatigue[4]. Generalized annular pustular psoriasis is typically a milder form of GPP causing pustules and extensive ring-shaped erythematous plaques. The exact prevalence of GPP is unknown, but estimates range from about 1-9 per million people, and it occurs most frequently in adults[4]. Life-threatening complications that can occur include sepsis, renal, hepatic, cardiac, and respiratory failure[6]. Mortality ranges from 2-16%[10].

Studies of familial cases of GPP have detected mutations in the IL36RN gene which encodes the interleukin-36 receptor antagonist (IL36Ra). IL36Ra is an anti-inflammatory cytokine that plays a role in regulating the production of proinflammatory signal pathways by inhibiting the binding of IL-36 to its receptor. It is thought that the overexpression of IL-1, IL-36, and also IL-17 may play a large role in the pathology of GPP[7,10].

GPP is unpredictable and without treatment flares can be prolonged with frequent recurrence. Drug, infections, and pregnancy have been known to trigger flares; however, flares may also occur spontaneously. Continued therapy is typically required to help prevent recurrent flares. Prior to the approval of spesolimab, there were no other approved treatments for GPP in the United States. Goals of treatment have been to improve skin and systemic symptoms and to minimize risk for life-threatening systemic complications. For stable GPP, off-label standard of care therapies include acitretin and methotrexate. These drugs have a slow onset of action and are not helpful in more severe disease. For more severe, acute GPP,

cyclosporine and infliximab are used off-label. Apremilast, adalimumab, or etanercept can also be used[8]. In Japan, TNF-alpha inhibitors (adalimumab, infliximab), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab) are approved for the treatment of individuals with GPP who have had an inadequate response to conventional therapy[9]. Due to the severity and multisystemic nature of acute GPP flares, hospitalization is often required to ensure appropriate supportive care.

There is currently no validated grading system for GPP severity, and no standardized method of assessing response to treatment.

Clinical Evidence
Effisayil-1 (NCT03782792)

- Phase 2, R, DB, PC clinical trial
- Study Duration: The primary endpoint was analyzed one week after treatment. Patients were followed to week 12.
- Patient Population: Patients (N=53) aged 18 to 75 years old with a history of GPP consistent with the European Rare and Severe Psoriasis Expert Network diagnostic criteria. Eligible patients had a moderate-severe GPP flare, as defined by: a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of >3 (moderate); presence of fresh pustules (new appearance or worsening of pustules); GPPPGA pustulation subscore of >2 (mild), and >5% BSA covered with erythema and the presence of pustules.
    - Key exclusion criteria: Plaque psoriasis without pustules or pustules restricted to psoriatic plaques; drug-triggered acute generalized exanthematous pustulosis; an immediate life-threatening flare of GPP warranting intensive care treatment; current treatment with restricted medications (such as biologics within 2 months of trial, systemic immunomodulating agents within 30 days of trial, methotrexate, cyclosporine, retinoids within 2 weeks of trial)
- Intervention: During the double-blind portion of the trial, patients with a GPP flare were randomly assigned to receive a single 900-mg IV dose of spesolimab (n=35) or placebo (n=18). Patients in both groups could then receive an open-label dose of spesolimab on day 8, an open-label dose of spesolimab as a rescue medication after day 8, or both.
- Primary Endpoint: The proportion of subjects with a GPPPGA pustulation subscore of 0 (indicating no visible pustules) at Week 1 after treatment.
    - Key Secondary Endpoint: a GPPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1.
- Results:

- Primary Endpoint: At the end of week 1, 19 out of 35 patients (54%) in the spesolimab group had a pustulation subscore of 0, vs. 1 out of 18 patients (6%) in the placebo group (difference, 49 percentage points; 95% confidence interval [CI], 21 to 67;p<0.001).
- Secondary endpoint: 15 out of 35 patients (43%) in the spesolimab group had a GPPPGA total score of 0 or 1, vs. 2 of 18 patients (11%) in the placebo group (difference, 32 percentage points; 95% CI, 2 to 53; p=0.02).
- Patients in either treatment group who continued to experience flare symptoms at Week 1 were eligible to receive a single open-label IV dose of 900 mg of spesolimab. At Week 1, 12 (34%) patients in the spesolimab group and 15 patients (83%) in the placebo group received open label spesolimab.
    - In patients who were randomized to spesolimab and received an open-label dose at Week 1, 5 (42%) patients had a GPPPGA pustulation subscore of 0 at Week 2 (one week after their second dose of spesolimab).

- Safety:
    - Most common adverse reactions (>5%): asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, and urinary tract infection.
    - Among patients assigned to the spesolimab group, infections occurred in 6 of 35 patients (17%) through the first week; among patients who received spesolimab at any time in the trial, infections occurred in 24 of 51 patients (47%) at week 12.
- GRADE evidence rating: C+
    - Strengths: randomized and placebo controlled
    - Limitations: unvalidated grading system, small study size, insufficient numbers of patients to determine differences in response according to biological sex, age, race, baseline GPPPGA pustulation subscore, and baseline GPPPGA total score, short trial duration leads to unknown long-term safety and efficacy.

Generalized Pustular Psoriasis Physician Global Assessment (GPPGA)[11]

GPPGA is a modified Physician Global Assessment which has been adapted and used in the clinical trial to evaluate a patient's symptoms of generalized pustular psoriasis (GPP). Using the table below, the erythema, pustules, and scaling of all psoriatic lesions is scored from 0 to 4. Scores are combined and averaged to determine the final GPPGA score. A GPPGA total score can be calculated by combining the average score for erythema + pustules + scaling then dividing by 3. A score of 0 or 1 indicates clear, or almost clear skin presentation. To receive a score

of 0 or 1, the patient must have no fever, in addition to the skin presentation requirements on the following chart.

Score	Erythema	Pustules	Scaling
0 (clear)	Normal or post-inflammatory hyperpigmentation	No visible pustules	No scaling or crusting
1 (almost clear)	Faint, diffuse pink or slight red	Low-density occasional small discrete pustules (noncoalescent)	Superficial focal scaling or crusting restricted to periphery of lesions
2 (mild)	Light red	Moderate density grouped discrete small pustules (noncoalescent)	Predominantly fine scaling or crusting
3 (moderate)	Bright red	High-density pustules with some coalescence	Moderate scaling or crusting covering most or all lesions
4 (severe)	Deep fiery red	Very high-density pustules with pustular lakes	Severe scaling or crusting covering most or all lesions

Ongoing clinical trials:

- Spesolimab is currently being studied in patients with hidradenitis suppurativa, ulcerative colitis, and palmoplantar pustulosis
- Long-term administration of spesolimab is being evaluated with a subcutaneous formulation in a 5-year open-label extension trial and the Effisayil-2 trial on prevention of flares

REFERENCE/RESOURCES:

1. Spevigo® (spesolimab-sbzo) prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Revised 9/2022. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=41a481ee-3062-45d1-aed5-17e8b105634d
2. Spevigo® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed October 26, 2022

3. Spevigo® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed October 26, 2022
4. Orphanet. Generalized Pustular Psoriasis. Available at: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=247353. Accessed 10/27/22
5. FDA/CDER. Multidiscipline Review. BLA 761244. Spevigo (spesolimab-sbzo). August 29,2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761244Orig1s000MultidisciplineR.pdf
6. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol 2014;53:676-684.
7. Boehner, A, Navarini, AA, Eyerich, K. Generalized pustular psoriasis – a model disease for specific targeted immunotherapy, systematic review. Exp Dermatol. 2018; 27: 1067– 1077. https://doi.org/10.1111/exd.13699 American Academy of Dermatology Association. Pustular Psoriasis: Treatment Options. Available at: https://www.aad.org/public/diseases/psoriasis/treatment/genitals/pustular. Accessed 10/27/22
8. Fujita, H., Terui, T., Hayama, K. et al; Japanese guidelines for the management and treatment of generalized pustular psoriasis: The new pathogenesis and treatment of GPP. J Dermatol, 45: 1235-1270. https://doi.org/10.1111/1346-8138.14523
9. Bachelez H, Choon SE, Marrakchi S, et al; Trial of Spesolimab for Generalized Pustular Psoriasis N Engl J Med 2021; 385:2431-2440. DOI: 10.1056/NEJMoa2111563
10. Bachelez H, Choon SE, Marrakchi S, et al; Trial of Spesolimab for Generalized Pustular Psoriasis Supplementary Appendix. N Engl J Med 2021; 385:2431-2440. Available at: https://www.nejm.org/doi/suppl/10.1056/NEJMoa2111563/suppl_file/nejmoa2111563_appendix.pdf
11. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017;31:1792-1799.

CPT/HCPCS CODES

Brand Name	Generic Name	HCPCS Code
Spevigo®	spesolimab-sbzo	J1747

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU021.0823	**NEUROMUSCULAR DRUGS** **SPINRAZA®** (nusinersen vial)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 03/17, 07/17, 07/18, 07/19, 07/20, 06/21, 06/22, 06/23 (MTW) P&T Committee Meeting Date: 04/17, 08/17, 08/18, 08/19, 08/20, 08/21, 08/22, 08/23 Original Effective Date: 06/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:

1. Confirmed genetic diagnosis of spinal muscular atrophy (SMA) with documentation of bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and less than or equal to three copies of SMN2, **AND**
2. Documentation that patient is presymptomatic or has symptoms with an onset at age less than 30 years, **AND**
3. Documentation of baseline motor function, with one of the following standardized test appropriate based on the patient's age and level of function:
    a. CHOP-INTEND: Children's hospital of Philadelphia Infant Test of Neuromuscular Disorders
    b. HINE: Hammersmith Infant Neurological Examination
    c. HFSME: Hammersmith Functional Motor Scale Expanded
    d. 6MWT: six-minute walk test
    e. RULM: Revised Upper Limb Module

NOTE the following guidance on selecting an appropriate test:

- **Non-sitters (infants and kids):** CHOP-INTEND, HINE (may need HFSME as they transition to sitting).
- **Sitters**: HFSME, RULM
- **Walkers (kids):** 6WWT, HFSME
- **Walkers (adults):** 6MWT, RULM
- **Non-walkers (adults):** RULM

For reauthorization: Improvement or maintenance of motor function, evidenced by stabilization or improvement in motor function test scores performed at baseline

EXCLUSION CRITERIA:

1. Concomitant use with, or following, gene therapy for SMA (such as onasemnogene abeparvovec)
2. Use in combination with risdiplam (Evrysdi®)
3. Advanced symptoms of SMA (such as complete paralysis of limbs, tracheostomy or ongoing invasive ventilator support in the absence of an acute reversible illness)

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Spinal muscular atrophy (SMA) is a progressive and severe neurodegenerative disease

- Incidence ~1 in 10,000 live births
- Characterized by mutations in the survival motor neuron 1 (SMN1) gene and insufficient production of functional SMN protein, causing degeneration and loss of motor neurons
- Classified into four subtypes (SMA types 1–4) based on the severity of symptoms and the age of onset.

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.[9]
Number of *SMN2* copies based on Calucho et al. 2018.[16]

  - SMA Type 1 – most common and most severe; often symptomatic within first months of life and fail to reach basic motor milestones, resulting in 8% survival to 20 months
    - Does not affect cognitive function
- CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale is used to measure motor function in patients with SMA
  - Scores range from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but 1 of the patients did not reach a score of at least 40 after 6 months of age. In another study, CHOP INTEND scores decreased by a mean of 10.7 points from 6 months to 12 months of age

Nusinersen (Spinraza®) increases the amount of full length SMN protein made by SMN2 genes, for patients with SMA.

FDA APPROVED INDICATIONS:
Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients

POSITION STATEMENT:

Regarding confirmation of SMA diagnosis based on genetic testing, in 95% of cases there is a homozygous deletion of SMN1, but there can be compound heterozygotes where there is one deleted copy of SMN1 and one copy with a sequence variant. Rarely, there may be homozygous sequence variant.

Clinical Evidence

ENDEAR Trial (*N Engl J Med* 2017; 377:1723-1732)
A Phase III, multicenter, double-blind, sham procedure-controlled (n=122) study including patients with genetic documentation of a homozygous deletion or mutation in the SMN1 gene and two (2) copies of SMN2 gene, with an onset of clinical signs and symptoms of SMA at ≤6 months, and age 7 months or younger at screening.

The primary endpoints were two-fold:

1. Motor-milestone response, which was defined according to results on the Hammersmith Infant Neurological Examination (HINE), and
2. Event-free survival, which was defined as the time to death or the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event)

The study was stopped early due to positive results on planned interim analysis. Motor milestones were achieved by 41% in the nusinersen treated group compared to 0% with sham treatment (P < 0.001); 22% of the infants achieved full head control, 10% were able to roll over, 8% were able to sit independently, and 1% were able to stand. The risk of death or permanent ventilation was 47% lower in the nusinersen compared with sham treatment (HR 0.53, 95% CI 0.32-0.89, p=0.005).

CHERISH Trial (*N Engl J Med* 2018; 378:625-635)
A phase III randomized, double-blind, sham-procedure controlled study of nusinersen in children ages 2-12 with later-onset SMA (at age > 6 months), consistent with Type II or III SMA (n=126).

The primary endpoint was the least-squares mean change in the Hammersmith Functional Motor Scale (HFMSE), which is a measure of motor function in children with type II and type III SMA. The study was stopped early due to positive results on planned interim analysis. There was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group and a least-squares mean decrease in the control group (least-squares mean difference in change, 5.9 points; 95% CI 3.7-8.1; P<0.001). A change of three (3) or more points is considered clinically significant.

NURTURE trial

An on-going phase II, open-label, single arm trial including presymptomatic infants (≤6 weeks of age) with SMA with two or three copies of SMN2. Patients received the first dose of nusinersen prior to age 6 weeks. The treatment regimen consists of four loading doses (administered on Days 1, 15, 29, and 64), followed by a maintenance dose every 119 days over five years.

The primary endpoint is time to death or respiratory intervention (invasive or non-invasive for ≥6 h per day continuously for ≥7 days or tracheostomy). At the planned interim analysis, median (range) age at last visit was 34.8 (25.7–45.4) months and time on study was 33.9 (25.3–45.1). All patients (N=25) were alive and none required permanent ventilation. In addition, all patients achieved "sitting without support", 23/25 achieved "walking with assistance" motor milestones.

There have not been any direct comparison studies between any of the agents for treatment of SMA; however, an indirect comparison study, using matching-adjusted indirect comparison (MAIC), suggests that risdiplam is more effective than nusinersen for the treatment of patients with Type 1 SMA. Authors of this study did not compare efficacy in Type 2 and 3 SMA due to substantial differences between study populations.[10]

REFERENCE/RESOURCES:

1. Spinraza® package insert. Cambridge, MA: Biogen Inc.; 2020 June.
2. Shababi M, Lorson CL, Rudnik-Schoneborn SS. Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease? *J Anat*. 2014; 224(1): 15-28.
3. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve*. 2015;51(2):157-67.
4. ECRI Institute. FDA approves first treatment for rare, fatal genetic disease in infants. 2016 Dec 28.
5. Formulary submission dossier: Spinraza (nusinersen) for spinal muscular atrophy. Biogen. December 30, 2016.
6. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1723-1732.
7. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2018;378(7):625-635.
8. De Vivo DC, Bertini E, Swoboda KJ, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29(11):842-856.
9. Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value Final

Evidence Report. Available at https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf (Accessed June 28, 2023)

10. Ribero VA, Daigl M, Martí Y, *et al*. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. *J Comp Eff Res*. 2022 Apr;11(5):347-370.

Appendix 1. Characteristics of spinal muscular atrophy (SMA) Types[5]

Type	Inheritance	Onset	Features	Prognosis
SMA 0	Usual 1 copy of SMN2	Usually prior to birth	Weakness, respiratory distress	Death within weeks
SMA 1	2-3 copies SMN2 (rare: 1 copy)	Preterm to 6 months (45% of cases)	Unable to sit	Death prior to age 2 in most cases
SMA 2	3 copies SMN2	6 to 18 months (20% of cases)	Able to sit, never able to stand or walk	Usually survive to 25, and many much longer
SMA 3	3-4 copies SMN2	Between ages 18 months and adulthood. (30% of cases)	Can stand or walk, but may lose ability	Normal lifespan
SMA 4	4 or more copies of SMN2	After age 30 (<5% of cases)	Ambulatory	Mildest form of SMA

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCNS054.0823	**CENTRAL NERVOUS SYSTEM DRUGS** **SPRAVATO®** (esketamine nasal spray)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 06/19, 08/19, 5/20, 08/20, 10/20, 07/21, 11/21, 06/22 (MTW), 07/23 (KN) P&T Committee Meeting Date: 06/19, 08/19, 8/20, 12/20, 08/21, 12/21, 08/22, 08/23 Original Effective Date: 08/19 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy, all the following criteria (1-4) must be met:

1. Confirmed diagnosis of one of the following:
    a. For treatment-resistant depression (TRD), clinical documentation must be provided that outlines the patient evaluation. TRD is defined as use of the following regimens (i and ii) for the current depressive episode:
        i. Inadequate response to at least three oral antidepressants in two different therapeutic classes for at least eight weeks of treatment at a therapeutic dose for major depressive disorder (MDD).
        ii. Inadequate response to augmentation therapy (i.e., two antidepressants with different mechanisms of action used concomitantly or an antidepressant and a second-generation antipsychotic, lithium, thyroid hormone, or anticonvulsant used concomitantly).

   b. For MDD with acute suicidal ideation or behavior, documentation must be provided that patient has current suicidal ideation with intent defined as both of the following:
      i. Patient has thoughts, even momentarily, of self-harm with at least some intent or awareness that they may die as a result, or member thinks about suicide, and
      ii. Patient intends to act on thoughts of killing themselves.
2. Baseline score from one of the following standardized depression rating scales confirming severe depression:
   a. Patient Health Questionnaire-9 (PHQ-9) score of at least 20
   b. Hamilton Depression Scale (HAMD17) score of at least 24
   c. Quick Inventory of Depressive Symptomatology, Clinician-Rated (QIDS-C16) score of at least 16
   d. Montgomery Asberg Depression Rating Scale (MADRS) total score of at least 28
3. Documentation that esketamine (Spravato®) will be used in combination with oral antidepressant therapy
4. Dosing is in accordance with the United States Food and Drug Administration approved labeling

For patients established on therapy for MDD, **all** the following criteria must be met:
1. Documentation of clinical improvement or sustained improvement from baseline in depression symptoms, documented by depression rating scores
2. Documentation that esketamine (Spravato®) will continue to be used in combination with oral antidepressant therapy
3. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Reauthorization requests for MDD with acute suicidal ideation or behavior will not be covered. Patient must meet criteria for initiation of therapy in TRD.

EXCLUSION CRITERIA:
- Concomitant use with another dissociative agent, specifically phencyclidine (PCP), ketamine, or dextromethorphan
- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation
- History of intracerebral hemorrhage
- Current or prior DSM-5 diagnosis of a psychotic disorder or MDD with psychosis, bipolar or related disorders, comorbid obsessive-compulsive disorder, intellectual disability, autism spectrum disorder, borderline personality disorder, antisocial personality disorder, histrionic personality disorder, or narcissistic personality disorder

- Current or recent history (i.e. within the last six months) of moderate or severe substance or alcohol use disorder

AGE RESTRICTIONS:
Approved for 18 years and older

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, a psychiatrist or a psychiatric nurse practitioner.

COVERAGE DURATION:
For TRD, initial authorization will be approved for three months. Reauthorization will be approved for six months

For MDD with suicidal ideation or behavior, initial authorization will be approved for four weeks.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Spravato® is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown.

FDA APPROVED INDICATIONS:
Spravato® is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of:

- Treatment-resistant depression (TRD) in adults

- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.
- Limitations of Use:
    - The effectiveness in preventing suicide or in reducing suicidal ideation or behavior has not been demonstrated. Use does not preclude the need for hospitalization if clinically warranted, even if patients experience improvement after an initial dose
    - This is not approved as an anesthetic agent. The safety and effectiveness as an anesthetic agent have not been established

POSITION STATEMENT:
Major depressive disorder (MDD) is one of the most common mental disorders in the United States. In 2017, the NIH estimated 17 million adults in the United States had at least one major depressive episode. It is estimated that about 30–40% of patients with MDD fail to respond to first-line therapies including oral antidepressants and/or psychotherapy. To date, effective therapies for treatment resistant depression (TRD) is an unmet medical need.

Although the definition of TRD has not been standardized, the generally accepted definition is based on failure of two trials of antidepressant monotherapy for an adequate duration of therapy and at an adequate dose. This definition is based on data from the Sequenced Treatment Alternatives to Relieve Depression (STAR-D) Study that showed evidence of declining rates of remission as sequential therapies were added in patients not responding to their prior therapy. In this study, 3671 patients with unipolar major depression were treated with up to four sequential trials of antidepressant medication. The rate of remission for the initial and second courses of treatment were comparable (37% and 31%) while the remission rate was substantially lower for patients receiving a third or fourth therapy (14% and 13%).

Esketamine efficacy was established in a 4-week study in 224 adult patients with TRD. Participants were randomized to receive twice weekly doses of intranasal Spravato® or intranasal placebo. All patients also had concomitant treatment with a newly initiated daily oral antidepressant (AD). The primary outcome was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. Statistical superiority of the primary outcome measure vs. placebo (least-squares mean difference: -4.0; 95% CI: -7.3, -0.6) was demonstrated by esketamine.

Long-term efficacy of esketamine was also demonstrated in a long-term, maintenance-of-effect study in adults. Participants were responders in one of two short-term controlled studies or in an open-label direct-enrollment study in an initial 4-week phase. At the completion of 16 weeks of treatment with esketamine and oral AD, stable remitters and stable responders were randomized separately to continue

intranasal treatment with esketamine or switch to placebo nasal spray, both groups continued taking their oral AD. The primary outcome was time to relapse in the stable remitter group. Patients in stable remission who continued treatment with esketamine plus oral AD experienced a statistically significant longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral AD (Hazard Ratio [HR]: 0.49; 95% CI: 0.29, 0.84). Time to relapse was also significantly delayed in the stable responder population (HR: 0.30; 95% CI: 0.16, 0.55).

Esketamine efficacy in major depressive disorder with acute suicidal ideation or behaviors was demonstrated in two identical phase 3 trials with 224 and 226 patients, respectively. Participants were randomized to receive treatment with esketamine 84 mg or placebo nasal spray twice-weekly for 4 weeks. All patients were receiving standard of care treatment and at least one antidepressant. The primary efficacy measure was the change from baseline in the MADRS total score at 24 hours after first dose (Day 2). In Study 3 and Study 4, esketamine plus standard of care demonstrated statistical superiority (least square means difference: -3.8; 95% CI -6.56; -1.09 and -3.9; 95% CI -6.60; -1.11) on the primary efficacy measure compared to placebo nasal spray plus standard of care.

Esketamine contains a boxed warning to alert health care professionals and patients about the increased risk of sedation and dissociation, abuse/misuse, and suicidal thoughts and behaviors. In addition, healthcare settings and dispensing pharmacies must be certified in the Spravato® REMS program.

REFERENCE/RESOURCES:

1. [Spravato] package insert. Titusville, NJ; Janssen Pharmaceuticals; Aug 2020.
2. [Spravato] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. [Accessed May 16, 2019].
3. [Spravato] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. [Accessed May 16, 2019].
4. A Study to Evaluate the Efficacy, Safety, and Tolerability of Flexible Doses of Intranasal Esketamine Plus an Oral Antidepressant in Adult Participants With Treatment-resistant Depression (TRANSFORM-2). 2019. Retrieved from https://www.clinicaltrials.gov/ct2/show/NCT02418585 (Identification No. NCT02418585).
5. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. Published online June 05, 2019.

6. IPD Analytics. Spravato (esketamine) nasal spray. https://secure.ipdanalytics.com/User/Pharma/RxStrategy/Search?q=spravato/ [Accessed May 17, 2019].
7. Institute for Clinical and Economic Review. Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value. Evidence report. May 9, 2019. https://icer-review.org/wp-content/uploads/2018/10/ICER_TRD_Evidence_Report_050919.pdf [Accessed May 20, 2019].
8. American Psychiatry Association. Practice Guidelines for the Treatment of Patients with Major Depressive Disorder: Third Edition. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf [Accessed May 16, 2019].
9. National Institute of Mental Health. Major Depression. https://www.nimh.nih.gov/health/statistics/major-depression.shtml [Accessed May 16, 2019].
10. Fu DJ, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). J Clin Psychiatry. 2020 May 12;81(3). [Accessed August 17, 2020].

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP043.1223	**TOPICAL PRODUCTS** **SYFOVRE®** (pegcetacoplan-pf vial)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/23 (JN)
Original Effective Date: 08/23	**P&T Committee Meeting Date**: 06/23, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization, all the following criteria must be met:

1. Documentation of diagnosis of geographic atrophy (GA) confirmed by clinical exam or diagnostic imaging (such as Color Fundus Photography, Fundus Autofluorescence, Near Infrared Reflectance Imaging, Optical Coherence Tomography)
2. Documentation that GA is secondary to age-related macular degeneration (AMD)
3. If active choroidal neovascularization (CNV) present, documentation must be submitted attesting that treatment with the requested medication is medically necessary and appropriate monitoring of CNV will be conducted (such as a comprehensive eye exam within three months of starting the requested therapy)

For reauthorization, the following must be met: Documentation of response to therapy defined as one of the following:

1. Reduction in GA growth lesion
2. Documentation of improvement in visual function through visual function assessment test (such as normal luminance best-correct visual acuity

[BCVA], maximum reading speed, Functional Reading Independence Index, microperimetry)

EXCLUSION CRITERIA:

- Active ocular or periocular infections in the requested eye being treated
- History of endophthalmitis, retinal detachments, or increased intraocular pressure in the requested eye being treated

AGE RESTRICTIONS:
May be approved for patients age equal to 60 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an ophthalmologist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Pegcetacoplan-pf vial (Syfovre®) is a complement C3 inhibitor and is the first FDA-approved treatment of geographic atrophy (GA) secondary to age-related macular degeneration.

FDA APPROVED INDICATIONS:
Indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

POSITION STATEMENT:

- GA is an advanced form of AMD affecting more than 5 million people worldwide, including 22% of people over 90 years old. GA is responsible for 10-20% of all incidences of legal blindness caused by AMD. Risk factors for GA include genetic polymorphisms, advanced age (especially over 85 years old), smoking, and presence of early AMD to GA in the fellow eye. Genes that may play a significant role in GA include: Complement Factor H (CFH), Complement Factor B (CFB), Complement 2 (C2), Complement 3 (C3), and ARMS2. Polymorphisms in six complement genes (CFH, CFI, C2/CFB, C3, C9) account for almost 60% of the AMD genetic risk. Symptoms of GA can include scotomas (large dark or blind spots in the visual field), difficulty recognizing faces, decreased reading speed (measured in words per minute, wpm), impaired dark adaptation, low luminance deficit (LLD), impaired contrast sensitivity, and difficulty driving at night.[5]
- Per expert opinion consultation, GA can occur in both wet and dry AMD.
- Most recent guidelines for GA include Age-Related Macular Degeneration Preferred Practice Pattern guideline, published in 2019, which states that at the time there was no proven therapy to prevent or treat GA.[6]
- Pegcetacoplan-pf was approved based off of two phase 3 clinical trials (DERBY and OAKS). The primary endpoint (Change from Baseline to Month 12 in total area of GA lesion[s] in the study eye [in mm2] based on Fundus Autofluorescence [FAF]) was not statistically significant at 12 months in the DERBY trial, but was statistically significant in the OAKS trial at month 12, month 18, and month 24 results as well as in the DERBY trial at month 18 and month 24 results. Reductions in overall GA lesion growth compared to sham injection controlled increased more-so as the months went on. However, at 24 months, there was no statistically significant difference in measures of visual function. Therefore, it is not clear if treatment with Syfovre demonstrated clinically significant results. Inclusion criteria in both trials included age equal or greater to 60 years of age, and clinical diagnosis of GA of the macular secondary to AMD. Exclusion criteria in both trials included GA secondary to a condition other than AMD, any history or active CNV associated with AMD or any other cause, and any contraindication to intravitreal injection including current ocular or periocular infection.
- Safety: Warnings and precautions include endophthalmitis and retinal detachments, neovascular AMD, intraocular inflammation, and increased intraocular pressure. The most common adverse reactions (≥5%) reported in Syfovre clinical trials were ocular discomfort, neovascular age-related macular degeneration (nAMD), vitreous floaters, and conjunctival hemorrhage.

REFERENCE/RESOURCES:

1. Syfovre® package insert. Waltham, MA: Apellis Pharmaceutical, Inc; 2023 Feb.
2. Syfovre® In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. Syfovre® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.
4. Syfovre® (pegcetacoplan-pf) vial Prime Therapeutics Monograph. Updated on March 1, 2023.
5. Geographic atrophy. Pathways and targets for geographic atrophy. Geographic Atrophy (accessed 2023 March 13).
6. Flaxel CJ, Adelman RA, Bailey ST, et al. Age-related macular degeneration preferred practice pattern. *American Academy of Ophthalmology*. 2019;127(1):1-65.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH010.1023	**MISCELLANEOUS PRODUCTS** **SYLVANT®** (siltuximab for infusion)
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 03/16, 03/17, 03/18, 07/18, 03/19, 09/19, 07/20, 08/21, 09/22, 09/23 (CJD) P&T Committee Meeting Date: 02/15, 04/16, 04/18, 08/18, 04/19, 10/19, 10/20, 10/21, 10/22, 10/23 Original Effective Date: 04/15 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 3

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
Initial Authorization:
1. Confirmed diagnosis of Multicentric Castleman Disease (MCD) and the following criteria:
    a. Documentation of negative human immunodeficiency virus (HIV) status
    b. Documentation of negative human herpes-virus 8 (HHV-8) status
    c. Documentation that siltuximab (Sylvant®) will be used as a single agent
    OR
2. Use of the requested medication is supported by National Comprehensive Cancer Network guidelines with recommendation 2A or higher

Reauthorization:
For Multicentric Castleman Disease (MCD): positive response to therapy as well as documentation that patient remains HIV and HHV-8 negative.

For NCCN-supported Diagnosis: documentation of adequate response to the medication must be provided.

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an oncologist, hematologist, or rheumatologist.

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Siltuximab (Sylvant®) is a monoclonal antibody that binds to human interleukin-6 (IL-6) and prevents the binding of IL-6 to both soluble and membrane-bound IL-6 receptors. IL-6 has been shown to be involved in diverse normal physiologic processes such as induction of immunoglobulin secretion. Overproduction of IL-6 has been linked to systemic manifestations in patients with Multicentric Castleman disease (MCD).

FDA APPROVED INDICATIONS:
Treatment of patients with MCD who are HIV negative and HHV-8 negative.

Limitation of Use:
- Not studied in patients with MCD who are HIV positive or HHV-8 positive because siltuximab did not bind to virally produced IL-6 in a nonclinical study

POSITION STATEMENT:
MCD is a rare lymphoproliferative disease that is characterized by symptoms such as fever, night sweats, fatigue, anorexia, and cachexia. Patients often have lymphadenopathy and hepatosplenomegaly with evidence of fluid retention (lower extremity edema, pleural/pericardial effusions, and abdominal ascites) as well as hematologic abnormalities including anemia, elevated inflammatory markers, hypergammaglobulinemia, and hypoalbuminemia.

Treatment for MCD is limited and the evidence in well-designed clinical trials is lacking. Systemic glucocorticoid therapy can work for short-term control of symptoms, but long-term efficacy is lacking. Chemotherapy agents have also been used to treat MCD, although clinical evidence is minimal (case reports and case series). Agents such as etoposide, vinblastine, cyclophosphamide, cladribine, chlorambucil, and liposomal doxorubicin haven been used, but responses are reported to be short in duration. Rituximab therapy is commonly used, although the data supporting use in HIV-seronegative patients is not as robust as in HIV-seropositive patients.

Siltuximab (Sylvant®) represents the first drug approved for use in HIV-seronegative MCD. The approval of siltuximab was based on a Phase 2 randomized placebo-controlled clinical trial. Patients (N=79) with HIV-seronegative, herpesvirus-8 negative MCD were randomized in 2:1 fashion to receive either siltuximab (11 mg/kg intravenously every three weeks) or matching placebo. The primary endpoint was looking at durable tumor and symptomatic response, defined as a complete or partial response with improvement or stabilization of disease-related symptoms for at least 18 weeks. Patients were treated for a mean of 375 days and 18 patients (34%) on siltuximab achieved the primary endpoint, compared to zero of the patients on placebo. Median duration of response was 383 days.

REFERENCE/RESOURCES:
1. Sylvant package insert. Horsham, PA: Janssen Biotech, Inc.; 2022 April.
2. Siltuximab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. Van Rhee, Wong RS, Munshi N et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2014;15(9):966-74.
4. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and Management of Castleman Disease. *Cancer Control*. 2014;21(4):266-78.

CODING:
J2860 = injection, siltuximab, 10mg

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCONC104.0224	**ANTINEOPLASTIC AGENTS** **T-CELL THERAPY** See Appendix A for medications covered by policy
Effective Date: 4/1/2024	**Review/Revised Date**: 12/17, 01/18, 07/18 , 08/18, 01/19, 03/19, 12/19, 09/20, 12/20, 03/21, 06/21, 12/21, 05/22, 02/23, 12/23, 01/24 (CJD)
Original Effective Date: 03/18	**P&T Committee Meeting Date**: 12/17, 02/18, 08/18, 09/18, 02/19, 04/19, 10/20, 02/21, 04/21, 06/21, 02/22, 06/22, 02/23, 12/23, 02/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 21	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For all requests, the following criteria must be met:
1. Use must be for an indication supported by National Comprehensive Cancer Network (NCCN) guidelines with recommendation 2A or higher
2. Documentation of adequate bone marrow, cardiac, pulmonary and organ function (such as kidney, liver)
3. One of the following regarding functional status must be met:
    a. For Kymriah® for B-cell precursor acute lymphoblastic leukemia (ALL) only: Karnofsky or Lansky Scale greater than or equal to 50%
    b. Provider attestation/documentation that the patient's functional status is sufficient to undergo treatment. This may include but is not limited to a documented Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 or a written statement acknowledging that the patient is fit to tolerate therapy.
4. No evidence of active infection or inflammatory disorder (including hepatitis B or C, active graft vs. host disease)

5. For B-cell lymphomas, patient does not have primary central nervous system lymphoma

For patients established on therapy for Talvey, Tecvayli, Elrexfio, all the following must be met (Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy): Member is responding positively to therapy

EXCLUSION CRITERIA:
Combination use of T-cell therapies included in this policy. Talvey, Tecvayli, or Elrexfio use may be considered following CAR-T therapy with evidence of disease progression after CAR-T therapy administration.

For CAR T-cell therapy: Previous treatment with chimeric antigen receptor (CAR) T-cell therapy. Repeat administration is not considered medically necessary as the effectiveness of this approach has not been established.

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an oncologist

COVERAGE DURATION:
For Talvey, Tecvayli, Elrexfio: Initial authorization and reauthorization will be approved for one year and with up to four doses of tocilizumab (Actemra®) at up to 800 mg per dose.

For chimeric antigen receptor (CAR) T-cell therapy: Two months (limited to one treatment course per lifetime, with four doses of tocilizumab [Actemra®] at up to 800 mg per dose).

For off-label use criteria please see the Chemotherapy Treatment Utilization Criteria; Coverage for Non-FDA Approved Indications ORPTCOPS105.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,

formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Lisocabtagene maraleucel, tisagenlecleucel, brexucabtagene autoleucel and axicabtagene ciloleucel are chimeric antigen receptor T-cell (CAR-T) targeted therapies that are directed against CD19 and idecabtagene vicleucel and ciltacabtagene autoleucel are a BCMA-directed CAR-T therapy. CAR-T therapy is a type of immunotherapy that utilizes a patient's own immune system to attack cancer cells with engineered T cells. CAR-T therapy is intended as a one-time treatment of a single infusion of the patient's own engineered T cells. The process begins with harvesting the patient's white blood cells via leukapheresis. The T cells are then isolated and activated and engineered with chimeric antigen components (CARs) which allow the T cells to recognize an antigen on target cancer cells. Once the CAR-T cells are constructed, they are stimulated to proliferate, and once a sufficient number of cells are available, they are infused into the patient.

Elranatamab (Elrexfio), teclistamab (Tecvayli) and talquetamab (Talvey) are T-cell engaging bispecific antibodies for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM). Bispecific antibodies simultaneously bind to CD3 on T-cells and the targeted antigen on tumor cells. Elrexfio and Tecvayli are bispecific B-cell maturation antigen (BCMA)-directed CD3 T cell engagers. BCMA is expressed on the surface of multiple myeloma cells with limited expression on normal tissues other than plasma cells. Talvey is a bispecific GPRC5D-directed CD3 T-cell engager. G protein-coupled receptor class C group 5 member D (GPRC5D) is primarily expressed multiple myeloma cells with low expression in normal human tissue other than plasma cells and hard keratinized healthy tissue such as epithelial tissue of skin and tongue. These bispecific antibodies for RRMM are administered subcutaneously and are available "off-the shelf". They do not require patient specific manufacturing like chimeric antigen receptor T-cell therapies which may take four weeks or longer to produce and administer. Tecvayli, Talvey and Elrexfio require hospitalization for initiation of therapy and step up dosing due to the risk of cytokine release syndrome and neurologic toxicity.

Acute lymphoblastic leukemia

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with the highest risk of developing ALL in children younger than five years of age. Per the American Cancer Society, there was an estimated 6,150 new cases in the United States in 2020.

Relapse occurs in about 20% of ALL patients with a survival rate for refractory/relapsed acute lymphoblastic leukemia (r/r ALL) of 16-30%.Currently available therapy in r/r ALL may include blinatumomab (Blincyto®), inotuzumab ozogamicin (Besponsa®), as well as allogenic hematopoietic stem cell transplant. Stem cell transplant allows for use of higher doses of chemotherapy; however, not all patients may be eligible based on factors such as age, organ function (renal/hepatic/pulmonary function), disease progression.

Large B-cell lymphoma
Outcomes for refractory aggressive Non-Hodgkin's Lymphoma (NHL) are poor. NHL accounts for about 4% of all cancers in the United States, DLBCL being the most common form of this disease (33% of all NHL cases). If adults with DLBCL do not respond to initial chemotherapy, they often receive second-line therapy. If patients respond to second-line chemotherapy, they are then considered candidates for autologous stem cell transplant (SCT). However, even after SCT, five-year disease-free survival is only about 10-20%. Patients who do not respond to second-line therapy or progress after transplant only have palliative options available. According to SCHOLAR-1 study, the median survival rate for refractory large B cell lymphoma is 6.3 months.

Drug combinations commonly used for salvage therapy of large B-cell lymphoma (LBCL) include ifosfamide / carboplatin/ etoposide (ICE), etoposide/ methylprednisolone/ cytarabine/cisplatin (ESHAP), and dexamethasone/ cytarabine/ cisplatin (DHAP), generally in combination with rituximab. Palliative radiation therapy and supportive care may also be an option.

Mantle cell lymphoma
Mantle cell lymphoma (MCL) is a type of B-cell non-Hodgkin lymphoma (NHL) in which tumor cells originate from the "mantle zone" of the lymph node. MCL makes up about 7% of adult NHL with the median age at diagnosis of 68 years. Despite advances in therapy, most patients will experience refractory or recurrent disease. Potential treatment options for r/r MCL include R-CHOP, lenalidomide, ibrutinib. National Comprehensive Cancer Network (NCCN) recommends brexucabtagene autoleucel only after chemoimmunotherapy and a Bruton's tyrosine kinase inhibitor.

Multiple Myeloma

Multiple myeloma is a type of cancer that begins in the plasma cells. Abnormal plasma cells build up in the bone marrow, often causing skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic features. Multiple myeloma is often suspected when one or more of the following are present: bone pain with lytic lesions, increased total serum protein and/or presence of a monoclonal protein in urine/serum, signs, or symptoms suggestive of malignancy such as unexplained anemia, hypercalcemia, or acute renal failure. According to the National Cancer Institute, 34,920 new cases of multiple myeloma will be diagnosed, and 12,410 deaths will occur in 2021.

Relapses of multiple myeloma are common, and outcomes are poor for those who do not experience complete responses, with a median progression-free survival of three to four months, and a median overall survival of eight to nine months. The main three classes of therapy for multiple myeloma are the immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies.

FDA APPROVED INDICATIONS:

CAR T-cell therapies:

Abecma®:

1. Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Breyanzi®:

1. Adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have:
    a. refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
    b. refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
    c. relapsed or refractory disease after two or more lines of systemic therapy

Carvykti®:

1. Adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Kymriah®:

1. B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse for patients up to 25 years of age.
2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not

otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Tecartus™:
1. Adult patients with relapsed or refractory mantle cell lymphoma (MCL).
2. Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Yescarta®:
1. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
2. Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

Limitation: Breyanzi®, Kymriah® and Yescarta® are NOT indicated for treatment of patients with primary central nervous system lymphoma.

T-cell engaging bispecific antibodies:
Tecvayli®, Elrexfio™, Talvey™:
1. Adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody

POSITION STATEMENT:
Acute lymphoblastic leukemia: Kymriah®, Tecartus™
According to the National Comprehensive Cancer Network (NCCN), blood and bone marrow response is considered complete (CR) when there are no circulating blasts or extramedullary disease (no lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/ central nervous system involvement); trilineage hematopoiesis (TLH) and less than 5% blasts; absolute neutrophil count (ANC) greater than 1000/ microliter; platelets greater than 100,000 per microliter; no recurrence for four weeks. Disease is considered refractory if there is a failure to achieve CR at end of induction. Relapsed disease is characterized by the reappearance of blasts in the blood or bone marrow greater than 5% or in any extramedullary site after CR.

- FDA approval of tisagenlecleucel (Kymriah®) was based on a single arm, open-label, multi-center, phase II study to determine the efficacy and safety of a single infusion of tisagenlecleucel in young patients with relapsed/refractory B-cell ALL (ELIANA; NCT02435849).
    - Inclusion criteria: Patients aged three to 21 years with relapsed or refractory B-cell ALL, positive for CD19 tumor expression, Karnofsky (participants age greater than or equal to 16 years) or Lansky (participants age less than 16 years) performance status of greater than or equal to 50 at screening.
    - Exclusion criteria: Patients with isolated extra-medullary relapse, concomitant genetic syndrome (except Down Syndrome), Burkitt's lymphoma/leukemia, uncontrolled infection, grade 2-4 graft versus host disease, active central nervous system disease, treatment with a prior gene therapy product or anti-CD19/anti-CD3 therapy, active or latent hepatitis B or active hepatitis C within eight weeks of screening, or any uncontrolled infection at screening, positive HIV test within eight weeks of screening.
    - The primary endpoint was overall remission rate (complete remission + complete remission with incomplete recovery) at three months' post infusion. ORR =83% with a 95% confidence interval 71-91.
    - Tisagenlecleucel (Kymriah®) is associated with cytokine release syndrome (CRS), including fatal or life-threatening reactions. Of all patients in the ELIANA study, 78% experienced CRS and 43% (N=32) experienced grade 3-4 CRS. CRS may result in hypotension, altered mental status, and seizures. It is not recommended to administer tisagenecleucel to patients with active infection or inflammatory disorders. CRS may be treated with tocilizumab (Actemra®).

- For adults with relapsed or refractory B-cell ALL, brexucabtagene autoleucel (Tecartus™) was studied in the ZUMA-3 trial (NCT02614066) which was an open-label, single arm, phase 1/2 study.
    - Inclusion criteria included: Adults with primary refractory ALL, first relapse following a remission lasting ≤ 12 months, relapsed or refractory ALL after second-line or higher therapy, or relapsed or refractory ALL at least 100 days after allogeneic stem cell transplantation (HSCT); EOCG 0 to 1; adequate renal, hepatic, cardiac function; Philadelphia chromosome positive (Ph+) disease are eligible if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or if they have relapsed/refractory disease despite treatment with at least two different TKIs.
    - Exclusion criteria: Patients with active or serious infections, active graft-vs-host disease or taking immunosuppressive medications within four weeks prior to enrollment, and any history of CNS disorders, including CNS-2

disease with neurologic changes and CNS-3 disease irrespective of neurological changes.
- The primary endpoint was completed remission (CR) within three months after infusion and the duration of CR (DOCR). Twenty-eight (51.9%) of the 54 evaluable patients achieved CR, and with a median follow-up for responders of 7.1 months, the median DOCR was not reached (Table 8). The median time to CR was 56 days (range: 25 to 86 days). All efficacy evaluable patients had potential follow-up for ≥ 10 months with a median actual follow-up time of 12.3 months (range: 0.3 to 22.1 months).

The NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (patients aged 18 years and younger) also give a category 2B recommendation for Kymriah® (tisagenlecleucel) as single-agent therapy for Ph-negative or Ph-like B-ALL that is minimal residual disease (MRD) positive after consolidation therapy and for Ph-positive B-ALL with less than complete response, MRD+ at end of consolidation, or high-risk genetics, noting "the use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial."

Large B-cell lymphoma: Breyanzi®, Kymriah® and Yescarta®
The Lugano response criteria is used to define response to treatment (complete response, partial response, no response or stable disease, progressive disease), taking into consideration history, physical examination, laboratory studies, and imaging studies.

- For adult relapsed or refractory diffused large B-cell lymphoma, tisagenlecleucel (Kymriah®) was studied in the JULIET trial (NCT02445248) which was an international, open-label, single arm, phase 2 study
  - Eligible patients were greater than or equal to 18 years of age with relapsed or refractory DLBCL, who received greater than or equal to two lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT).
  - The study excluded patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status greater than or equal to two, a creatinine clearance less than 60, alanine aminotransferase more than times normal, cardiac ejection fraction less than 45%, or absolute lymphocyte concentration less than 300/µL.
  - The primary endpoint was the best overall response rate (i.e., the combined percentage of patients who achieved complete or partial response rate), as determined by an independent review committee.
  - The best overall response rate was 52% (95% CI 41 to 62) with 40% of all patients achieving complete response and 12% had partial response.

- The FDA approval of axicabtagene ciloleucel (Yescarta®) for large B-cell lymphoma was based on efficacy data from the ZUMA-1 trial (NCT02348216).
    - This phase 1 & 2 (phase 2 expansion) study was single-arm, open-label and included patients with refractory or relapsed disease to two or more lines of therapy.
    - Inclusion criteria – adults with aggressive B-cell non-Hodgkin's lymphoma (NHL), including diffuse large B-cell lymphoma (DLBCL), T-cell rich large B-cell lymphoma, primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (FL), that is primary refractory, refractory to second or greater line of therapy, or relapsed ≤ 1 year after autologous stem cell transplant (SCT), received prior anthracycline and anti-CD20 therapies, eastern cooperative oncology group (ECOG) performance status <2.
    - Exclusion criteria - prior allogeneic hematopoietic stem cell transplant (HSCT), prior CD19-directed therapy, any history of central nervous system lymphoma, ECOG performance status of two or greater, absolute lymphocyte count < 1000/µL, creatinine clearance <60 mL/min, hepatic transaminases > 2.5 times the upper limit of normal, cardiac ejection fraction <50%, or active serious infection.
    - At a minimum of 12 months follow up, the ORR was 82% (95% CI 72-89), including a CR of 58%.
    - At a median of 15.4 months' post-infusion, 42% of patients remained in response, including 40% in complete remission.
    - The progression-free survival rates was 41% (95 CI, 31-50) with an overall survival rate of 52% (95% CI, 41-62) at 18 months. However, CR may be skewed as it does not include patients who enrolled into the trial but did not receive the study medication.
    - 95% of all patients had grade 3 or higher adverse events; the most common of these being neutropenia (78%), anemia (43%), and thrombocytopenia (38%). CRS occurred in 93% of all patients, 13% of whom experienced grade 3 or higher CRS.

- The FDA approval of axicabtagene ciloleucel (Yescarta®) for relapsed or refractory follicular lymphoma was based on efficacy data from the ZUMA-5 trial (NCT02348216).
    - This phase 2 study was single-arm, open-label and included patients with refractory or relapsed disease to two or more lines of therapy.
    - Inclusion criteria: Adults with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy including the combination of an anti-CD20 monoclonal antibody and an alkylating agent, eastern cooperative oncology group (ECOG) performance status 0-1.

  - Exclusion criteria: Active or serious infections, transformed lymphoma or other aggressive lymphomas, prior allogeneic HSCT, or any history of CNS lymphoma or CNS disorders.
  - Efficacy was established on the basis of ORR and DOR
    - ORR was 91% (95% CI 83-96), including a CR of 60%.
    - The median DOR was not reached, and the 1-year rate of continued remission was 76.2% (95% CI: 63.9, 84.7).

- The FDA approval of lisocabtagene maraleucel (Breyanzi®) for large B-cell lymphoma was based on efficacy data from the TRANSCEND NHL 001 trial (NCT03105336).
  - This phase 1 study was single-arm, open-label and included patients who received two or more previous lines of systemic treatment.
  - Inclusion criteria - received two or more previous lines of systemic treatment (including previous chemoimmunotherapy containing anti-CD20 and anthracycline) with subsequent relapse; ECOG performance status < 2; could have received prior autologous and/or allogenic hematopoietic stem cell transplant.
  - Exclusion criteria- central nervous system only involvement; active hepatitis B, hepatitis C, or human immunodeficiency virus infection at time of screening; uncontrolled systemic fungal, bacterial, viral, or other infection despite appropriate treatment; presence of acute or chronic graft-versus-host disease; prior CAR-T or other genetically modified T-cell therapy.
  - ORR was 73% (95% CI 67-80).
  - Median duration of response (DOR) was 16.7 months (95% CI: 5.3, not reached).
  - Among the complete responders, 68 (65%) had remission lasting at least six months and 64 (62%) had remission lasting at least nine months.
  - Serious adverse reactions occurred in 46% of patients. The most common non-laboratory, serious adverse reactions (>2%) were CRS, encephalopathy, sepsis, febrile neutropenia, aphasia, pneumonia, fever, hypotension, dizziness, and delirium.

Mantle cell lymphoma: Tecartus™

Accelerated approval of (brexucabtagene autoleucel) Tecartus™ was based on the ZUMA-2 trial (NCT02601313), a single-arm, open-label, phase 2 trial

- The ZUMA-2 trial included patients with relapsed or refractory disease who had previously received therapy with all of the following: anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a Bruton tyrosine kinase inhibitor (BTKi; ibrutinib or acalabrutinib); and had an Eastern Cooperative Oncology Group performance status of 0 or 1.

- Patients were excluded if they had prior CART-T therapy, history of allogenic stem cell transplantation, presence of uncontrolled infection, history of human immunodeficiency virus infection or acute or chronic active hepatitis B or C infection, detectable cerebrospinal fluid malignant cells or brain metastases, history or presence of CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with CNS involvement.
- 87% of the 60 evaluable patients had an objective response, and 62% had a complete response.
- Tecartus™ is a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or refractory disease (only given after chemoimmunotherapy and Bruton's tyrosine kinase inhibitor).

Multiple Myeloma: Abecma®, Carvykti®, Tecvayli®, Elrexfio™, Talvey™
NCCN guidelines Version 2.2024 for multiple myeloma[7] lists the following as preferred regimens, after at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent, (all NCCN category 2A):

- CAR T-cell therapy:
  - Ciltacabtagene autoleucel (Carvykti®)
  - Idecabtagene vicleucel (Abecma®)
- Bispecific antibodies
  - Talquetamab (Talvey™)
  - Teclistamab (Tecvayli®)
  - Elranatamab (Elrexfio™)

NCCN guidelines note that patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy, but optimal order is unclear.[7]

- Limited data for selecting which 5th line agent is used first. Choice will depend on patient specific characteristics and availability of therapies.
- Optimal sequencing and time from one therapy to the next is not yet known. This is an area of active study. There is some published evidence from small cohorts of individuals with previous T cell therapy. Other current active areas of investigation include CAR T in earlier lines of therapy and combination use of bispecific antibodies.

Idecabtagene vicleucel was the first CAR-T therapy approved for multiple myeloma and the first CAR-T therapy that targets the BCMA protein. The FDA approval of idecabtagene vicleucel (Abecma®) for multiple myeloma was based on efficacy data from the KarMMa trial (NCT03361748).

- This phase 2 study was open-label, single arm and included patients who received at least three prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
- Inclusion criteria- age 18 years or older, ECOG performance status of 0 or 1, had disease that was refractory to their last regimen (progression within 60 days after the last dose) according to International Myeloma Working Group (IMWG) criteria, had measurable disease.
- Exclusion criteria - Known central nervous system involvement with myeloma, creatinine clearance of less than or equal to 45 mL/minute, alanine aminotransferase >2.5 times upper limit of normal and left ventricular ejection fraction <45% , absolute neutrophil count <1000 cells/mm3 and platelet count <50,000/mm3, previous history of an allogeneic hematopoietic stem cell transplantation or treatment with any gene therapy-based therapeutic for cancer or investigational cellular therapy for cancer or BCMA targeted therapy, evidence of human immunodeficiency virus (HIV) infection, seropositive for and with evidence of active viral infection with hepatitis B virus (HBV), seropositive for and with active viral infection with hepatitis C virus (HCV), subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study. This includes systemic fungal, bacterial, viral, or other infection that is uncontrolled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antimicrobial treatment) or requiring IV antimicrobials for management
- 72% of evaluable patients had an overall response and 28% had a complete response.
- Median overall survival = 19.4 months; 95% CI: 18.2, NE, with an overall survival of 78% at 12 months (OS data immature).
- Abecma® has a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or progressive disease who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

The FDA approval of ciltacabtagene autoleucel (Carvykti®) for multiple myeloma was based on efficacy data from the CARTITUDE-1 trial (NCT03548207).

- This phase 1b/2 study was open-label, single arm and included patients who received at least three prior lines of antimyeloma therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
- Inclusion criteria- age 18 years or older, ECOG performance status of 0 or 1
- Exclusion criteria - Known central nervous system involvement with myeloma, previous history of treatment with any CAR-T therapy directed at any target or

BCMA targeted therapy, seropositive for human immunodeficiency virus (HIV), seropositive for and with evidence of active viral infection with hepatitis B virus (HBV), seropositive for and with active viral infection with hepatitis C virus (HCV), serious underlying medical condition, such as: evidence of uncontrolled systemic fungal, bacterial, or viral infection, creatinine clearance <40 mL/min, absolute lymphocyte concentration <300/µL, absolute neutrophil count <750 cells/mm3, platelet count <50,000/mm3, hepatic transaminases >3 times the upper limit of normal, cardiac ejection fraction <45%

- 97% of evaluable patients had an overall response
- Carvykti® has a 2A recommendation by the National Comprehensive Cancer Network (NCCN) for patients with relapsed or progressive disease who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Teclistamab-cqyv (Tecvayli®) is a bispecific T-cell engager (BiTE) approved for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) through the Phase 1-2 study MajesTEC-1 (NCT03145181 and NCT04557098):

- This was a single-arm, multicohort, open label Phase ½ study (MajesTEC-1) with n = 110 patients who previously received three or more prior therapies
- Inclusion criteria: Age >18 years old; documented diagnosis of relapsed or refractory MM; receipt of >3 lines of therapy including an IMiD, a PI, and an anti-CD38 antibody; Eastern Cooperative Oncology Group (ECOG) score of 0 or 1.
- Exclusion criteria: Previous treatment with a BCMA-directed therapy.
- With median duration of treatment of about 10 months, results of the study include an overall response rate of 61.8%, complete response rate of 28.2%, and estimated duration of response rate among responders of 90.6% at six months and 66.5% at nine months.
- Potentially life-threatening adverse events include cytokine release syndrome (CRS) (72%, grade 3, 0.6%; no grade 4), all grade neurotoxicity (57%), and immune effector cell–associated neurotoxicity syndrome (ICANS) (6%). Boxed warnings for fatal CRS and ICANs were included in package labeling.
- Drug labeling and REMS guidance do not recommend specific supportive agents for CRS. In clinical trial, tocilizumab was used for 60 patients (36.4%) and glucocorticoids for 14 patients. Five patients used more than one dose of tocilizumab at any time during the study and four patients used more than one dose for a single CRS event.
- The recommended dosage of teclistamab is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly until disease progression or unacceptable toxicity. Nearly 96% of CRS events occurred during step-up dosing.

Elranatamab (Elrexfio) was studied in a phase II, single-arm, open-label trial (MagnetisMM-3), for patients with relapsed/refractory MM who had previously received at least four prior systemic therapies. Patients received subcutaneous elranatamab once weekly.

- The primary study population were patients (n= 123) without prior BCMA-directed therapy.
- Efficacy:
    - Overall response rate (ORR) was 61% (95% CI, 51.8-69.6)
    - 39 patients (31.7%) experienced complete response (CR) or stringent CR, 29 (23.6%) achieved very good partial response and 7 (5.7%) achieved partial response
    - Median DOR had not been reached; probability of maintaining response at 12 months was 74.1% (95% CI, 60.5-83.6).
    - 48 responders, after 24 weeks, switched to biweekly dosing, and 45 of those (93.8%) improved or maintained their response for greater than 12 weeks.
- Safety:
    - Most common adverse effects (>20%): pyrexia, CRS, injection site reaction, musculoskeletal pain, fatigue, upper respiratory infection, pneumonia, cough, rash, diarrhea, nausea, decrease appetite. With biweekly dosing, grade 3–4 adverse events decreased from 58.6% to 46.6%
    - Most common Grade 3 or 4 laboratory abnormalities (≥30%): decrease count of white blood cells, lymphocytes, neutrophils, platelets and hemoglobin
    - Serious infections, including opportunistic infections, occurred in 42% of patients receiving elranatamab, including Grade 3 or 4 infections in 31% of patients and fatal infections in 7% of patients. The most common infections were pneumonia and sepsis.
    - Fatal adverse reactions occurred in 10% of patients
- In MagnetisMM-3 trial a cohort of 64 patients with a history of BCMA-targeted therapy (33% exposed to CAR T-cell therapy and 72% exposed to an antibody-drug conjugate e.g., belantamab, teclistamab) had an ORR of 33%, (95% CI: 22.0%, 46.3%) with an estimated 84% of responders maintaining response for at least 9 months. The median duration of response was not reached.

Talquetamab (Talvey) was evaluated in a single-arm, open-label, multicenter trial, (MonumenTAL-1). Patients (n=187) with relapsed/refractory MM had previously received at least four prior systemic therapies received either talquetamab subcutaneously weekly or talquetamab biweekly until disease progression or unacceptable toxicity.

- Efficacy:

  - Overall response rate (ORR) in 0.4 mg/kg weekly cohort (N=100) was 73% (95% CI: 63.2%, 81.4%) and median duration of response (DOR) was 9.5 months (95% CI: 6.5, not estimable)
  - ORR in 0.8 mg/kg biweekly cohort (N=87) was 73.6% (95% CI: 63%, 82.4%) and median DOR was not estimable
  - About 85% of responders maintained response for at least 9 months
- Safety:
  - Most common adverse effects (>20%): pyrexia, CRS, dysgeusia, nail disorders, musculoskeletal pain, skin disorders, rash, fatigue, decreased weight, dry mouth, xerosis, dysphagia, upper respiratory infection, diarrhea, hypotension, headache
  - Most common Grade 3 or 4 laboratory abnormalities (≥30%): decrease count of white blood cells, lymphocytes, neutrophils, and hemoglobin
  - Serious adverse reactions reported in >2% of patients included CRS (13%), bacterial infections including sepsis (8%), pyrexia (4.7%), ICANS (3.8%), COVID-19 (2.7%), neutropenia (2.1%), and upper respiratory tract infection (2.1%)
  - Fatal adverse reactions occurred in 3.2% of patients
- In the Monumental-1 trial there was a cohort of 32 people who had a history of T-cell redirecting therapy (81% exposed to CAR T-cell therapy and 25% exposed to a bispecific antibody). The over-all response rate (ORR) was 72% (95% CI: 53%, 86%) and the median duration of response was not reached. The median duration of follow-up was 10.3 months (95%CI: 6.5, 11.4).

Safety of T-cell therapies
Infections are common with both CAR-T and bispecific antibodies. Bispecific antibodies may have more persistent infection risk as well as higher incidence of severe infections.

The CAR-T agents and other T cell therapies are only available through the respective REMS programs which mitigates risks of cytokine release syndrome (CRS) and neurological toxicities of these agents. Neurological toxicities of CAR-T therapy include encephalopathy, headache, delirium, aphasia, anxiety, and tremors. CRS may be treated with tocilizumab (Actemra®). Due to the rigor of therapy, as well as the lag time between evaluation and receipt of therapy, therapy may not be appropriate for clinically fragile patients. The Eastern cooperative oncology group (ECOG) performance status scale and the Karnofsky performance status scale are two commonly used methods to assess a patient's functional status in clinical trials. These as well as other performance status scales can be utilized to help assess whether an individual is fit to tolerate CAR-T therapy.

Other considerations

Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD): 110.24

- Effective for services performed on or after August 7, 2019, CMS covers autologous treatment for cancer with T-cells expressing at least one CHIMERIC antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia.

Administration of CAR T- cell therapies in patients who have previously received CAR T- cell therapy or use in primary CNS lymphomas is not considered medically necessary. There is insufficient evidence to establish safety and efficacy. The NCCN Central Nervous System Cancers guideline does not include use of CAR T-cell therapy in primary CNS lymphoma.

CODING:

HCPCS Codes	Code Description
C9399	Unclassified drugs or biologicals
J3490	Unclassified drugs
J3590	Unclassified biologics
J9999	Not otherwise classified, antineoplastic drugs
Q2042	Tisagenlecleucel, up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion
Q2041	Axicabtagene Ciloleucel, up to 200 million autologous Anti- CD19 CAR T Cells, Including leukapheresis and dose preparation procedures, per infusion
Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Q2055	Idecabtagene vicleucel, up to 460 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
C9076	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

S2107	Adoptive immunotherapy, i.e., development of specific anti-tumor reactivity (e.g., tumor infiltrating lymphocyte therapy) per course of treatment
XW033C3	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into peripheral vein, percutaneous approach, new technology group 3 [when specified as Yescarta or Kymriah]
XW043C3	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into central vein, percutaneous approach, new technology group 3 [when specified as Yescarta or Kymriah]

REFERENCE/RESOURCES:

1. Relevant package inserts.
2. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.
3. Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically.
4. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia. NCCN Guidelines Version 3.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf . Accessed January 6, 2023.
5. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia. NCCN Guidelines Version 1.2023. Available at https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf . Accessed January 6, 2023.
6. National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology: B-cell Lymphomas. Version 5.2022 Available at https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 3, 2023.
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Multiple myeloma, version 2.2024.
8. Food and Drug Administration. FDA Briefing Document Oncologic Drugs Advisory Committee Meeting BLA 125646 Tisagenlecleucel. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566166.pdf. Accessed January 6, 2021.
9. Abramson JS, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND-NHL-001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
10. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014; 371(16):1507-1517.

11. Maude SL, Laetsch TW, Buechner JB, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med*. 2018; 378:439-448. DOI: 10.1056/NEJMoa1709866
12. Shah BD, Bishop MR, Oluwole OO, Logan AC, et al. KTE-X19 anti-CD19 CAR T-cell therapy in adult relapsed/refractory acute lymphoblastic leukemia: ZUMA-3 phase 1 results. Blood. 2021 Jul 8;138(1):11-22. doi: 10.1182/blood.2020009098. PMID: 33827116.
13. Food and Drug Administration. BLA Clinical Review Memorandum. https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM585388.pdf Accessed 11/28/17.
14. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377(26):2531-2544. doi:10.1056/NEJMoa1707447
15. Jacobson C, Chavex JC, Sehgal AR, et al. Primary analysis of Zuma-5: A phase 2 study of axicabtagene ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) [abstract]. Blood 2020; 136: 40-41.
16. Mueller KT, Waldron E, Grupp SA, et al. Clinical Pharmacology of Tisagenlecleucel in B-cell Acute Lymphoblastic Leukemia. *Clin Cancer Research*. 2018; 24(24). DOI: 10.1158/1078-0432.CCR-18-0758
17. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. 2019; 380:45-56. DOI: 10.1056/NEJMoa1804980
18. Institute for Clinical and Economic Review. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. 2018. https://icer.org/wp-content/uploads/2020/10/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Accessed January 6, 2021.
19. Wang M, et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2020;382(14):1331-1342.
20. Understanding chimeric antigen receptor (CAR) T cell technology. Kite Pharma, Inc. https://www.kitepharma.com/-/media/kite/images/news/mediakit/understanding-chimeric-antigen-receptor.pdf. Accessed January 6, 2021.
21. Getting the facts: mantle cell lymphoma. Lymphoma Research Foundation. Updated February 2018. https://lymphoma.org/wp-content/uploads/2019/08/LRF1702-MantleCellLymphomaFS_D3V4.pdf. Accessed January 6, 2021.
22. Freedman AS, Aster JC. Clinical manifestations, pathologic features, and diagnosis of mantle cell lymphoma. Lister A, Rosmarin AG, eds. UpToDate. Waltham, MA: UpToDate Inc. Updated August 5, 2019. https://www.uptodate.com/contents/clinical-manifestations-pathologic-

features-and-diagnosis-of-mantle-cell-lymphoma. Accessed January 6, 2021.
23. American Cancer Society ACS Journals. Cancer statistics, 2020. January 8, 2020. https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21590. Accessed January 6, 2021.
24. Lymphoma Research Foundation. Diffuse Large B-Cell Lymphoma. 2021. Accessed March 4, 2021. Available at: https://lymphoma.org/aboutlymphoma/nhl/dlbcl/.
25. Munshi NC, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716. doi:10.1056/NEJMoa2024850.
26. American Cancer Society. Multiple myeloma. Available at: https://www.cancer.org/cancer/multiple-myeloma.html. Accessed May 7, 2021.
27. Centers for Disease Control and Prevention.Myeloma. Available at: https://www.cdc.gov/cancer/myeloma/. Accessed May 7, 2021.
28. Multiple Myeloma Research Foundation. About multiple myeloma. Available at: https://themmrf.org/multiple-myeloma/what-is-multiple-myeloma/. Accessed May 7, 2021.
29. National Cancer Institute [internet]. Maryland: Cancer Stat Facts: Myeloma. Available at: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed May 7, 2021.
30. Laubach JP. Multiple myeloma: Clinical features, laboratory manifestations, and diagnosis. In: UpToDate, Rajkumar SV (Ed), UpToDate, Waltham, MA, 2021. Accessed May 7, 2021.
31. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019;33:2266-2275.
32. Mikhael J. Treatment options for triple-class refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2020;20:1-7.
33. Centers for Medicare and Medicaid. National Coverage Determination Chimeric Antigen Receptor (CAR) T-cell Therapy. Available at: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=374&ncdver=1&keyword=chimeric&keywordType=starts&areaId=all&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1. Accessed January 6, 2023.
34. Berdeja JG, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study [published correction appears in Lancet. October 2, 2021;398(10307):1216]. Lancet. 2021;398(10297):314–324. doi:10.1016/S0140-6736(21)00933-8

35. Gandhi UH, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33, 2266–2275. doi:10.1038/s41375-019-0435-77
36. Martin T, et al. 549 updated results from CARTITUDE-1: Phase 1b/2 study of ciltacabtagene autoleucel, a b-cell maturation antigen–directed chimeric antigen receptor T cell therapy, in patients with relapsed/refractory multiple myeloma. Poster presented at: American Society of Hematology (ASH) Annual Meeting & Exposition; December 10–13, 2021; New Orleans, LA. https://ash.confex.com/ash/2021/webprogram/Paper146060.html
37. Martin T, et al. Matching-adjusted indirect comparison of efficacy outcomes for ciltacabtagene autoleucel in CARTITUDE-1 versus idecabtagene vicleucel in KarMMa for the treatment of patients with relapsed or refractory multiple myeloma [published correction appears in Curr Med Res Opin. October 6, 2021;1–12]. Curr Med Res Opin. 2021;37(10):1779–1788. doi:10.1080/03007995.2021.1953456
38. Institute for Clinical and Economic Review. Anti B-Cell Maturation Antigen CAR T-cell and Antibody Drug Conjugate Therapy for Heavily Pre-Treated Relapsed and Refractory Multiple Myeloma: Final Policy Recommendations. May 11, 2011. https://icer.org/wp-content/uploads/2020/10/ICER_Multiple-Myeloma_Policy-Recommendations_05112021.pdf
39. National Comprehensive Cancer Network® (NCCN). Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 2.2022 Available at https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf Accessed January 8, 2023
40. Teclistamab-cqvy in: IPD Analytics [Internet database]. Aventura, Florida: IPD Analytics LLC. Updated periodically. Accessed November 4, 2022.
41. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 761342Orig1s000. Multi-discipline review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761342Orig1s000TOC.cfm (Accessed November 1, 2023)
42. Food and Drug Administration. Center for Drug Evaluation and Research. Application number: 761345Orig1s000. Multi-discipline review. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761345Orig1s000TOC.cfm (Accessed November 1, 2023)

APPENDIX A.

Brand Name	Generic Name
CAR T-cell therapies	
Abecma®	idecabtagene vicleucel
Breyanzi®	lisocabtagene maraleucel
Carvykti®	ciltacabtagene autoleucel
Kymriah®	tisagenlecleucel
TecartusTM	brexucabtagene autoleucel
Yescarta®	axicabtagene ciloleucel
T-cell engaging bispecific antibodies	
Talvey™	talquetamab-tgys
Tecvayli®	teclistamab-cqyv
Elrexfio™	elranatamab-bcmm

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND080.0823	**ENDOCRINE & METABOLIC AGENTS** **TEPEZZA®** (teprotumumab-trbw vial)
Effective Date: 10/01/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/23 (BS) P&T Committee Meeting Date: 04/23, 08/23 Original Effective Date: 06/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 2

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet all the following criteria:
    a. Confirmed diagnosis of moderate-to-severe thyroid eye disease/Grave's Orbitopathy, as defined as eye disease that significantly impacts quality of life and at least one of the following:
        i. Lid retraction of at least 2 mm, marginal reflex distance-1 (MRD1) greater than four, or presence of lagophthalmos
        ii. Moderate or severe soft-tissue involvement (such as swelling or redness of the eyes)
        iii. Inconstant diplopia (diplopia at extremes of gaze) or constant diplopia (continuous diplopia in primary or reading position)
    b. Documentation of active disease, defined as a Clinical Activity Score (CAS) of at least four
    c. Laboratory evidence of euthyroid state
    d. Inadequate response to at least two weeks of therapy with high-dose intravenous (IV) glucocorticoid therapy (equivalent to methylprednisolone

0.5 g once weekly) unless there is a contraindication, intolerance, or presence of proptosis or diplopia.

e. Dosing is within the Food and Drug Administration approved label dose

2. For patients established on the requested therapy (within the previous year): Documentation that the member has not received 8 doses of Tepezza®

EXCLUSION CRITERIA:
Sight-threatening thyroid eye disease (defined as presence of direct optic neuropathy or corneal breakdown)

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an ophthalmologist

COVERAGE DURATION:
Authorization will be approved for six months for a total of up to eight infusions

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Teprotumumab-trbw is the first and only FDA approved drug for the treatment of thyroid eye disease. Teprotumumab-trbw is a monoclonal antibody of the insulin-like growth factor type-1 receptor.[1]

FDA APPROVED INDICATIONS:
Thyroid Eye Disease regardless of Thyroid Eye Disease activity or duration

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCEND080.0823	ENDOCRINE & METABOLIC AGENTS **TEPEZZA®** (teprotumumab-trbw vial)

POSITION STATEMENT:
Thyroid eye disease (TED), or Grave's orbitopathy (GO), is one of the main extra thyroidal manifestations of Graves' disease (been noted to develop in approximately 40% of patients). TED/GO causes inflammation and tissue expansion behind the eye which leads to proptosis (abnormal protrusion) and is often accompanied by diplopia (double vision) and pain. Severe cases of TED can cause blindness.

The most widely used assessment of TED activity is the clinical activity score (CAS). It is a 7-point scale that evaluates pain, erythema, and edema. A score greater than or equal to 3 usually implies active disease.[8]

There is a lack of treatment options for thyroid eye disease currently available, other than glucocorticoids. Teprotumumab represents the first in class for treatment of thyroid eye disease. This agent is a monoclonal antibody that blocks the activation and signaling of insulin-like growth factor-1, which is thought to play a role in thyroid eye disease via immunoglobulin signaling.

This drug carries warnings[1] for:
1. Exacerbation of preexisting inflammatory bowel disease (IBD) – consider discontinuation if IBD exacerbation suspected, and
2. Hyperglycemia - 10% of patients (two thirds of whom had pre-existing diabetes or impaired glucose tolerance) experienced hyperglycemia

The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines recommend that high-dose systemic glucocorticoids (GCs) be used as first-line treatment in combination with mycophenolate for moderate to severe disease. For sight-threatening disease therapy with that high-dose systemic glucocorticoids (GCs) is also recommended as primary therapy with surgery recommended as second-line therapy.[6]

The American Thyroid Association and European Thyroid Association joined forces to develop a consensus statement (2022). Intravenous glucocorticoid (IVGC) therapy is a preferred treatment for active moderate-to-severe thyroid eye disease when disease activity is the prominent feature in the absence of either significant proptosis or diplopia. Teprotumumab is a preferred therapy, if available, in patients with active moderate-to-severe thyroid eye disease with significant proptosis and/or diplopia. Lastly, treatment with IVGC is recommended for sight-threatening disease.[8]

Clinical Trials:

Smith TJ *et al* (Pubmed ID #28467880)[4]

- Study Design: Phase 2, R, DB, PC
- Study Duration: 24 weeks
- Patient population: Patients (N=88), aged 18-75 years old with diagnosis of orbitopathy no more than 9 months after onset of symptoms. Patients must have active disease, defined as a Clinical Activity Score (CAS) of at least 4 in the more severely affected eye, and have not received surgical or medical treatment other than glucocorticoids (up to 1 g methylprednisolone equivalent)
- Intervention:
    - Randomized in a 1:1 ratio to receive IV infusion of teprotumumab every three weeks (10 mg/kg for one dose and 20 mg/kg thereafter) or placebo once every three weeks for a total of 8 infusions.
- Primary endpoint: Composite of 1) reduction of 2 mm or more in proptosis and 2) clinical activity score reduction of at least 2 points
- Results:

	Teprotumumab	Placebo	Odds Ratio
% patients that met primary endpoint at week 24			
ITT population	69% (29/42)	20% (9/45)	8.86 (p<0.001)
Per-protocol population	79% (26/33)	22% (8/36)	12.73 (p<0.001)

    - Efficacy:
    - Safety: The most common adverse events seen were nausea, muscle spasms, diarrhea, and hyperglycemia
- GRADE evidence rating: D
    - Strengths: Randomized, double-blind, allowed patients up to 75 years old, clinically significant endpoints
    - Limitations: Phase II trial, small sample size, exclusion of high-dose glucocorticoid patients (more than 1 g of methylprednisolone), study pharmacists were unblinded due to need to infusion preparation for study drug and not placebo, baseline characteristics not well balanced (patients in placebo group were older, higher proportion of females, fewer smokers, and had longer duration of eye symptoms), analytical methods were used to adjust for smoker status difference

Douglas RS, et al (Pubmed ID #31971679)[5]

- Phase 3, R, DB, PC
- Study Duration: 24 weeks
- Patient population: Patients (N=83), aged 18-80 years with a diagnosis of Grave's disease and active, moderate-to-severe thyroid eye disease with

symptoms that began within the previous nine months. Patients were considered to have active disease if their CAS was at least four (4) and moderate-to-severe disease if they had at least one of the following: lid retraction of ≥2 mm, moderate or severe soft-tissue involvement, proptosis of ≥3 mm above the normal values for race and sex, and periodic or constant diplopia. Patients were required to by euthyroid.
    - Exclusion Criteria:
        - Previous orbital irradiation or surgery for thyroid eye disease
        - Decreasing visual acuity, defect in visual field or color vision from optic nerve involvement within the previous six months
        - Glucocorticoid use (defined as cumulative dose equivalent to ≥1 g of methylprednisolone for the treatment of thyroid eye disease)
        - Previous treatment with rituximab or tocilizumab
- Intervention:
    - Randomized in a 1:1 ration to receive IV infusion of teprotumumab every three weeks (10 mg/kg for one dose followed by 20 mg/kg thereafter) or placebo once every three weeks for a total of 8 infusions.
- Primary endpoint: Proptosis response at week 24, defined as a reduction in proptosis of ≥2 mm from baseline in the study eye without a corresponding increase of ≥2 mm in the fellow eye
- Secondary endpoints:
    - Overall response at week 24, defined as a reduction of ≥2 points in the Clinical Activity Score plus a reduction in proptosis of ≥2 mm without a corresponding increase [of ≥2 points or ≥2 mm] in the fellow eye
    - Proportion of patients achieving a Clinical Activity Score of 0 or 1 at week 24
    - Mean change in proptosis (in mm) from baseline to week 24
- Results:
    - Notes:
        - Primary endpoint data in **bold**
        - Secondary endpoints calculated in ITT population
        - No confidence intervals for difference crossed 0

	Teprotumumab	Placebo	Difference
% patients with proptosis response at week 24 **ITT population** **Per-protocol population**	 **83% (34/41)** **88% (29/33)**	 **10% (4/42)** **12% (4/34)**	 **73 (p<0.001)** **76 (p<0.001)**
Overall response at week 24 (% patients)	78% (32/41)	7% (3/42)	71 (p< 0.001)
Clinical Activity Score of 0 or 1 at wk 24	59% (24/41)	21% (9/42)	36 (p<0.001)

Mean change in proptosis from baseline to wk 24 (mm)	-2.82±0.19	-0.54±0.19	-2.28 (p<0.001)
Mean change in GO-QOL (Graves' ophthalmology-specific quality-of-life) score from baseline through week 24	13.79±2.07	4.43±2.10	9.36 (p<0.001)

    - Safety: The most common adverse events that occurred were muscle spasms, alopecia, nausea, and fatigue
- GRADE evidence rating: C
    - Strengths: Randomized by interactive voice response system, double-blind, allowed patients up to 80 years old, proptosis measured by same observer at each visit, baseline characteristics well balanced
    - Limitations: Small sample size, short duration, exclusion of patients with use of high-dose glucocorticoids (≥1 g of methylprednisolone), study pharmacists were unblinded due to need to infusion preparation for study drug and not placebo
- Note: Patients in this study who did not have a proptosis response, or had relapse could enter an open-label extension study and receive eight additional infusions of teprotumumab.
    - 51 patients have enrolled in this study; not data available (NCT03461211)

REFERENCE/RESOURCES:

1. Tepezza Package insert. Lake Forest, IL. Horizon Therapeutics USA, Inc. December 2022.
2. Teprotumumab-trbw In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed March 7, 2023.
3. Teprotumumab-trbw In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed March 7, 2023.
4. Smith TJ, Kahaly GJ, Ezra DG, et al. Teprotumumab for Thryroid-Associated Ophthalmopathy. *N Engl J Med*. 2017;376(18):1748-1761. doi:10.1056/NEJMoa1614949.
5. Douglas RS, et al. Teprotumumab for the Treatment of Active Thyroid Disease. *New Engl J Med.* 2020;382(4):341-352. doi:10.1056/NEJMoa1910434.
6. Bartalena L, Kahaly GJ, Baldeschi L, et al. EUGOGO The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *European Journal of Endocrinology*. 2021;185(4):G43–G67.

7. Zhou et al. Treatment strategies for Graves' ophthalmopathy: a network meta-analysis. Br J Ophthalmology 2020;104:551–556.
8. Burch HB, Perros P, Bednarczuk T, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. *Thyroid*. Dec 2022.1439-1470.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY CRITERIA ORPTCRES019.0823	**REPIRATORY AGENTS** **TESZPIRE®** (tezepelumab-ekko syringe)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/23, 08/23 (SNM) P&T Committee Meeting Date: 06/22, 08/23 Original Effective Date: 07/22 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
1. For patients initiating therapy, all the following criteria must be met:
    a. In the past three months, patient is adherent to treatment with maximally tolerated doses of both of the following, unless patient has an intolerance or contraindication to all therapies (This may be verified by pharmacy claims information):
        i. Inhaled corticosteroid
        ii. One of the following:
            a) A long-acting inhaled beta 2-agonist (LABA)
            b) A leukotriene receptor antagonist (LTRA)
            c) A long-acting muscarinic antagonist (LAMA)
    b. Inadequate asthma control despite above therapy, defined as one of the following:
        i. Asthma Control Test (ACT) score less than 20 or Asthma Control Questionnaire (ACQ) score greater than or equal to 1.5
        ii. At least two exacerbations requiring oral systemic corticosteroids in the last 12 months

iii. At least one exacerbation requiring hospitalization, emergency room or urgent care visit in the last 12 months
i. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
ii. Baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

2. For patients established on therapy for asthma (within the previous year): Response to therapy indicating improvement or stabilization of condition

EXCLUSION CRITERIA:
Concurrent use with anti-IL5 (such as mepolizumab, reslizumab, benralizumab), anti-IgE, anti-TSLP (such as tezepelumab), or anti-IL4 (such as dupilumab) monoclonal antibodies

AGE RESTRICTIONS:
For all indications, the patient's age must be within FDA labeling for the requested indication

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with an asthma specialist (such as a pulmonologist, immunologist, or allergist)

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY CRITERIA ORPTCRES019	REPIRATORY AGENTS **TEZSPIRE®** (tezepelumab-ekko syringe)

INTRODUCTION:
Tezepelumab-ekko (Tezspire®) is a human monoclonal antibody thymic stromal lymphopoietin (TSLP) blocker, which reduces markers inflammation, such as blood eosinophils, airway submucosal eosinophils, interleukin-5 (IL-5), and IL-13.

Per package labeling, the vial and pre-filled syringe formulations are intended for administration by a healthcare provider. The pre-filled pen formulation can be administered by patients/caregivers or healthcare providers.

FDA APPROVED INDICATIONS:
Add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

- Limitations of Use: not indicated for the relief of acute bronchospasm or status asthmaticus.

POSITION STATEMENT:
Global Initiative for Asthma (GINA) 2023 guidelines define severe asthma as that which is not controlled with high-dose ICS-LABA therapy, despite good adherence to therapy. It can also be patients with symptoms that return/worsen when the dose of ICS-LABA therapy is lowered. The management of severe asthma should be based on the phenotype and add-on treatments may include long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA), low-dose azithromycin, and/or biologics.[4]

Alternative biologic therapy options:

Drug	Dosing	Mechanism	Indication
Omalizumab (Xolair®)	75-375 mg SC Q2W or Q4W	Anti-IgE	Age ≥6 years with moderate to severe persistent asthma testing positive for perennial aeroallergen whose symptoms are inadequately controlled with ICS
Dupilumab (Dupixent®)	200-300 mg SC Q2W	Anti-IL-4Rα	Age ≥12 years with moderate to severe asthma with an eosinophilic phenotype or with OCS-dependent asthma
Mepolizumab (Nucala®)	100 mg SC Q4W	Anti-IL-5	Age ≥6 years with severe asthma with an eosinophilic phenotype
Benralizumab (Fasenra®)	30 mg SC Q4W for 3 doses, then Q8W	Anti-IL-5Rα	Age ≥12 years with severe asthma with an eosinophilic phenotype
Reslizumab (Cinqair®)	3 mg/kg IV infusion Q4W	Anti-IL-5	Age ≥18 years with severe asthma with an eosinophilic phenotype

Clinical Trials for tezepelumab-ekko:
NAVIGATOR (PubMed ID #NCT03347279)[5]

- R, DB, PC, phase 3 study
- Study Duration: 52 weeks
- Patient population: Patients (N=1061) between 12 to 80 years of age with physician diagnosed asthma for at least 12 months, taking a controller regimen of medium/high dose ICS for at least 12 months plus one additional controller for at least three months. In addition, patients must have had severe disease, defined as one of the following in the 12 months prior to informed consent:
    - History of at least two asthma exacerbations that led to hospitalization
    - An emergency department visit that resulted in the use of systemic glucocorticoids for at least three consecutive days
- Key Exclusion criteria: patients with any clinically important pulmonary disease other than asthma or pulmonary or systemic diseases, other than asthma, that are associated with elevated peripheral eosinophil count.
- Intervention: Randomized in 1:1 ratio to TEZ 210 mg (N=529) and placebo (N=532) subcutaneously every four weeks for 52 weeks
- Primary endpoint: AAER over 52 weeks
- Results:
    - Baseline characteristics: Mean age 50 years; 36.5% male sex; 62.2% white race, 27.9% Asian, 5.8% Black Americans; 75% on high dose ICS, 9% on OCS, 50% on LABA
    - Efficacy:
        - TEZ treatment reduced AAER by 56% compared to placebo group; ARR 1.17 and NNT 1.

	TEZ	Placebo	Rate Ratio
AAER	0.93	2.10	0.44 (0.37-0.53); P<0.001

        - TEZ group had a greater improvement in baseline prebronchodilator FEV1 (0.23 vs. 0.09 liters; 95% CI, 0.08 to 0.18; P<0.001). The minimum clinically important difference (MCID) is 0.1 liter
        - TEZ group had improvement in other symptom scores like Asthma Control Questionnair-6 (-1.55 vs. -1.22; 95% CI, -0.46 to -0.20; P<0.001), Asthma Quality of Life Questionnaire (1.49 vs. 1.15; 95% CI, 0.20 to 0.47; P<0.001), and Asthma Symptom

Dairy (-0.71 vs. -0.59; 95% CI, -0.19 to -0.04; P=0.002), but did not meet MCID of at least 0.5 points
        - Based on subgroup analysis, patients with eosinophil count at least 300 cells/µl (rate ratio, 0.30, 95% CI, 0.22 to 0.40) at baseline had a greater reduction in AAER compared to eosinophil count <300 cells/µl (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001)
    - Safety: There was no meaningful difference in adverse events between the two groups. The most common adverse events were nasopharyngitis, upper respiratory tract infection, headache, and asthma.
        - The incidence of severe infections such as pneumonia and diverticulitis did not differ between two groups
        - Two deaths were reported (heart failure and unknown cause) in the placebo group
- GRADE evidence rating: Moderate
    - Strengths: Randomized, double-blind, multicenter trial; well-balanced patient characteristics
    - Limitations: Reduced generalizability due to under-enrollment of ethnic minorities (Black Americans have a higher prevalence of severe asthma than White Americans, but represent very small proportion of patients in this trial); placebo controlled trial; Manufacturer coordinated data management and performed statistical analysis; Small number (9.4%) of patients were on oral corticosteroids (OCS)

SOURCE (PubMed ID: 35364018)[6]

- R, DB, PC, Phase 3 study
- Study Duration: 48 weeks
- Patient population: Patients (N=150) 18-80 years of age with physician diagnosed asthma for at least 12 months on controller regimen including all the following: 1) medium/high dose ICS for at least 12 months (patients on medium-dose ICS were required to increase to a high dose for at least three months before screening), 2) LABA for at least three months, and 3) OCS for at least six months. Patients must have had severe asthma, defined as one of the following in the 12 months prior to screening:
    - History of at least two asthma exacerbations that led to hospitalization
    - An emergency department visit that resulted in the use of systemic glucocorticoids for at least three consecutive days
    - Need for use of systemic corticosteroids for at least three consecutive days

- Key exclusion criteria included any clinically important pulmonary disease, other than asthma, associated with high peripheral eosinophil counts, any clinically significant infection including helminth or parasitic infections.
- Intervention: 1:1 randomization into TEZ 210 mg SC every four weeks and placebo SC every four weeks, after a 2-week screening/run-in followed by an OCS optimization phase of up to eight weeks. Eligible patients were then randomized for the treatment period with the following phases:
    - Induction (four weeks of stable OCS dose)
    - Dose-reduction (36 weeks, protocol-driven dose reduction)
    - Maintenance (eight weeks without any dose reductions)
- Primary endpoint: Percent reduction from baseline in the daily OCS dose at week 48 while not losing asthma control
    - Key secondary endpoint: AAER over the treatment period
- Results:
    - Baseline Characteristics: Mean age 54 years, 37% male sex, 84% white race (1% Black American); 99% on high dose ICS, 100% on OCS; Median baseline eosinophil count 200-215 cells/µL, FeNO 26-28 ppb, IgE 109-123 mg/L
    - Efficacy:
        - The study did not meet the primary endpoint with no statistical difference in reduction of daily OCS dose between TEZ and placebo [Odds Ratio (95% CI): 1.28 (0.69, 2.35); P=0.434].

Reduction from baseline daily OCS dose	TEZ 210 mg n (%)	Placebo (N=76)
≥90% to 100% reduction	40 (54.1)	35 (46.1)
≥75% to <90% reduction	5 (6.8)	4 (5.3)
≥50% to <75% reduction	10 (13.5)	14 (18.4)
>0% to <50% reduction	5 (6.8)	9 (11.8)
No change or any increase	14 (18.9)	14 (18.4)

        - In subgroup analysis, the odd ratio favored those with higher baseline levels of blood eosinophils (≥150 cells/µL), higher FeNO (≥25 ppb), positive allergic status, lower daily OCS (≤10 mg/day), but these findings were difficult to interpret due to the small number of subjects.
        - The reduction in AAER was a secondary outcome, and it did show a reduction in subjects treated with TEZ compared to placebo, but it was not statistically significant.
            - TEZ: 1.38 (.98-1.95

    - Placebo: 2.00 (1.46-2.74)
    - Rate ratio 0.69 (95% CI 0.44–1.09)
  - Safety: No difference in adverse events between two groups.
    - The most common adverse events reported were nasopharyngitis, upper respiratory tract infection, bronchitis, and oral candidiasis.
- GRADE evidence rating: Low
  - Strengths: Randomized trial, well-balanced patient characteristics
  - Limitations: Small sample size (N=150); Reduced generalizability due to under-enrollment of ethnic minorities (Black Americans have a higher prevalence of severe asthma than White Americans, but represent very small proportion of patients in this trial); Protocol amendment to increase number of subjects enrolled to provide more power to reject the null hypothesis

Cost-effectiveness studies:[7]

Institute for Clinical and Economic Review (ICER) conducted a review of tezepelumab for Severe Asthma in December 2021. Summary of conclusions:

- Tezepelumab is considered “Comparable or Better” than placebo therapy in patients with severe, uncontrolled asthma
  - Tezepelumab reduced exacerbation rates in patients with severe asthma compared to placebo.
  - It also exhibited trends towards improved symptom scores but did not meet minimal clinically important differences versus placebo.
  - Tezepelumab showed similar improvement in symptom scores and reduction in AAER in patients with and without eosinophilic asthma
- There was insufficient evidence to rate tezepelumab against dupilumab in patients with eosinophilic asthma or omalizumab in patients with allergic asthma
- Tezepelumab did not show a benefit for reducing oral corticosteroid use in adult patients with severe steroid-dependent asthma and was rated as “Comparable or Inferior” to dupilumab
- Of note, the report outlines that severe asthma is more common in Black Americans, but the clinical trials did not include a robust Black population to determine a true effect in these patients
- Tezepelumab treatment likely not considered cost-effective in the US market

REFERENCE/RESOURCES:

1. Package insert. Tezspire™ injection, Tezepelumab-ekko injection, Amgen Inc. and AstraZeneca AB (per FDA), Thousand Oaks, CA. 2023 Feb.

2. Tezspire In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 21, 2023.
3. Tezspire In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed April 21, 2023.
4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2023 Update). Available at: http://www.ginasthma.org. Accessed on May 9, 2023.
5. Menzies-Gow, Andrew et al. "Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma." *NEJM. 2021:* 384(19):1800-1809. doi:10.1056/NEJMoa2034975
6. Wechsler M, Menszies-Gow A, Brightling CE, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. *Lancet Respir Med. 2022 Mar 29;S2213-2600(21)00537-3.*
7. Rind DM, McQueen RB, Herron-Smith S, et al. Tezepelumab for Severe Asthma; Final Report. Institute for Clinical and Economic Review, December 16, 2021. https://icer.org/wp-content/uploads/2021/12/ICER_Severe-Asthma_Key-Policy-Recommendations_121621.pdf Accessed May 13, 2023.

CPT/HCPCS CODES

Brand Name	Generic Name	HCPCS Code
Tezspire	Tezepelumab-ekko	J2356

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM034.1223	**HEMATOLOGICAL AGENTS** **THROMBOCYTOPENIA MEDICATIONS** **Nplate®** (romiplostim SQ injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/22 , 11/23 (KN)
Original Effective Date: 08/15	**P&T Committee Meeting Date**: 12/21, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications, some medically accepted Indications.

REQUIRED MEDICAL INFORMATION:
For initiation of therapy, must meet indication-specific criteria below:

1. For **Oncologic Diagnoses:** Use must be for an FDA approved indication or indication supported by National Comprehensive Cancer Network guidelines with recommendation 2A or higher
2. For **Immune Thrombocytopenia (ITP)**, Nplate®, may be covered if all the following criteria are met**:**
    a. Documented risk for bleeding as indicated by at least one of the following:
        i. Severe ITP (bleeding symptoms)
        ii. Risk factors for bleeding are present (such as uncontrolled hypertension, active peptic ulcer disease, anticoagulation, recent surgery, head trauma)
        iii. In preparation for procedures or surgery with risk of bleeding
        iv. Professional or lifestyle risk factors for trauma
    b. Persistent or chronic disease (greater than 6 months)
    c. Documented lack of response (defined as platelet count less than 30,000 cells per microliter or less than 2-fold increase in baseline platelets) to at least one first-line therapy:
        i. Corticosteroids in a dosing regimen standard for ITP treatment

ii. Intravenous Immune globulin (IVIg)
iii. Intravenous anti-D

1. For **Hematopoietic Syndrome of Acute Radiation Syndrome [HSARS]**, Nplate® may be covered if the patient has suspected or confirmed exposure to radiation levels greater than 2 gray (Gy)

For patients established on therapy, must meet indication-specific criteria below:

1. For **ITP:**
    a. Documentation of response to therapy (defined as platelet count of at least 30,000 cells per microliter or a 2-fold increase in baseline platelets)
2. For **HSARS**: Members must meet the initial approval criteria above for each request

EXCLUSION CRITERIA:
Concomitant use with other thrombopoietin receptor agonists (e.g., Mulpleta®, Promacta®) or with spleen tyrosine kinase inhibitors (e.g., Tavalisse®).

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an oncologist, hematologist, gastroenterologist or hepatologist.

COVERAGE DURATION:

- For **ITP**: Initial authorization will be approved for six months. Reauthorization will be approved for one year
- For **HSARS**: Authorization will be approved for three months

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Thrombocytopenia is a condition characterized by a low blood platelet count. Platelets (thrombocytes) are colorless blood cells that help blood clot. Thrombopoietin receptor agonists (TPO-RAs; e.g., Mulpleta®, Promacta®, Nplate®) and spleen tyrosine kinase (SYK) inhibitors (e.g., Tavalisse®) are medications used to treat thrombocytopenia when standard therapies, such as corticosteroids, are not sufficient. TPO-RAs increases the production of platelets by stimulating bone marrow cells, whereas the SYK inhibitors work by preventing the breakdown of platelets.

FDA APPROVED INDICATIONS:

- Pediatric patients one year of age and older with immune (idiopathic) thrombocytopenia (ITP) for at least six months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- Adults with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- To increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HSARS]).

POSITION STATEMENT:

Chronic Immune (idiopathic) Thrombocytopenia

ITP is an autoimmune disorder characterized by isolated thrombocytopenia (low blood platelet count) with otherwise normal complete blood count in the absence of other apparent causes (i.e., associated conditions, drugs). The main clinical manifestations of ITP are related to excessive bleeding, which is typically mucocutaneous including petechiae, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia. More overt bleeds such as gastrointestinal bleeds, gross hematuria, and intracranial hemorrhage are rare.

The American Society of Hematology (ASH) 2019 guidelines recommend short courses of corticosteroids (less than or equal to six weeks) as first-line treatment. Intravenous immunoglobulin (IVIg) either as single agent or in combination with corticosteroids may also be appropriate. Second-line treatments include splenectomy, TPO-receptor agonists (e.g., eltrombopag, romiplostim), and rituximab. Splenectomy is the only treatment that provides sustained remission off all treatments at one year and beyond in a high proportion of ITP patients. The goal in treatment of ITP is not to achieve a normal platelet count but a safe level that avoids bleeds.

Evidence of romiplostim (Nplate®) in chronic ITP

- The safety and efficacy of romiplostim in adults with ITP were assessed in two double-blind, placebo-controlled clinical studies, an open-label single-arm study, and in an open-label extension study.
- In the two double-blind, placebo-controlled clinical studies (Studies 1 and 2), patients with ITP who had completed at least one prior treatment and had a platelet count of ≤ 30 × 109/L prior to study entry were randomized (2:1) to 24 weeks of romiplostim (1 mcg/kg subcutaneous [SC]) or placebo given weekly. Prior ITP treatments in both study groups included corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e., corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin) were permitted for bleeding, wet purpura, or if the patient was at immediate risk for hemorrhage.
    - Study 1 evaluated patients who had *not* undergone a splenectomy. The patients had been diagnosed with ITP for approximately 2 years and had received a median of three prior ITP treatments. Overall, the median platelet count was 19 × 10^9/L at study entry. During the study, the median weekly romiplostim dose was 2 mcg/kg
    - Study 2 evaluated patients who had undergone a splenectomy. The patients had been diagnosed with ITP for approximately 8 years and had received a median of six prior ITP treatments. Overall, the median platelet count was 14 × 10^9/L at study entry. During the study, the median weekly romiplostim dose was 3 mcg/kg
    - The results showed that 88% and 79% of patients in the romiplostim groups of Studies 1 and 2 achieved an overall platelet response (platelet counts of ≥ 50 × 109/L in any four weeks of the 24-week study period) versus 14% and 0% in the placebo group respectively. Durable platelet response (platelet counts of ≥ 50 × 109/L in any six of the last eight weeks of the 24-week study period) was achieved in 61% and 38% of patients in the romiplostim groups, versus 5% and 0% in placebo, respectively.

Hematopoietic Syndrome of Acute Radiation Syndrome (HSARS)

Hematopoietic Syndrome of Acute Radiation Syndrome (HSARS) occurs in adult and pediatric patients exposed to myelosuppressive doses of radiation. Symptoms include nausea, vomiting, diarrhea, headache, weakness, or drop in blood counts.

Romiplostim garnered approval for this indication based on efficacy studies conducted in animals, effect on platelets counts in health human volunteers, and effect on thrombocytopenia in patients with ITP for ethical and feasibility reasons. The animal study was a randomized, blinded, placebo-controlled study in Rhesus

monkeys exposed to a total body irradiation of 6.8 Gy from a Cobalt^{60} gamma ray source, representing a dose that would be lethal in 70% of animals by 60 days of follow-up (LD70/60). They were then administered either a single subcutaneous dose of blinded treatment (control article [sterile saline] or romiplostim [5 mg/kg]) 24 hours post-irradiation

- The primary endpoint was survival was statistically significant for romiplostim treated group. 72.5% survival (29/40) in the romiplostim group compared to 32.5% survival (13/40) in the control group
    - An exploratory cohort of n=40 animals received romiplostim (5 mg/kg) on day one and pegfilgrastim (0.3 mg/kg) on days one and eight post-irradiation.
    - Combined treatment group survival was 87.5% (95% CI: (73.2%, 95.8%)).
- The safety was assessed based on the clinical experience in patients with ITP and from healthy volunteers.
- The 10 mcg/kg dosing regimen for humans is based on population modeling and simulation analyses.

REFERENCE/RESOURCES:

1. Nplate® (romiplostim) package insert. Thousand Oaks, CA: Amgen; 2022 February.
2. [Respective Drugs] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed [November 4, 2022].
3. [Respective Drugs] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed [November 4, 2022].
4. Neunert C, Terrell DR, Arnold DM *et al*. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.Erratum in: *Blood Adv*. 2020;4(2):252.
5. Barnett CL, Mladsi D, Vredenburg M, Aggarwal. Journal of Medical Economics. 2018; 21:8, 827-834.
6. Stasi R. How to approach thrombocytopenia. American Society of Hematology Education Book 2012; 2012(1):191-197.
7. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenia purpura: a double-blind randomized controlled trial. *Lancet.* 2008 Feb 2; 371(9610):395-403.
8. Newland C, Sanz MA, Bourgeois E, et al. Evaluating the long-term efficacy of romiplostim (AMG 531) in patients with chronic immune thrombocytopenic purpura (ITP) during an open-label extension study. *Haematologica.* 2008;93(suppl 1):377.

9. Kistangari G, McCrae KR. Immune thrombocytopenia. Hematol Oncol Clin North Am. 2013;27(3):495-520. doi: 10.1016/j.hoc.2013.03.001.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNUT003B.0423	**NUTRITIONAL PRODUCTS TOTAL PARENTERAL NUTRITION (TPN)**
Effective Date: 6/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/18, 07/19, 07/20, 10/20, 03/21, 03/22, 02/23 (MTW) P&T Committee Meeting Date: 06/17, 08/18, 08/19, 08/20, 12/20, 04/21, 04/22, 04/23 Original Effective Date: 09/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 7

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B – Local Coverage Determination L38953

POLICY CRITERIA:

COVERED USES: All Medically-Accepted Indications

REQUIRED MEDICAL INFORMATION:

1. Documentation that the member has a medical condition which does not allow for absorption of sufficient nutrients to maintain weight and strength as defined by one of the following:
    a. A condition involving the small intestine and/or its exocrine glands which significantly impairs the absorption of nutrients, or
    b. A disease of the stomach and/or intestine which is a motility disorder and impairs the ability of nutrients to be transported through and absorbed by the gastrointestinal (GI) system

AND

2. Documentation that the condition is of long and indefinite duration as deemed by the judgment of the attending provider or substantiated in the medical records

AND

3. Documentation that enteral nutrition has been considered and ruled out, tried and been found ineffective, or that enteral nutrition exacerbates gastrointestinal tract dysfunction

AND

The treating provider has evaluated the member within 30 days prior to initiation of parenteral nutrition. If the treating provider does not see the beneficiary within this timeframe, they must document the reason why and

describe what other monitoring methods were used to evaluate the beneficiary's parenteral nutrition needs.

Reauthorization requires documentation of ongoing medical necessity of total parenteral nutrition.

EXCLUSION CRITERIA:
Parenteral nutritional therapies are not covered under Medicare Part B in situations involving temporary impairments. **Non-Part B uses may be coverable under the Part D benefit.**

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Authorization will be approved for a minimum three months, up to 12 months.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Parenteral nutrition (PN) is the provision of nutritional requirements through a central or peripheral venous catheter. The purpose of initiating parenteral nutritional therapy is to prevent or correct specific nutrient deficiencies and the adverse effects of malnutrition when the gastrointestinal tract cannot be used safely or effectively. The PN benefit will include all related supplies, equipment and nutrients. Skilled assessment of nutritional status will be done at a frequency consistent with the member's diagnosis and general nutritional condition.

FDA APPROVED INDICATIONS: N/A

POSITION STATEMENT:

- Total parenteral nutrition (TPN) therapy is a covered benefit when it is determined to be medically necessary to prevent or treat malnutrition and nutritional needs which cannot be met by oral or enteral feedings. Parenteral nutrition will be covered under the member's medical benefit. For Medicare members, coverage under the Part B benefit is for individuals with permanent dysfunction. Permanence does not require a determination that there is no possibility that the member's condition may improve sometime in the future. If the judgment of the doctor, substantiated in the medical record, the test of permanence is considered met. This is consistent with Center for Medicare and Medicaid Services (CMS) guidelines.
- TPN is not considered medically necessary for conscious patients whose need for parenteral nutrition is solely due to a lack of appetite or cognitive problem.
- Whenever clinically appropriate, attempts to wean the patient off of parenteral nutrition in favor of oral or enteral routes should be undertaken.
- The medical policy and criteria are developed based on Medicare and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines.
- Parenteral nutrition may be covered in patients with the ability to obtain partial nutrition from oral intake or a combination of oral/enteral intake as long as the above criteria are met.
- If coverage requirements for parenteral nutrition are met, medically necessary nutrients, administration supplies, and equipment are covered.
- Parenteral nutrition provided to a patient in a Part A covered stay must be billed by the skilled nursing facility (SNF). No payment from Part B is available when parenteral nutrition services are furnished to a beneficiary in a stay covered by Part A. However, if a beneficiary is in a stay not covered by Part A, parenteral nutrition is eligible for coverage under Part B and may be billed by either the SNF or a supplier.
- When parenteral nutrition is administered in an outpatient facility, the pump used for its administration and IV pole will be denied as not separately payable. The pump and pole are not considered as rentals to a single patient but rather as items of equipment used for multiple patients.
- Dispensing of nutritional therapy is limited to a one month supply at any one time.

Refeeding Syndrome

In malnourished patients, aggressive delivery of calories, specifically carbohydrates, can induce refeeding syndrome. Refeeding syndrome involves an intracellular shift of magnesium, potassium, and phosphorus. This can lead to low serum levels of magnesium, potassium, and phosphorus, as well as symptoms of fatigue, arrhythmia, edema, muscle weakness, and lethargy. Patients at risk of refeeding syndrome should have their TPN or PPN initiated in an inpatient setting for frequent monitoring of electrolytes and minimization of adverse effects.

Patients at High Risk for Refeeding Syndrome
Anorexia nervosa
Chronic alcoholism
Morbid obesity with rapid weight loss (ex. Gastric bypass surgery)
Protein Calorie Malnutrition
> 10% weight loss over 2-3 months
Chronic malnutrition or starvation
Unfed for 7-10 days or evidence of underfeeding
Prolonged fasting (ex. Observance of Ramadan, NPO status, Clear liquid diet)
Prolonged IV hydration with NPO status
Wasting diseases (ex. Cancer, AIDS)

HCPCS CODES

The following table includes codes that may be eligible for coverage under this policy. This list may not be all inclusive and does not guarantee coverage. This information is for reference purposes only.

Prior Authorization Required	
HCPCS Code	**Description**
B4164	Parenteral nutrition solution: carbohydrates(dextrose), 50% Dextrose or less (500 ml= 1unit), home mix
B4168	Parenteral nutrition solution; amino acid, 3.5%, (500 ml= 1unit), home mix
B4172	Parenteral nutrition solution; amino acid, 5.5% through 7%, (500 ml= 1unit), home mix
B4176	Parenteral nutrition solution; amino acid, 7% through 8.5%, (500 ml= 1unit), home mix
B4178	Parenteral nutrition solution; amino acid, greater than 8.5%, (500 ml= 1unit), home mix
B4180	Parenteral nutrition solution: carbohydrates(dextrose), greater than 50% Dextrose (500 ml= 1unit), home mix
B4185	Parenteral nutrition solution, per 10 grams lipids
B4187	Omegaven, 10 grams lipids
B4189	Parenteral nutrition solution: compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, 10 to 51 g of protein, premix
B4193	Parenteral nutrition solution: compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, 52 to 73 g of protein, premix

B4197	Parenteral nutrition solution: compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, 74 to 100 grams of protein, premix
B4199	Parenteral nutrition solution: compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, over 100 grams of protein, premix
B4216	Parenteral nutrition; additives (vitamins, trace elements, Heparin, electrolytes), home mix, per day
B4220	Parenteral nutrition supply kit; premix, per day
B4222	Parenteral nutrition supply kit; home mix, per day
B4224	Parenteral nutrition administration kit, per day
B5000	Parenteral nutrition solution compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, renal- Aminosyn RF, NephrAmine, RenAmine - premix
B5100	Parenteral nutrition solution compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength, hepatic, HepatAmine-premix
B5200	Parenteral nutrition solution compounded amino acid and carbohydrates with electrolytes, trace elements, and vitamins, including preparation, any strength,stress-branch chain amino acids-FreAmine-HBC - premix
No Prior Authorization Required	
B9004	Parenteral nutrition infusion pump, portable
B9006	Parenteral nutrition infusion pump, stationary
B9999	NOC for parenteral supplies
E0776	IV Pole

REFERENCE/RESOURCES:

1. Centers for Medicare & Medicaid Services. Medicare Part B/D Coverage Issues. Available at https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/BvsDCoverageIssues.pdf (accessed March 5, 2022)
2. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Enteral and Parenteral Nutritional Therapy (180.2). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=242&ncdver=1&bc=AAAAQAAAAAAA (accessed March 5, 2022)

3. Stephen A. McClave, Robert G. et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) *JPEN J Parenter Enteral Nutr*2016 40:159-211
4. Noridian Healthcare Solutions, LLC. Retirement of Parenteral Nutrition Local Coverage Determination (LCD) and Related Policy Article. https://med.noridianmedicare.com/web/jddme/policies/dmd-articles/2020/retirement-of-parenteral-nutrition-lcd-and-related-pa (accessed October 18, 2020)
5. Noridian Healthcare Solutions, LLC. Parenteral Nutrition Local Coverage Determination (LCD) and Related Policy Article. https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38953 (accessed March 5, 2022)
6. ASPEN Board of Directors. Guidelines for the use of parenteral and enteral nutrition in adults and pediatric patients. J Parenter Enteral Nutr. 2005; 26(1 suppl): 54SA-55SA
7. Brooks MJ, Melnik G. The Refeeding Syndrome: An approach to Understanding Its Complications and Preventing Its Occurrence. 1995; 15(6): 713-26
8. Brophy DF, Gehr TWB. Disorders of potassium and magnesium homeostasis. In: DiPiro JT, Talbert RL, Yee GC, Matzle GR, Wells BG, Posey LM (eds). Pharmacotherapy A pathophysiologic approach. McGraw-Hill Companies Inc; 2002:981-993
10. Btaiche IF, Khalidi N. Metabolic Complications of parenteral nutrition in adults, part 1. Am J Health-Syst Pharm. 2004; 61: 1938-49
11. Btaiche IF, Khalidi N. Metabolic complications of parenteral nutrition in adults, part 2. Am J Health-Syst Pharm. 2004; 61: 2050-2057
12. Chessman KH, Teasley-Strausburg KM. Assessment of nutrition status and nutrition requirements. In: DiPiro JT, Talbert RL, Yee GC, Matzle GR, Wells BG, Posey LM (eds). Pharmacotherapy A pathophysiologic approach. McGraw-Hill Companies Inc; 2002: 2445-2463
13. Gervasio JM. Fluids, electrolytes, and nutrition. A. Dickerson RN. New Practices in Nutrition Support In: ACCP Updates in therapeutics: updates in nutrition support. American College of Clinical Pharmacy; 2002: 136-154
14. Holcombe BJ, Seider DL. (eds) The science and practice of nutrition support. Dubuque, Iowa: ASPEN; 2001:663-673
15. Mattox TW. Parenteral nutrition. In: DiPiro JT, Talbert RL, Yee GC, Matzle GR, Wells BG, Posey LM (eds). Pharmacotherapy A pathophysiologic approach. McGraw-Hill Companies Inc; 2002:2475-2494
16. Shopbell JM, Hopkins B, Shronts EP. Nutrition Screening and Assessment. In: Gottschlich MM, Fuhrman MP, Hammond KA, Holcombe BJ, Seider DL.

(eds) The science and practice of nutrition support. Dubuque, Iowa: ASPEN; 2001:107-140.

17. Whitmire SF. Fluid and Electrolytes. In: Gottschlich MM, Fuhrman MP, Hammond KA, Holcombe BJ, Seider DL. (eds) The science and practice of nutrition support. Dubuque, Iowa: ASPEN; 2001:53-81

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH025.1023	**MISCELLANEOUS PRODUCTS** **TRANSTHYRETIN (TTR) LOWERING AGENTS** See Appendix A for medications covered by policy
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 12/18, 08/19, 08/20, 08/21. 08/22, 10/22, 09/23 (JN) P&T Committee Meeting Date: 02/19, 10/19, 10/20, 10/21, 12/22, 10/23 Original Effective Date: 04/19 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 11

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicare Part B: Amvuttra® and Onpattro® Only
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For initial authorization, all of the following criteria must be met:

1. Diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy

AND

2. Documentation of a pathogenic TTR mutation

AND

3. Patient has a baseline polyneuropathy disability (PND) score of less than or equal to IIIB **OR** has a baseline familial amyloid polyneuropathy (FAP) stage of I or II

AND

4. Baseline neuropathy impairment score (NIS) between 5 and 130

AND

5. Demonstrate symptoms consistent with polyneuropathy of hATTR amyloidosis including **at least two** of the following: Peripheral sensorimotor

polyneuropathy (such as tingling or increased pain in the hands, feet, hands and/or arms, loss of feeling in the hands and/or feet, numbness or tingling in the wrists, carpal tunnel syndrome, loss of ability to sense temperature, difficulty with fine motor skills, weakness in the legs, difficulty walking), autonomic neuropathy symptoms (such as orthostasis, abnormal sweating, sexual dysfunction, recurrent urinary tract infection, dysautonomia [constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety])

6. Dose and frequency are in accordance with FDA-approved labeling

Reauthorization:

1. Documentation that patient is tolerating applicable therapy (vutrisiran (Amvuttra®), inotersen (Tegsedi®) or patisiran (Onpattro®))

AND

2. Documented improvement or stabilization in polyneuropathy symptoms from baseline, defined as improvement or stabilization from baseline in the Neuropathy impairment score (NIS) **AND** at least one of the following measures:
    a. Baseline polyneuropathy disability (PND) score
    b. Familial amyloid polyneuropathy (FAP) stage

EXCLUSION CRITERIA:

- New York Heart Association (NYHA) Heart Functional class III or IV
- History of liver transplantation
- Peripheral neuropathy attributed to causes other than hATTR
- Used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [such as Amvuttra® (vutrisiran), inotersen (Tegsedi®), patisiran (Onpattro®), or tafamidis (Vyndaqel®, Vyndamax®)]

AGE RESTRICTIONS:

Approved for patients 18 years of age and older

PRESCRIBER RESTRICTIONS:

Prescribed by or in consultation with a neurologist, cardiologist, or a physician who specializes in the treatment of amyloidosis

COVERAGE DURATION:

Initial authorization will be approved for six months. Reauthorization will be approved for 12 months.

QUANTITY LIMIT:

Amvuttra® (vutrisiran): four syringes per year
Tegsedi® (inotersen): four syringes per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Hereditary ATTR (hATTR) amyloidosis with polyneuropathy is a progressive, life-threatening disease that is caused by misfolded transthyretin (TTR) protein. There have been over 120 TTR mutations that have been reported. The V30M mutation is strongly associated with polyneuropathy, and is the most prevalent cause of FAP worldwide[23]. The misfolded protein accumulates as amyloid fibrils in various organs including the nerves, heart, and gastrointestinal tract. Patients experience a range of life-impacting symptoms including burning neuropathic pain, loss of sensation in hands and feet, diarrhea/constipation, sexual impotence, and dizziness/fainting.

Patisiran (Onpattro®), Inotersen (Tegsedi®), and vutrisiran (Amvuttra®) are novel, orphan designated gene therapies approved by the FDA for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Patisiran is a double-stranded small interfering RNA (siRNA) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Patisiran is administered intravenously once every three weeks.

Inotersen is an antisense oligonucleotide that causes degradation of mutant and wild-type TTR messenger RNA (mRNA) through binding to the transthyretin (TTR) mRNA. Inotersen is administered subcutaneously once weekly.

Vutrisiran is a double-stranded small interfering RNA (siRNA) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Vutrisiran is administered subcutaneously once every three months.

FDA APPROVED INDICATION:

- Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

POSITION STATEMENT:

Patisiran and inotersen are the first FDA approved treatments for hATTR associated polyneuropathy. Vutrisiran was subsequently approved by the FDA for hATTR associated polyneuropathy.

There have been no direct comparisons among both transthyretin lowering agents (patisiran, inotersen) for the treatment of polyneuropathy of hATTR. Therefore, without direct comparison it is unknown if one agent is more effective than the other.

Disease Severity Measurement Tools for both patisiran, inotersen, and vutrisiran:

- **Familial Amyloid Polyneuropathy (FAP)** – FAP stage I- unimpaired ambulation, FAP stage II- requirement for assistance with ambulation, FAP stage III- wheelchair confinement
- **Neuropathy impairment score (NIS)** – This score is out of a total of 244 points, with higher scores indicating worse impairment. It is a clinical exam-based neuropathy evaluation that assesses motor strength/weakness (NIS-W) and reflexes (NIS-R)]. [weakness (NIS-W) and reflexes (NIS-R)]. The range of 5-130 was selected for study inclusion criteria to include patients with disease sufficiently advanced to show progression in the placebo group, but not so advanced as to preclude detection of a change in disease status.
- **Modified Neuropathy Impairment Score+7 (mNIS+7)** – Comprised of the NIS and the +7. The NIS is a clinical exam-based neuropathy evaluation [assessing both weakness (NIS-W) and reflexes (NIS-R)]; the +7 is an objective evaluation of small and large nerve fiber function [including NCS and quantitative sensory testing (QST)], as well as measurements of autonomic function (postural blood pressure). Higher scores indicate more severe neuropathy. The author's basis for using this modified score is because NIS does not adequately address sensory loss over the body and does not include nerve conduction scores.

  - Of note, the mNIS+7 scale used in the trial for patisiran is slightly different than the mNIS+7 scale used in the inotersen clinical trial.
  - At this time, a clinically meaningful decrease in the mNIS+7 score has not been established.
- **Polyneuropathy disability (PND) score** – This is how the disease is staged. Stage 0- no impairment, stage I- sensory disturbances, but preserved walking capability, stage II- impaired walking capability, but ability to walk without a stick or crutches, stage IIIA- walking only with the help one stick or crutch, stage IIIB- walking with the help of two sticks or crutches, and stage IV- confined to a wheelchair or bedridden. All patients in the clinical trial had a PND score ≤IIIb.
- **Norfolk-Quality of Life-Diabetic Neuropathy (Norfolk-QoL-DN)** – A 47-item questionnaire that assesses neuropathy symptoms and physical functioning, activities of daily living (ADL), symptoms of small and large fiber neuropathy, and autonomic neuropathy. Scores can range from -4 to 136, with higher scores indicating more impairment. This also evaluates small and large nerve fibers function in addition to automatic impairment and activities of daily living.

Clinical Summary for patisiran (Onpattro®):
The efficacy and safety of patisiran for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis was evaluated in a randomized, double-blind, global, phase III trial (APPOLO) consisting of 225 patients.

- Key inclusion criteria included: adults 18-85 years old, a documented pathogenic variant in TTR gene diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, NIS of 5 to 130, and a polyneuropathy disability (PND) score ≤IIIb.
- Key exclusion criteria included: New York Heart Association (NYHA) class III or IV, acute coronary syndrome within past 3 months, taking in combination with another transthyretin lowering agents (tafamidis, patisiran, or inotersen), uncontrolled cardiac arrhythmia or unstable angina, prior liver transplant, known type I or type II diabetes for ≥ 5 years, previous organ transplants requiring immunosuppression, and malignancy within the past 5 years.

Patients were randomized to receive either patisiran (0.3 mg/kg) or placebo intravenously once every three weeks with randomization stratified by NIS score, presence of the V30M mutation, and previous use of a transthyretin stabilizer.
The primary end point was the change from baseline to 18 months in the modified neuropathy impairment +7 score (mNIS+7). Selected secondary endpoints included a quality of life assessment (Norfolk QOL-DN questionnaire), motor strength (NIS-weakness), and serum TTR protein levels.

- At 18 months, the change from baseline in the mNIS+7 was significantly lower with patisiran than with placebo. The least-squares mean difference of -34.0 points was significant (95% confidence interval, -39.9 to -28.1; P<0.001) and no significant difference was observed in mNIS+7 scores at nine months.
- The change from baseline in the Norfolk QOL-DN questionnaire score was significantly lower in the patisiran group compared to placebo at 18 months. The least-squares mean difference was -21.1 points (95% confidence interval, -27.2 to -15.0; P<0.001) at 18 months.

Common side effects include infusion-related reactions and reduced vitamin A levels. Thus, patisiran is administered with pre-medications (dexamethasone, acetaminophen, H2 blocker and diphenhydramine) by a healthcare profession and it's recommended to monitor vitamin A levels. There are also safety concerns about the cardiovascular effects, specifically heart failure exacerbations and resulting death, with patisiran. Of note, patients with New York Heart Association Function Classification (NYHA) class III and IV heart failure were excluded from the trial. Although there isn't an FDA warning on the label, the FDA review noted in their review that these "findings are not reassuring with respect to patients with heart failure".

Clinical Summary for inotersen (Tegsedi®):

The efficacy and safety of inotersen for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis was evaluated in a randomized, double-blind, global, phase III trial (NEURO-TTR) consisting of 172 patients.

- Key inclusion criteria included: adults 18-82 years old, a documented pathogenic variant in TTR gene diagnosis of hereditary transthyretin amyloidosis with peripheral neuropathy, neuropathy Impairment Score (NIS) of 10 to 130, and familial amyloid polyneuropathy (FAP) stage I or II.
- Key exclusion criteria included: New York Heart Association (NYHA) class III or IV, acute coronary syndrome within past three months, taking in combination with another transthyretin lowering agents (tafamidis, patisiran, or inotersen), uncontrolled cardiac arrhythmia or unstable angina, prior liver transplant, known type I or type II diabetes for ≥ 5 years, previous organ transplants requiring immunosuppression, and malignancy within the past 5 years.

Patients were randomized to receive either inotersen 284 mg or placebo subcutaneously once weekly with randomization stratified by FAP stage, presence of the V30M mutation, and previous use of a transthyretin stabilizer.
The primary end points were the change from baseline to 15 months in the modified neuropathy impairment +7 score (mNIS+7) and a quality of life assessment (Norfolk QOL-DN questionnaire) at 15 months.

- At 35 weeks, the change from baseline in the mNIS+7 was significantly lower with inotersen than with placebo. The least-squares mean difference of -8.7 points was significant (95% confidence interval, -13.5 to -3.9; P<0.001)
    - The change from baseline in the mNIS+7 was significantly lower with inotersen than with placebo at 15 months. The least-squares mean difference of -19.7 points was significant (95% confidence interval, -26.4 to -13.0; P<0.001).
- At 35 weeks, the change from baseline in the Norfolk QOL-DN was significantly lower with inotersen than with placebo at 35 weeks. The least-squares mean difference of -6.1 points was significant (95% confidence interval, -11.8 to -0.5; P=0.03).
    - At 15 months, the change from baseline in the Norfolk QOL-DN was significantly lower with inotersen than with placebo at 15 months. The least-squares mean difference of -11.7 points was significant (95% confidence interval, -18.3 to -5.1; P<0.001)

Inotersen does carry black-box warning for thrombocytopenia and glomerulonephritis. Thus, a REMS program requires prescribers to be certified and complete training, and patients must enroll and comply with ongoing monitoring parameters (specifically, CBC weekly and renal function bi-weekly). However, there is evidence to support that these severe events may represent a drug-disease interaction based on integrated analysis of clinical data with antisense oligonucleotides from the same 2'-O-methoxy-ethyl modified chemical class.[21,22] Inotersen is the third antisense oligonucleotide that has been approved by the FDA.

Clinical Summary for vutrisiran (Amvuttra®):

The safety and efficacy of vutrisiran in adult patients with hATTR-PN is based on low quality evidence from a single open label, phase III trial comparing the vutrisiran arm (n= 122) with an external placebo group (n = 77) from the APOLLO study (patisiran trial).

- Key inclusion included: adults 18 to 85 years of age and diagnosis of hATTR with TTR mutation. Prior use of a TTR stabilizer was permitted (such as Vyndamax, Vyndaqel, diflunisal).
- Key exclusion included: Prior liver transplant or likely to undergo liver transplantation during the study, known other (non-hATTR) forms of amyloidosis or leptomeningeal amyloidosis, NYHA heart failure classification >2, clinically significant liver function test abnormalities, known HIV, HCV, HBV infection, received prior TTR-lowering treatment (e.g. Onpattro, Tegsedi), and has other known causes of neuropathy

The primary endpoint was change from baseline to Month 9 in modified Neuropathy Impairment Score +7 (mNIS+7). Secondary endpoints included

change from baseline to Month 9 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN Total Score), 10-meter walk test, and modified Body Mass Index (mBMI). Results are as follows:

Table 3: Clinical Efficacy Results (Comparison of AMVUTTRA Treatment in Study 1 to an External Placebo Control*)

Endpoint†	Baseline, Mean (SD)		Change from Baseline to Month 9, LS Mean (SEM)		AMVUTTRA-Placebo* Treatment Difference, LS Mean (95% CI)	*p*-value
	AMVUTTRA N=122 (Study 1)	Placebo* N=77 (NCT01960348)	AMVUTTRA (Study 1)	Placebo* (NCT01960348)		
mNIS+7‡	60.6 (36.0)	74.6 (37.0)	-2.2 (1.4)	14.8 (2.0)	-17.0 (-21.8, -12.2)	*p*<0.001
Norfolk QoL-DN‡	47.1 (26.3)	55.5 (24.3)	-3.3 (1.7)	12.9 (2.2)	-16.2 (-21.7, -10.8)	*p*<0.001
10-meter walk test (m/sec)§	1.01 (0.39)	0.79 (0.32)	0 (0.02)	-0.13 (0.03)	0.13 (0.07, 0.19)	*p*<0.001
mBMI¶	1058 (234)	990 (214)	7.6 (7.9)	-60.2 (10.1)	67.8 (43.0, 92.6)	*p*<0.001

CI = confidence interval; LS mean = least squares mean; mBMI = modified body mass index; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life-Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean

*External placebo group from another randomized controlled trial (NCT01960348)
†All endpoints analyzed using the analysis of covariance (ANCOVA) with multiple imputation (MI) method)
‡A lower number indicates less impairment/fewer symptoms
§A higher number indicates less disability/less impairment
¶mBMI: nominal p-value; body mass index (BMI; kg/m^2) multiplied by serum albumin (g/L).

The study authors concluded that compared to external placebo, vutrisiran improved the signs and symptoms of polyneuropathy, with over 50% of patients experiencing halting or reversal of their disease.

Vutrisiran (N=122) was also compared to an in-study group using 0.3 mg/kg patisiran (N=42) for an additional secondary point, non-inferiority in serum TTR level percent reduction through Month 18. It was determined that vutrisiran was noninferior to patisiran.

For safety, the most common adverse reactions with vutrisiran (≥5%) were arthralgia, dyspnea, and decreased vitamin A. No contraindications or black box warnings were identified for this drug upon FDA approval.

REFERENCE/RESOURCES:

1. [ONPATTRO] package insert. San Diego, CA. Alnylam Pharmaceuticals, Inc; Jan. 2023.

2. [ONPATTRO] In: DRUGDEX® System [Internet database]. Greenwood Village, CO: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed 2023 Sept. 13.
3. [ONPATTRO] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed 2023 Sept. 13.
4. Adams D., Suhr O.B., Dyck P.J., Litchy W.J., Leahy R.G., Chen J., Gollob J., Coelho T. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17:181.
5. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11–21.
6. Suanprasert N, Berk JL, Benson MD, et al. Retrospective study of a TTR FAP cohort to modify NIS+7 for therapeutic trials. J Neurol Sci 2014;344:121-8.
7. Center for drug evaluation and drug research: FDA other reviews. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000OtherR.pdf. Accessed November 08, 2018.
8. Center for drug evaluation and drug research: FDA multi-Discipline Review/Summary, Clinical, Non-Clinical. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000MultiR.pdf. Accessed November 08, 2018.
9. Center for drug evaluation and drug research: FDA risk assessment and risk mitigation review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210922Orig1s000RiskR.pdf. Accessed November 08, 2018.
10. Kessler Topaz Meltzer & Check, LLP - Important Deadline Reminder For Alnylam Pharmaceuticals, Inc. Investors. https://www.law.com/legalnewswire/news.php?id=1022293. Accessed November 17, 2018.
11. Alnylam Class Action Lawsuit: Bernstein Liebhard LLP Announces That a Securities Class Action Lawsuit Has Been Filed Against Alnylam Pharmaceuticals, Inc. – ALNY. https://www.marketwatch.com/press-release/alnylam-class-action-lawsuit-bernstein-liebhard-llp-announces-that-a-securities-class-action-lawsuit-has-been-filed-against-alnylam-pharmaceuticals-inc---alny-2018-09-28. Accessed November 17, 2018.
12. Swiecicki P. L., Zhen D. B., Mauermann M. L., et al. (2015). Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. Amyloid. 22(2):123-131.

13. Coelho T. Trial design and rationale for APOLLO, a Phase 3, placebo-controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol. 2017;17:181.
14. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med. 2018;379:11–21.
15. Hematology/Oncology Pharmacy Association. Dose rounding of biologic and cytotoxic anticancer agents: a position statement of the hematology/oncology pharmacy association. https://www.nccn.org/professionals/OrderTemplates/PDF/HOPA.pdf Accessed November 28, 2018.
16. [TEGSEDI] package insert. Carlsbad, CA. Ionis Pharmaceuticals, Inc; Aug 2021.
17. [TEGSEDI] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed 2018 Oct. 30.
18. [TEGSEDI] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed 2018 Oct. 30.
19. Waddington-Cruz M, Ackermann EJ, Polydefkis M, et al. Hereditary transthyretin amyloidosis: baseline characterisitcs of patients in the NEURO-TTR trial. Amyloid. 2018 Aug 31: 1-9.
20. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379:22–31. DOI: 10.1056/NEJMoa1716793.
21. Crooke ST, Baker BF, Kwoh TJ, et al. Integrated safety assessment of 2′-O-methoxyethyl chimeric antisense oligonucleotides in nonhuman primates and healthy human volunteers. Mol Ther 2016;24:1771-1782.
22. Crooke ST, Baker BF, Witztum JL, et al. The effects of 2′-O-methoxyethyl containing antisense oligonucleotides on platelets in human clinical trials. Nucleic Acid Ther 2017;27:121-129.
23. Crooke ST, Baker BF, Pham NC, et al. The effects of 2′-O-methoxyethyl oligonucleotides on renal function in humans. Nucleic Acid Ther 2018;28:10-22.
24. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol. 2011 Dec;10(12):1086-97. doi: 10.1016/S1474-4422(11)70246-0. PMID: 22094129.

Appendix A

Medication Brand Name	Generic Name	Jcode
Amvuttra®	vutrisiran subcutaneous injection	J0225, J3490, C9399
Onpattro®	patisiran intravenous injection	J0222, C9036
Tegsedi®	inotersen subcutaneious injection	J3490, C9399

Appendix B

Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults	
Body Weight (kilograms)	# of Vials (10mg/5mL)
<33.4	1
33.4-66.6	2
66.7-100	3
>100kg (maximum dose)	3

* Dosing for intravenously infused patisiran (Onpattro®), which may be subject to audit

** Dose rounding to the nearest vial will be required within 10% of calculated dose based on a dosing of 0.3mg/kg per dose

“Dose rounding to the nearest vial will be required within 10% of calculated dose based on a dosing of 0.3mg/kg per dose” was based on the recommendation from the Hematology/Oncology Pharmacy Association that states: “On the basis of the published data, HOPA recommends that monoclonal antibodies and other biologic agents currently available be dose rounded to the nearest vial size within 10% of the prescribed dose.”

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCCNS063.0823	**CENTRAL NERVOUS SYSTEM DRUGS** **TYSABRI®** (natalizumab intravenous solution)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/07, 04/08, 08/09, 04/10, 04/11, 10/11, 02/12, 08/12, 08/13, 08/14, 08/15, 07/16, 09/16, 07/17, 01/18, 07/19, 11/19, 07/20, 04/21, 07/21, 07/22, 07/23 (JN) P&T Committee Meeting Date: 10/06, 04/07, 04/08, 04/09, 04/10, 04/11, 10/11, 02/12, 08/12, 08/13, 08/14, 08/15, 08/16, 10/16, 08/17, 02/18, 08/18, 08/19, 12/19, 08/20, 04/21, 08/21, 08/22, 08/23 Original Effective Date: 01/07 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For **initiation of therapy** (new starts), must meet indication-specific criteria below**:**
    a. **For multiple sclerosis, all the following criteria (i-iii) must be met:**
        i. Must have one of the following confirmed diagnoses:
            1. Relapsing-remitting disease (RRMS)
            2. Secondary progressive multiple sclerosis (SPMS)
            3. Clinically isolated syndrome (CIS)
        ii. Documentation of one of the following:
            1. Documentation the patient has highly active disease defined as ONE of the following:
                a. Greater than or equal to two relapses in the previous year
                b. The patient has greater than or equal to one gadolinium enhancing lesion on MRI
                c. Presence of significant T2 lesion burden defined as ONE of the following:

i. Greater than ten (10) T2 burden as documented with MRI
ii. Significant increase in T2 lesion load compared with a previous MRI
iii. T2 lesion(s) located in spinal cord or brainstem

2. The patient has been treated with at least three multiple sclerosis agents from different drug classes
3. Inadequate response (after at least six months of continuous therapy) or intolerance to one (1) of the following: generic dimethyl fumarate, generic glatiramer acetate/Glatopa®, generic fingolimod, or generic teriflunomide
4. FDA labeled contraindication to ALL of the following: generic dimethyl fumarate, generic glatiramer/Glatopa®, generic fingolimod, and generic teriflunomide

iii. Negative anti-JCV antibody status OR If patient is anti-JCV antibody positive, the patient must meet the following criteria:
1. Confirmation patient has not used any of the following immunosuppressants agents: mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil, AND
2. Medical rationale is provided for continued use despite increased risk of developing progressive multifocal leukoencephalopathy (PML)

b. **For Crohn's disease:**
i. Diagnosis of moderate to severe Crohn's disease, **AND**
ii. Documentation of trial and failure (after at least three months of therapy), intolerance, or contraindication to a preferred TNF inhibitor [infliximab (Inflectra® or Renflexis®) and/or adalimumab (Humira®, Hadlima®)] indicated for Crohn's, **AND**
iii. Negative anti-JCV antibody status. If patient is anti-JCV antibody positive, the patient must meet the following criteria:
1. Confirmation patient has not used any of the following immunosuppressants agents: mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil, AND
2. Medical rationale is provided for continued use despite increased risk of developing progressive multifocal leukoencephalopathy (PML)

2. For patients **established on therapy** (within the previous year): Documentation of response to therapy must be provided

EXCLUSION CRITERIA:
1. Use of natalizumab in combination with other disease modifying therapy (DMT) to treat patients with multiple sclerosis (such as dimethyl fumarate, glatiramer).
2. Use of natalizumab in combination with immunosuppressants or TNF inhibitors (such as adalimumab).

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by either a neurologist (for multiple sclerosis) or gastroenterologist (for Crohn's disease)

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Natalizumab is a monoclonal antibody that binds to integrins on the surface of leukocytes (except neutropjils). It inhibits adhesion of leukocytes to receptors, thus preventing migration of leukocytes across the endothelium into parenchyma tissue.

FDA APPROVED INDICATIONS:
- Monotherapy for the treatment of patients with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
- Inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's 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 TNF-α
    - Natalizumab should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α

POSITION STATEMENT:

Boxed Warning: Progressive Multifocal Leukoencephalopathy (PML)

- Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability
- Risk factors for the development of PML include the presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment
- Monitor patients, and withhold treatment immediately at the first sign or symptom suggestive of PML
- Tysabri is available only through a special restricted distribution program called the TOUCH® Prescribing Program and must be administered only to patients enrolled in this program

In 2010, the FDA notified healthcare professionals and patients that the risk of developing progressive multifocal leukoencephalopathy (PML) increases with the number of Tysabri infusions received. Information about the occurrence of Immune Reconstitution Inflammatory Syndrome (IRIS) in patients who have developed PML and subsequently discontinued Tysabri® has also been added to the drug label. IRIS is a rare condition characterized by a severe inflammatory response that can occur during or following immune system recovery, causing an unexpected decline in a patient's condition after return of immune function.

Guidelines for Multiple Sclerosis include the American Academy of Neurology Publication "Comprehensive Systematic Review Summary: Disease-Modifying Therapies for Adults with Multiple Sclerosis" published in 2018 and a consensus paper by the Multiple Sclerosis Coalition titled "The Use of Disease-Modifying Therapies in Multiple Sclerosis" published in 2019. Guidelines state that initiating a disease modifying therapy (DMT) should be offered to patients as early as possible. The choice of initial DMT should be individualized to consider safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability. When switching therapies after failure of an agent, disease activity, adherence, AE profiles, and mechanisms of action should be considered when selecting a new agent to start. For advanced, aggressive, or highly active disease guidelines recommend

fingolimod (Gilenya®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), or alemtuzumab (Lemtrada®). Additionally, guidelines state categorize DMT therapies for evidence for lowering relapse rate (see Table 1).[5]

Tablet 1. DMT Evidence for Lowering Relapse Rate[5]

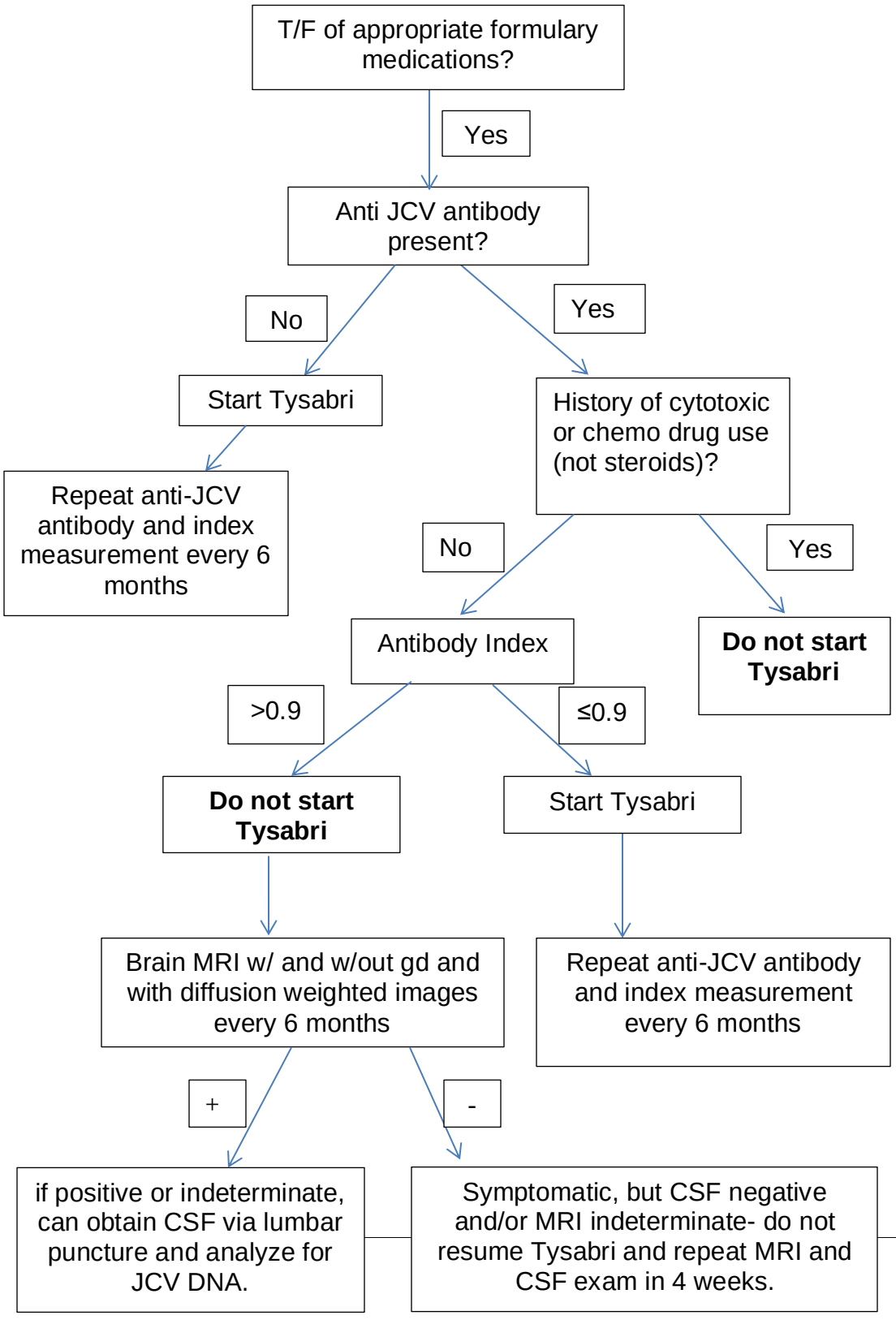
Very Low	Low	Moderate	Strong
Immunoglobulins	Cyclophosphamide	Azathioprine	Alemtuzumab
Methotrexate	Mycophenolate Mofetil	Interferon beta-1b	Cladribine
Rituximab			Dimethyl Fumarate†
Corticosteroids			Fingolimod†
			Glatiramer Acetate†
			Interferon beta-1a
			Mitoxantrone
			Natalizumab
			Ocrelizumab
			Pegylated Interferon
			Teriflunomide†

† Generic Available

REFERENCE/RESOURCES:

1. Tysabri® package insert. Cambridge, MA: Biogen Idec Inc.; 2023 April.
2. Gorelik L, Lerner, M, Bixler S, et al. Anti-JC Virus Antibodies: Implications for PML Risk Stratification. *Ann Neurol* 2010;68:295-303.
3. Yousry TA, Habil DM, Major EO, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. *N Engl J Med 2006*;354:924-33.
4. Yousry TA, Habil DM, Major EO, et al. Evaluation of Patients Treated with Natalizumab for Progressive Multifocal Leukoencephalopathy. N Engl J Med 2006;354:924-33.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology 2018;90:777–788.

APPENDIX


T/F of appropriate formulary medications?
Yes
Anti JCV antibody present?
No
Yes
Start Tysabri
History of cytotoxic or chemo drug use (not steroids)?
Repeat anti-JCV antibody and index measurement every 6 months
No
Yes
Antibody Index
Do not start Tysabri
>0.9
≤0.9
Do not start Tysabri
Start Tysabri
Brain MRI w/ and w/out gd and with diffusion weighted images every 6 months
Repeat anti-JCV antibody and index measurement every 6 months
+
-
if positive or indeterminate, can obtain CSF via lumbar puncture and analyze for JCV DNA.
Symptomatic, but CSF negative and/or MRI indeterminate- do not resume Tysabri and repeat MRI and CSF exam in 4 weeks.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCEND079.0223	**ENDOCRINE AND METABOLIC DRUGS** **TZIELD®** (teplizumab-mzwv vial)
Effective Date: 4/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: P&T Committee Meeting Date: 02/23 Original Effective Date: 04/23 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
Initial authorization requires all the following be met:

1. Diagnosis of stage 2 type 1 diabetes (meaning that the patient is at risk of developing symptomatic type 1 diabetes) as evidenced by both the following (a and b):
    a. Documentation of the presence of two or more of the following autoantibodies:
        - Glutamic acid decarboxylase 65 (GAD) autoantibody
        - Insulin autoantibody (IAA)
        - Insulinoma-associated antigen 2 autoantibody (IA-2A)
        - Zinc transporter 8 autoantibody (ZnT8A)
        - Islet cell autoantibody (ICA)
    b. Evidence of dysglycemia without overt hyperglycemia confirmed by an oral glucose tolerance test (meaning a 2-hour post prandial blood glucose of 140-199 mg/dL)

Note: If an oral glucose tolerance test is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia may be considered such as fasting plasma glucose 100–125 mg/dL

2. Dosing is within FDA-labeled guidelines

EXCLUSION CRITERIA:
Stage 3 (symptomatic) type 1 diabetes

AGE RESTRICTIONS:
May be approved for patients aged eight years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, an endocrinologist

COVERAGE DURATION:
Authorization will be approved for one 14-day treatment course per lifetime

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Teplizumab (Tzield®), is a CD3-directed monoclonal antibody to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients aged eight years and older with stage 2 type 1 diabetes (T1D). Teplizumab is given as a single treatment course of a once daily intravenous infusion given for 14 consecutive days. Administration does not require hospital administration and can be given in an outpatient setting.

FDA APPROVED INDICATIONS:

To delay the onset of stage 3 T1D in adults and pediatric patients aged eight years and older with stage 2 T1D.

POSITION STATEMENT:
Type 1 diabetes is due to cell-mediated autoimmune β-cell destruction and requires insulin replacement for survival. Both genetic and environmental factors appear to contribute to the risk of development. It most commonly occurs in children and young adults but can occur at any age. T1D accounts for 5-10% of all cases of diabetes[8]. A family history of T1D is present in about 10-15% of newly diagnosed T1D patients. The risk in general population is about 0.4-1% whereas it is about 5% in individuals with a first-degree relative. Other factors including genetic susceptibility and multiple first-degree relatives with T1D can further increase risk.[6]

Three distinct stages of T1D have been identified. In stage 1 there is autoimmunity, identified by two or more islet autoantibodies, and normoglycemia. In stage 2 there is autoimmunity and dysglycemia such as impaired fasting glucose and/or impaired glucose tolerance. In stage 3 there is autoimmunity and overt hyperglycemia. Individuals in stage 3 are symptomatic requiring insulin replacement and have diabetes by standard diagnosis criteria.[6,8]

The following table from the American Diabetes Association *Standards of Care in Diabetes – 2023*[8] outlines the three distinct stages of type 1 diabetes.

Table 2.1—Staging of type 1 diabetes (12,16)

	Stage 1	Stage 2	Stage 3
Characteristics	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• Autoimmunity • Overt hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple islet autoantibodies • No IGT or IFG	• Islet autoantibodies (usually multiple) • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Autoantibodies may become absent • Diabetes by standard criteria

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; 2-h PG, 2-h plasma glucose.

Prospective cohort studies give insight into the risk of developing symptomatic T1D (stage 3 T1D). These studies have included those with increased genetic risk identified through HLA screening in newborns, relatives of those with T1D and individuals in the general population, i.e., no confirmed family history. One study looking at risk of progression to symptomatic T1D in children with two or more islet autoantibodies (stage 1 T1D) found 44% developed symptomatic T1D within five years, 70% within ten years and 85% within fifteen years.[5,8] For individuals with two

or more islet autoantibodies and dysglycemia (stage 2 T1D) there is approximately 60% risk of developing symptomatic T1D within two years and a 75% risk in five years of developing symptomatic T1D. Lifetime risk of developing stage 3 T1D approaches 100% for those with stage 2 T1D.[6] Screening for autoantibodies can identify those at risk of progression to clinical diabetes (stage 3). The Standards of Care in Diabetes from the American Diabetes Association currently recommends screening to detect autoantibodies in the setting of a research study or as an option for individuals with a first-degree family member with T1D[8].

Efficacy data for teplizumab comes from one phase 2 trial (TN-10)[7]. In the TN-10 trial teplizumab delayed the onset of stage 3 type 1 diabetes (T1D) in high-risk patients by a median of two years compared to placebo. The primary endpoint was time from randomization to the clinical diagnosis of diabetes as assessed by oral glucose tolerance test. High risk patients were identified as those with stage 2 T1D (autoimmunity and dysglycemia). Autoimmunity was defined as two or more the following islet autoantibodies: glutamic acid decarboxylase 65 (GAD) autoantibody, insulin autoantibody (IAA), insulinoma-associated antigen 2 autoantibody (IA-2A), zinc transporter 8 autoantibody (ZnT8A) and/or islet cell autoantibody (ICA). Dysglycemia was defined as a fasting plasma glucose of 110 to 125 mg/dL or a 2-hour postprandial plasma glucose of 140–199 mg/dL or an intervening postprandial glucose level at 30, 60, or 90 minutes that was greater than 200 mg/dL. Participants less than 18 years needed to have one abnormal glucose test whereas those 18 years or older needed two abnormal glucose tests, both within 52 days before enrollment.

Most common adverse events were lymphopenia, rash, leukopenia and headache. Lymphopenia was transient and resolved by day 45 in all participants except for one individual.

Potential future uses for teplizumab may include an age range expansion down to two years of age, re-dosing prior to diagnosis of clinical T1D and/or treatment courses after diagnosis of type 1 diabetes. Currently additional treatment courses beyond one 14-day course has not been studied. Teplizumab is currently under investigation in the PROTECT trial (NCT03875729) to determine whether it slows β cell loss and preserves β cell function in those recently diagnosed with T1D in the previous six weeks. At this time there is insufficient evidence to establish safety and efficacy for use in recent onset clinical type 1 diabetes (stage 3).

REFERENCE/RESOURCES:

1. Tzield package insert. Provention Bio, Inc. Red Bank, NJ: November 2022
2. Teplizumab In: DRUGDEX® System [Internet database]. Greenwood Village,

Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed December 31, 2022
3. Teplizumab In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed January 2, 2023
4. Tzield monograph. Prime Therapeutics. Created on November 18, 2022.
5. Ziegler AG, Rewers M, Simell O, *et al*. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. *JAMA*. 2013 Jun 19;309(23):2473-9.
6. Insel RA, Dunne JL, Atkinson MA, *et al*. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care*. 2015 Oct;38(10):1964-74.
7. Herold KC, Bundy BN, Long SA, *et al*. An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. N Engl J Med. 2019 Aug 15;381(7):603-613.
8. ElSayed NA, Aleppo G, Aroda VR, *et al*. Diabetes Technology: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023 Jan 1;46(Supplement_1):S111-S127.
9. Mital S, Nguyen HV. Cost Effectiveness of Teplizumab for Prevention of Type 1 Diabetes Among Different Target Patient Groups. *Pharmacoeconomics*. 2020 Dec;38(12):1359-1372.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCHEM035.1223	**HEMATOLOGICAL AGENTS** **ULTOMIRIS(TM)** (ravulizumab-CWVZ vial for injection)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/22, 11/23 (JN)
Original Effective Date: 10/22	**P&T Committee Meeting Date**: 08/22, 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For Paroxysmal Nocturnal Hemoglobinuria (PNH):

1. For initiation of therapy (new starts) all the following criteria (a-c) must be met:
    a. Confirmed diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by Flow Cytometric Immunophenotyping (FCMI) using at least two independent flow cytometry reagents on at least two cell lineages (for example, RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycophosphatidylinositol (GPI)-linked proteins (which may include CD59, CD55, CD14, CD15, CD16, CD24, CD45, and CD64), and
    b. Symptomatic hemolytic PNH defined as lactate dehydrogenase (LD) levels greater than or equal to 1.5 times the upper limit of normal and at least one of the following:
        i. Documented history of thrombosis,
        ii. Transfusion dependence (for example, hemoglobin less than 7 g/dL or symptomatic anemia with hemoglobin less than 9 g/dL)
        iii. Disabling fatigue
        iv. End-organ complications

v. Frequent pain paroxysms (for example, dysphagia or abdominal pain)

c. Dose and frequency is in accordance with FDA-approved labeling

2. For patients **currently on eculizumab (Soliris®) or pegcetacoplan (Empaveli®)** switching to ravulizumab (Ultomiris®) for PNH:
    a. Confirmed documentation of paroxysmal nocturnal hemoglobinuria (criteria 1a above) and severe disease (criteria 1b above). However, this can be based on patient's history prior to starting eculizumab or pegcetacoplan.
    b. Dose and frequency are in accordance with FDA-approved labeling
3. For patients **established on the requested agent** for PNH, both of the following criteria must be met for continuation of therapy:
    a. Documentation of reduced LDH levels, reduced transfusion requirements, increase or stabilization of hemoglobin levels or improvement in PNH related symptoms
    b. Dose and frequency are in accordance with FDA-approved labeling

For Complement-Mediated Hemolytic Uremic Syndrome (HUS)

1. For initiation of therapy (new starts) all the following criteria (a-c) must be met:
    a. Diagnosis of non-infectious HUS, meaning HUS is not due to infection with Shiga toxin-producing Escherichia coli, and
    b. Clinical presentation that includes: microangiopathic hemolytic anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelets less than 150), and acute kidney injury (elevations in serum creatinine)
    c. Dose and frequency are in accordance with FDA-approved labeling
2. For patients currently on eculizumab (Soliris®) switching to ravulizumab (Ultomiris®) for HUS, both of the following criteria must be met
    a. Confirmed documentation of Complement-Mediated Hemolytic Uremic Syndrome (criteria 1a and 1b above). However, this can be based on patient's history prior to starting eculizumab, and
    b. Dose and frequency are in accordance with FDA-approved labeling
3. For patients established on the requested agent for HUS, both of the following criteria must be met:
    a. Documentation of improvement in at least two thrombotic microangiopathy endpoints, such as:
        i. Maintenance of platelet counts, defined as an improvement or reduction less than 25%
        ii. Reductions in LDH
        iii. Reduction in number of needed plasmapheresis or plasma infusion events
        iv. Improvement in kidney function and reduction of dialysis
    b. Dose and frequency are in accordance with FDA-approved labeling

For Generalized Myasthenia Gravis (gMG)

1. For initiation of therapy (new starts), all the following must be met:
    a. Anti-acetylcholine receptor (anti-AChR) antibody positive
    b. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
    c. Myasthenia Gravis -Activities of Daily Living (MG-ADL) total score greater than five
    d. Failed treatment for at least one year with ONE of the following:
        i. At least TWO immunosuppressive therapies ([ISTs] such as azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus, corticosteroids)
        ii. ONE immunosuppressive therapy and required at least four infusions/ year of either intravenous immunoglobulin (IVIg) OR plasma exchange (PE)
    e. Dose and frequency are in accordance with FDA-approved labeling
2. For patients currently on eculizumab (Soliris®) switching to ravulizumab (Ultomiris®) for gMG, both the following must be met:
    a. Confirmed documentation of gMG (criteria 1a-c above. However, this can be based on patient's history prior to starting eculizumab.
    b. Dose and frequency are in accordance with FDA-approved labeling
3. For patients established on the requested agent for gMG, both the following criteria must be met:
    a. Documentation of improvement in MG-ADL by at least two points from baseline.
    b. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA:
Concurrent therapy with Soliris® or Empaveli®

AGE RESTRICTIONS:
The patient's age must be within FDA labeling for the requested indication

PRESCRIBER RESTRICTIONS:

- PNH or HUS: Prescribed by a hematologist/oncologist or nephrologist
- MG or NMOSD: Prescribed by a neurologist

COVERAGE DURATION:
Initial authorization for up to three months and reauthorization will be approved for up to one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Ravulizumab (Ultomiris®) is a monoclonal antibody that inhibits terminal complement mediated intravascular hemolysis. It was engineered from previously FDA approved eculizumab (Soliris®) to have an extended half-life; its terminal half is approximately four times longer than that of eculizumab.

FDA APPROVED INDICATIONS:

Treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH)

Treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitations of Use:
Ravulizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

POSITION STATEMENT:

Paroxysmal Nocturnal Hemoglobinuria (PNH)

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired, life threatening disorder of the blood that develops as a result of somatic mutation of hematopoietic stem cell and is characterized by destruction of red blood cells by the complement system. Symptoms associated with PNH include hemolytic anemia, thrombosis, peripheral blood cytopenia and fatigue.
- The FDA approval for ravulizumab (Ultomiris®) for use in the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) was based on two phase 3 open-label non-inferiority clinical trials.

  - The 301 study looked at ravulizumab vs eculizumab in 246 adult patients with PNH naive to complement inhibitors.
    - The transfusion avoidance rate was 73.6% and 66.1% for ravulizumab vs eculizumab (difference of 6.8, 95% CI: -4.66, 18.14). LDH normalization occurred in 53.6% and 49.4% of ravulizumab and eculizumab patients, respectively (OR 1.19, 95% CI: 0.80, 1.77)
  - The 303 study looked at ravulizumab vs eculizumab in 195 C5-inhibitor-experienced adult patients with PNH
    - The transfusion avoidance rate was 87.6% and 82.7% for ravulizumab and eculizumab (difference of 5.5, 95% CI: -4.3, 15.7). LDH percent change from baseline was -0.82% and 8.4% for ravulizumab vs eculizumab (difference of 9.2, 95% CI: -0.42, 18.8).
- Based on these trials there is moderate quality of evidenced that ravulizumab is as effective and safe as eculizumab for the treatment of PNH in adult patients that are treatment naïve and those stable on eculizumab.
  - While ravulizumab has an advantage of a longer half-life, in clinical trials it has not been shown to be clinically superior to eculizumab.

Atypical Hemolytic Uremic Syndrome (aHUS)

- The FDA approval for ravulizumab for atypical hemolytic uremic syndrome (aHUS) was based on two open-label, single-arm studies.
- Study 1 included 56 adults who displayed signs of TMA. To qualify for enrollment, patients were required to have a platelet count ≤150 × 109/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis.
- Study 2 included 14 pediatric patients. To qualify for enrollment, patients were required to have a platelet count ≤150 × 109/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥97.5% percentile at screening or required dialysis.
- The efficacy evaluation for both studies was based on complete TMA response during the 26-week initial evaluation period, as evidenced by normalization of hematological parameters (platelet count and lactate dehydrogenase) and ≥ 25% improvement in serum creatinine from baseline.
  - In study 1, complete TMA response was observed in 30 of the 56 patients (54%). Complete TMA response was achieved at a median time of 86 days (range: 7 to 169 days).
  - In study 2, complete TMA response was observed in 10 of the 14 patients (71%). Complete TMA response was achieved at a median time of 30 days (range: 15 to 88 days).
- Ravulizumab has not been directly compared to eculizumab in aHUS.

Generalized Myasthenia Gravis (gMG)

- Generalized Myasthenia gravis (gMG) is an autoimmune disorder of neuromuscular transmission. It is characterized by muscle weakness including ocular motor disturbances, oropharyngeal, respiratory, and limb muscle weakness. Symptoms can fluctuate and can become progressively severe. This disorder occurs when proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors and/or receptor-associated proteins) are attacked by antibody-mediated T-cells. The diagnosis of myasthenia gravis can be established by clinical and serologic testing.
- The myasthenia gravis activities of daily living (MG-ADL) is a categorical scale that assesses the impact on daily function of eight signs or symptoms that are typically affected in gMG. Cumulative scores range from 0-24, with higher scores representing more severe disease. A 2-point decrease in the MG-ADL indicates clinical improvement. The MG-ADL correlates with the Quantitative Myasthenia Gravis (QMG) score, which is a 13-item direct physician assessment scoring system quantifying disease severity based on body function impairment. QMG cumulative scores range from 0-39, with higher scores representing more severe disease. A 2-3 point decrease in the QMG indicates clinical improvement.
- The ALXN1210-MG-306 study evaluated the safety and efficacy of ravulizumab compared to placebo in patients (n=89) with gMG positive for anti-AChR antibodies.
    - Treatment with ravulizumab demonstrated a statistically significant improvement in the MG-ADL (-1.6, confidence interval [CI] -2.6 to -0.7, $p < 0.001$) and Quantitative Myasthenia Gravis (QMG) total scores (-2.0, CI -3.2 to -0.8, $p < 0.001$) from baseline at Week 26 as compared to placebo. Notably, the least squares mean of the MG-ADL score improvement did not reach a clinically significant decrease of 2 or more.

Other Information

- Ravulizumab carries a Boxed Warning for serious meningococcal infection:
    - Life-threatening meningococcal infections/sepsis have occurred in patients treated with ravulizumab-cwvz. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies.
    - Immunize patients with meningococcal vaccines at least two weeks prior to administering the first dose of ravulizumab-cwvz unless the risks of delaying ravulizumab-cwvz therapy outweigh the risk of developing a meningococcal infection.
- Ravulizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

- Prescribers must enroll in the program. Enrollment in the Ultomiris REMS program and additional information are available at www.ultomirisrems.com.

- The recommended dosing regimen in adult and pediatric patients one month of age and older with aHUS weighing 5 kg or greater, consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. A loading dose is given followed by maintenance dosing two weeks later. Maintenance dosing is continued at either four- or eight-week intervals. Dose and dosing interval is based on the patient's body weight, as shown in table below.

Indications	Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and dosing interval	
PNH and aHUS	Greater than or equal to 5 to less than 10	600	300	Every 4 weeks
	Greater than or equal to 10 to less than 20	600	600	
	Greater than or equal to 20 to less than 30	900	2,100	Every 8 weeks
	Greater than or equal to 30 to less than 40	1,200	2,700	
PNH, aHUS, and gMG	Greater than or equal to 40 to less than 60	2,400	3,000	
	Greater than or equal to 60 to less than 100	2,700	3,300	
	Greater than or equal to 100	3,000	3,600	

- If switching from eculizimab, start loading dose of ravulizumab two weeks after last eculizimab infusion.
- Eculizumab (Soliris®) is FDA approved for the treatment of PNH, atypical hemolytic uremic syndrome, generalized myasthenia gravis and Neuromyelitis Optica Spectrum Disorder (NMOSD)
- Ravulizumab (Ultomiris®) is currently only FDA for the treatment of PNH, atypical hemolytic uremic syndrome, and generalized myasthenia gravis. Use of ravulizumab (Ultomiris®) in other conditions, such as ocular myasthenia gravis (OMG) and NMOSD is considered investigational at this time and is not considered medical necessary.

REFERENCE/RESOURCES:

1. [Ultomiris®] package insert. Boston, CT: Alexion Pharmaceuticals; April 2023.
2. [Ravulizumab-cwvz] In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed [November 7, 2023].
3. [Ravulizumab-cwvz] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed [November 7, 2023].
4. [Soliris®] package insert. Cheshire, CT: Alexion Pharmaceuticals; 2011.
5. [Eculizumab] In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed [November 7, 2023].
6. Lee JW, Fontbrune S, Lee WL, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naïve to complement inhibitors: the 301 study. Blood. 2018.
7. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. *Blood*. 2018.
8. Sahin F, Akay OM, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. Am J Blood Res. 2016; 6(2): 19-27.
9. Brodsky, RA. Treatment and prognosis of paroxysmal nocturnal hemoglobinuria. In: UpToDate, Rosmarin AG (Ed), UpToDate, Waltham, MA, Sept 2021.
10. National Organization for Rare Disorders (NORD). Atypical hemolytic uremic syndrome. Available from: https://rarediseases.org/rare-diseases/atypical-hemolytic-uremic-syndrome/. Accessed November 6, 2021.
11. Goodship T, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney International. 2017; 91(3): 539-551.
12. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. *Neurol Clin*. 2018;36(2):339-353. doi:10.1016/j.ncl.2018.01.006

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH038.1023	**MISCELLANEOUS PRODUCTS** **UPLIZNA®** (inebilizumab injection)
Effective Date: 01/01/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 07/21, 09/22, 09/23 (KN) P&T Committee Meeting Date: 10/20, 08/21, 10/22, 10/23 Original Effective Date: 01/21 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts) for Neuromyelitis Optica Spectrum Disorder (NMOSD), all of the following must be met:
    a. Diagnosis of neuromyelitis optica spectrum disorder as defined as both of the following:
        i. Presence of at least one core clinical characteristic (optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions), **AND**
        ii. Anti-AQP4 antibody positive
    b. Trial and failure, intolerance, or contraindication to rituximab
    c. Medication will not be used in combination with complement-inhibitor, anti-CD20-directed, anti-CD19 directed, or IL-6 inhibition pathway therapies
    d. Dose and frequency are in accordance with FDA-approved labeling
2. For patients established on therapy (within the previous year) for Neuromyelitis Optica Spectrum Disorder (NMOSD):

a. Documentation of positive clinical response to therapy
b. Medication will not be used in combination with complement-inhibitor, anti-CD20-directed, anti-CD19 directed, or IL-6 inhibition pathway therapies
c. Dose and frequency are in accordance with FDA-approved labeling

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged 18 years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Uplizna® is a humanized monoclonal antibody that binds to the CD19 surface antigen of B cells resulting in depletion of lymphocytes derived from B cell lineage. Evidence suggests that Neuromyelitis Optica Spectrum Disorder (NMOSD) is predominantly a B cell-mediated disorder resulting from pathological autoantibody production, pro-inflammatory cytokine secretion, and B-cell antigen presentation.

FDA APPROVED INDICATIONS:
For the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

POSITION STATEMENT:

- Neuromyelitis Optica Spectrum Disorder (NMOSD), previously known as Devic disease or neuromyelitis optica (NMO), is an autoimmune inflammatory disorder of the central nervous system. It is primarily characterized by recurrent optic neuritis and myelitis often resulting in poor recovery.
- Aquaporin-4 (AQP4) is a water channel protein that astrocytes in the central nervous system express. Preclinical data indicate that AQP4-IgG triggers the complement cascade, which leads to inflammation and the formation of the membrane attack complex.
- Diagnostic criteria for NMOSD require at least one core clinical characteristic (e.g., optic neuritis, acute myelitis, area postrema syndrome), a positive test for AQP4-immunoglobulin G (IgG), and exclusion of alternative diagnoses.
- Currently there are two other FDA approved drugs for NMOSD in adult patients who are anti-AQP4 antibody positive, eculizumab (Soliris®) and recently, satralizumab (Enspryng®); however, immunosuppression therapy, such as rituximab, azathioprine and mycophenolate, have been commonly used for relapse prevention.
    - **Eculizimab (Soliris®):** In the PREVENT trial,143 patients with NMOSD, who were seropositive for aquaporin-4 (AQP4) IgG antibodies, were treated with Soliris® in a randomized controlled trial to evaluate the risk of relapse. The annualized relapse rates for the eculizumab and placebo groups were 0.02 and 0.35 (absolute risk reduction [ARR] 33 percent, rate ratio 0.04, 95% CI 0.01-0.15).
    - **Satralizumab (Enspryng®)**: There is moderate quality of evidence based on two Phase 3 studies (SakuraStar and SakuraSky) that Enspryng® is effective for treatment of anti-AQP4 positive NMOSD in adult patients.
        - Study 1: In the AQP4-IgG seropositive subgroup, nine (22%) of 41 patients receiving Enspryng® versus 13 (57%) of 23 receiving placebo experienced a protocol-defined relapse (HR 0.26, 95% CI 0.11–0.63).
        - Study 2: In the AQP4-IgG–seropositive subgroup, 3 of 27 patients (11%) receiving Enspryng® had a protocol-defined relapse, as compared with 12 of 28 patients (43%) receiving placebo (hazard ratio, 0.21; 95% CI, 0.06 to 0.75).
        - There was no evidence of a benefit in the anti-AQP4 antibody negative patients.
    - **Other Immunosuppressants:** In an open-label randomized trial of 86 patients who had NMOSD with or without anti-AQP4 antibodies, the reduction in the annualized relapse rate at 12 months was significantly greater for patients assigned to rituximab compared with those assigned to azathioprine. In a retrospective, nonrandomized study evaluating

relapse in patients with NMOSD, patients were treated with azathioprine and concomitant prednisone (n = 32) for at least six months, or with mycophenolate (n = 28) for at least six months, or with rituximab (n = 30) for at least one month, and followed up after treatment for at least six months. Rituximab reduced the relapse rate up to 88.2%, with 2 in 3 patients achieving complete remission. Mycophenolate reduced the relapse rate by up to 87.4%, with a 36% failure rate. Azathioprine reduced the relapse rate by 72.1% but had a 53% failure rate despite concurrent use of prednisone.

- The efficacy of Uplizna® was established in a randomized, double-blind, placebo-controlled study, N-Momentum, in 213 patients with NMOSD who were anti-AQP4 antibody positive and 17 who were anti-AQP4 antibody negative. Patients received Uplizna® or placebo. The primary efficacy endpoint was the time to the onset of the first adjudicated relapse on or before day 197.
    - The time to first adjudicated relapse was significantly longer in patients treated with Uplizna® compared to those who received placebo (relative risk reduction 73%; HR:0.272; p<0.0001).
    - For those patients who were anti-AQP4 antibody positive, there was a 77.3% relative reduction (HR: 0.227; p<0.0001).
    - No benefit was detected in patients who were anti-AQP4 antibody negative.

REFERENCE/RESOURCES:

1. Uplizna (inebilizumab) package insert. Gaithersburg, MD: Viela Bio, Inc; Revised June 2020.
2. Inebilizumab In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September 15, 2022.
3. Inebilizumab In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed September 15, 2022.
4. Cree BAC, et al. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. The Lancet. 2019;394(10206):1352-1363.
5. Flanagan EP, et al. Epidemiology of aquaporin-4 Autoimmunity and Neuromyelitis Optica Spectrum. Ann Neurol. 2016;79(5):775-783.
6. National Organization for Rare Disorders. Neuromyelitis Optica Spectrum Disorder. Available at https://rarediseases.org/rare-diseases/neuromyelitis-optica/ (Accessed July 21, 2020).
7. Pittock S, et al. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. NEJM. 2019;381(7):614-625.

8. Nikoo Z, et al. Comparison of the Efficacy of Azathioprine and Rituximab in Neuromyelitis Optica Spectrum Disorder: A Randomized Clinical Trial. J Neurol. 2017;264(9):2003-2009.
9. Mealy M, et al. Comparison of Relapse and Treatment Failure Rates Among Patients With Neuromyelitis Optica: Multicenter Study of Treatment Efficacy. JAMA Neurol. 2014;71(3):324-30.
10. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Wesinsheker BG. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006;66(10).
11. Wingerchuk DM, Banwell B, Bennet JL et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2).
12. UpToDate: Neuromyelitis optica spectrum disorders. Accessed 9/1/2020.
13. Yamamura K, Kleiter I, Fujihara K et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-2124.
14. Traboulsee A, Greenberg B, Bennet J et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 2020; 19(5):402-412.
15. Pittock SJ, Berthele A, Fujihara K et al. Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder. N. Engl. J. Med. 2019;381:614-625.

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY CRITERIA ORPTCANA052.0823	**ANALGESICS & ANESTHETICS** **VYEPTI®** (eptinezumab-jjmr vial)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 08/18, 09/18, 12/18, 05/19, 08/19, 04/20, 06/20, 05/21, 07/21, 07/22, 07/23 (SNM) P&T Committee Meeting Date: 08/18, 10/18, 12/18, 06/19, 08/19, 10/19, 04/20, 06/20, 08/20, 06/21, 08/21, 08/22, 08/23 Original Effective Date: 09/18 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 2

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:

1. For initiation of therapy for migraine prophylaxis (chronic and episodic):
    a. Diagnosis of migraine headaches with at least four headache days per month **AND**
    b. One of the following:
        i. Trial and inadequate response to at least six weeks of at least one prophylactic medication from one of the following categories:
            1. Anticonvulsants (specifically divalproex, valproate, topiramate)
            2. Beta-blockers (specifically metoprolol, propranolol, timolol)
            3. Antidepressants (specifically amitriptyline, venlafaxine)
        ii. Documented intolerance or contraindication to an anticonvulsant, a beta blocker, AND an antidepressant listed above, **AND**

c. The patient has been evaluated for, and does not have, medication overuse headache
d. Documented trial and failure, intolerance, or contraindication to two of the preferred CGRP agents (Aimovig®, Emgality®, Ajovy®, Nurtec® ODT or Qulipta®)
e. For patients established on botulinum toxin for migraine prophylaxis, combination therapy may be considered medically necessary if the following criteria are met:
    i. The patient has been established on, and adherent to botulinum toxin for at least six months and has a documented 30% reduction in headache days from baseline
    ii. Patient continues to have at least four headache days per month with headaches lasting four hours or longer, despite use of botulinum toxin prophylaxis monotherapy
    iii. Combination therapy is prescribed by, or in consultation with, a neurologist

2. For patients established on therapy within the previous year: Documented reduction in the severity or frequency of headaches.

EXCLUSION CRITERIA:
Concomitant use with another calcitonin gene-related (CGRP) agent used for prophylaxis treatment

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes.

QUANTITY LIMIT:
Vyepti: 3 mL (300 mg) per 90 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,

formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Erenumab, fremanezumab, eptinezumab, galcanezumab, atogepant and rimegepant are medications indicated for the prevention of migraine in adults. This new class of medications is known as the calcitonin gene-related peptide (CGRP) receptor inhibitors. This peptide may play an important role in the physiology of migraines and is the first class of medications that specifically targets migraines.

FDA APPROVED INDICATIONS:
Preventive treatment of migraine in adults.

POSITION STATEMENT:
Migraine is a common neurological disorder that is associated with a high degree of disability. It affects about 10-12% of the population. Women are more commonly impacted by this disorder than men. There are several medications approved for the treatment and prevention of migraine. Topiramate, propranolol, and timolol are FDA approved for the prevention of migraines. Amitriptyline, venlafaxine, and valproate have compendial support. These oral agents are associated with unwanted adverse effects that limit their use due to tolerability issues. Botox is FDA approved for the prevention of chronic migraine. This medication requires intramuscular administration of the medication every 12 weeks. The efficacy of the medication may start to wane around 10 weeks.

The 2018 American Headache Society Consensus Statement[14] recommends preventive treatment to be initiated when any of the following occurs:

- Attacks significantly interfere with patients' daily routines despite acute treatment
- Frequent attacks (≥4 monthly headache days)
- Contraindication to, failure, or overuse of acute treatments, with overuse defined as:
    - 10 or more days per month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
    - 15 or more days per month for non-opioid analgesics, acetaminophen, and nonsteroidal anti-inflammatory drugs
- Adverse events with acute treatments

- Patient preference

In addition, the statement recommends initiating CGRP inhibitor:

- Intolerance or inadequate response to a 6-week trial of at least two of the following :
  - Topiramate
  - Divalproex sodium/valproate sodium
  - Beta-blocker: metoprolol, propranolol, timolol, atenolol, nadolol
  - Tricyclic antidepressant: amitriptyline, nortriptyline
  - Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
  - Other Level A or B treatments (established efficacy or probably effective) according to AAN-AHS guideline
  - (or botulinum toxin for patients with chronic migraines)
- For patients with 4-7 monthly headache days, recommendation is that there must also be moderate disability

Eptinezumab was studied in two phase-3 randomized, placebo controlled, clinical trials: PROMISE-1 and PROMISE-2. The primary endpoint of both trials was change from baseline in mean monthly migraine days over months 1-3. These two trials demonstrated that eptinezumab 100 mg and 300 mg exhibited a statistically significant change of mean migraine monthly migraine days compared to placebo in patients with episodic migraine and chronic migraine. In the PROMISE-1 trial, treatment with eptinezumab resulted in 0.7 to 1.1 fewer monthly migraine days compared to placebo. In the PROMISE-2 trial, treatment with eptinezumab resulted in 2.0 to 2.6 fewer monthly migraine days compared to placebo. The most common adverse events (≥2%) in the PROMISE-1 trial were upper respiratory tract infection and fatigue. The most common adverse events in the PROMISE-2 trail were fatigue and nausea. Six patients (1.6%) withdrew from the PROMISE-2 trial due to hypersensitivity. [12,13]

REFERENCE/RESOURCES:

1. Relevant package inserts
2. Goadsby, P J, Reuter, et al. A Controlled Trial of Erenumab for Episodic Migraine. *NEJM*. 2017;377(22):2123-2132.
3. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-434.
4. Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomized, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol. 2016;15(4):382-390.

5. Institute for Clinical and Economic Review. Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final report. July 3, 2018. https://icer.org/wp-content/uploads/2020/10/ICER_Migraine_Final_Evidence_Report_070318-1.pdf. Accessed July 10, 2023.
6. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med. 2017;377:2113-2122.
7. Cohen JM, Dodick DW, Yang R, et al. Fremanezumab as add-on treatment for patients treated with other migraine preventive medicines. Headache. 2017;57:1375-1384.
8. Dodick, D. W., Silberstein, S. D., Bigal, M. E., et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 319, 1999–2008. [Emgality] package insert.
9. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial. JAMA Neurol. 2018;75(9):1080-1088.
10. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. Cephalalgia 2018;38(8):1442–1454.
11. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 2018;91:e1-e11.
12. 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):214-254.
13. Lipton R.B., Goadsby P.J., Schaeffler B.A., et al. Efficacy and safety of eptinezuamb in patients with chronic migraine (PROMISE-2). Neurology. 2020, 94(13).
14. American Headache Society .The American headache society position statement on integrating new migraine treatment into clinical practice (2018). Available at https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/head.13456 (Accessed on June 22, 2023).

Appendix 1. Billing Code

HCPCS Code	Drug	Dose
J3032	Injection, eptinezumab-jjmr, 1 mg	Not to exceed 300 code units every 90 days. 1 billable unit = 1 mg

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP045.0823	**TOPICAL PRODUCTS** **VYJUVEK®** (beremagene geperpavec-svdt gel)
Effective Date: 10/1/2023	Review/Revised Date:
	P&T Committee Meeting Date: 08/23
	Original Effective Date: 10/23
	Approved by: Oregon Region Pharmacy and Therapeutics Committee
Robert Gluckman, M.D. **Chief Medical Officer**	Page 1 of 6

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

Coverage for Medicaid is limited to a condition that has been designated a covered line-item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions falls under this benefit when they impact the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
Initial authorization requires all the following be met:
1. Diagnosis of dystrophic epidermolysis bullosa (DEB)
2. Documentation of mutation(s) in the collagen type VII alpha 1 chain (*COL7A1)* gene
3. Treatment will be used on a cutaneous wound (or wounds) that are clean in appearance with adequate granulation tissue, excellent vascularization, and do not appear infected

4. Dosing is within FDA-labeled guidelines

Reauthorization requires all the following be met:
1. Documentation of successful response to therapy as indicated by complete wound healing or decrease in wound size
2. Patient continues to have incomplete wound closures that are clean in appearance with adequate granulation tissue, excellent vascularization, and do not appear infected
3. Dosing is within FDA-labeled guidelines

EXCLUSION CRITERIA:
1. Skin graft within the past three months
2. Current evidence or a history of squamous cell carcinoma in the area(s) that will undergo treatment

AGE RESTRICTIONS:
May be approved for patients aged six months and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a with a dermatologist or provider with experience in treating epidermolysis bullosa

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
Four vials (10 mL) per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION: Beremagene geperpavec (Vyjuvek®) is a topical HSV-1 vector based gene therapy that delivers functional *COL7A1* genes to both keratinocytes and fibroblasts. Expression of *COL7A1* leads to secretion of type VII collagen. Type VII collagen is a major component of the anchoring fibrils which hold the dermis and epidermis together. Individuals with dystrophic epidermolysis bullosa (DEB) have lower than normal or no functional anchoring fibrils[1].

Beremagene geperpavec does not prevent new wounds from occurring and continued application may be necessary to maintain effect. As local acting gene therapy, patients may require intermittent or ongoing therapy throughout their life[4,5]. It is possible for decreased requirements over time as wounds heal and stabilize.

FDA APPROVED INDICATIONS:
Treatment of wounds in patients six months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene.

POSITION STATEMENT:
Epidermolysis bullosa (EB) is a rare genetic connective tissue disorder characterized by fragile and blistering skin and mucosal membranes. Significant scaring can occur which can lead to complications such as difficulty swallowing, fusion of skin between fingers and toes, joint deformities and vision loss[7].

There are many variations of EB, which are classified into four major types. These types are then further classified into subtypes[7]. Beremagene geperpavec (Vyjuvek®) is approved for treatment of wounds in individuals with dystrophic epidermolysis bullosa (DEB) only.

- Dystrophic epidermolysis bullosa – recessive (RDEB) (more severe form) or dominant (DDEB)
    - Caused by mutations in the type VII collagen (*COL7A1*) gene leading to reduced or absent levels of type VII collagen.
    - Individuals with DEB have lower than normal or no functional anchoring fibrils which are required for maintaining the integrity of the skin.
    - Prevalence of RDEB in the US is estimated around 1.4 per million with an incidence of 3.1 per million[6]
    - Prevalence of DDEB is approximately 1.5 per million with an incidence of 2.1 per million[6]
- Epidermolysis bullosa simplex (EBS)

  - Most common type with estimated prevalence of 6 per million[6]
- Junctional epidermolysis bullosa (JEB)
- Kindler epidermolysis bullosa (KEB)

Depending on subtype, symptoms can range from mild (e.g., blistering to hands, feet, knees, elbows with normal life expectancy) to severe (e.g., death during infancy due to complications such as sepsis, dehydration, obstructive airway, electrolyte imbalances). Individuals are also at an increased risk of squamous cell carcinoma.

Management of dystrophic epidermolysis bullosa is supportive care including wound care, pain management, infection control and nutritional support. Management also includes prevention and treatment of complications[7]. Beremagene geperpavec (Vyjuvek®) is the first FDA-approved pharmacologic treatment for DEB.
Some standard care therapies for DEB include:

- Reducing skin friction
- Keeping skin cool
- Daily skin care and dressings
- Managing blisters (not self-limiting)
- Addressing nutritional deficiencies
- Monitoring for skin cancer

The European Network for Rare Skin Disorders have put out recommendations for emergency management in EB for both in home and hospital care. Topics include sepsis, feeding inability in infants, esophageal obstruction, upper airway obstruction, urinary retention and corneal erosion[8].

Approval for Vyjuvek® was based on a phase 3 randomized, double blind, intrapatient placebo controlled trial of 31 patients with dystrophic epidermolysis bullosa. At 6 months, complete wound healing occurred in 67% of wounds exposed to Vyjuvek® compared to 22% with placebo. Absolute difference 38.7% (13.9-63.5) 95% CI p=0.012[4].

- Patient population: Patients (N=31) six months and older with dystrophic epidermolysis bullosa characterized by blistering, wounds and scarring and genetically confirmed mutations in the *COL7A1* gene.
  - Key exclusion criteria: current treatment with immunotherapy, chemotherapy or other investigational products; skin graft within past three months; wounds with current or history of squamous-cell carcinoma or active infection were excluded from being application sites.
- Intervention: For each patient, a primary wound pair was selected. Wounds were matched for size, region and appearance (i.e., wounds were clean with adequate granulation tissue, excellent vascularization and did not appear infected).
  - Wounds within each pair were assigned 1:1 to weekly application of either beremagene geperpavec (B-VEC) or placebo

- Baseline characteristics: 30 participants with RDEB and 1 with DDEB, median age 16 years with range 1-44
- Primary endpoint: complete wound healing
    - Defined as 100% wound closure as indicated by skin re-epithelialization without drainage, confirmed at two consecutive study visits two weeks apart (assessed at Weeks 22 and 24 or at Weeks 24 and 26)
- Efficacy:
    - 20 of 31 wounds exposed to B-VEC and 8 of 31 wounds exposed to placebo met the primary end point. Absolute difference of 38.7% (13.9-63.5) 95% CI, p=0.012.
    - Durability, which was defined as complete wound healing at both 3 and 6 months, was seen in 50% of wounds exposed to B-VEC and 7% of those exposed to placebo (difference of 43%; 95% CI, 23 to 63).
- Safety:
    - Most frequent adverse reactions (incidence >5%): pruritis, chills, erythema, rash, cough, and rhinorrhea
    - Warnings and precautions: Accidental exposure - avoid direct contact with treated wounds and dressings of treated wounds for approximately 24 hours following application. Clean the affected area if accidental exposure occurs.
    - Pharmacokinetic data suggest a lack of systemic exposure after topical application

Study limitations include that only one participant with DDEB was included in the trial and most wounds exposed to B-VEC were less than 20 cm^2 meaning efficacy or time to complete wound healing could differ for larger wounds.

Vyjuvek® is a biological suspension mixed into an excipient gel by a specialty pharmacy. Gel droplets are applied to wound(s) once weekly. Package labeling states that only a healthcare professional should apply Vyjuvek® either in a professional setting or in the home. The dose is dependent on the wound size with a maximum weekly volume based on age.

Dosing tables[1]

Age Range	Maximum Weekly Dose (plaque forming units; PFU)	Maximum Weekly Volume (milliliter; mL)*
6 months to <3 years old	1.6×10^9	0.8
≥ 3 years old	3.2×10^9	1.6

*Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.

Wound Area (cm^2)*	Dose (PFU)	Volume (mL)
<20	4×10^8	0.2
20 to <40	8×10^8	0.4
40 to 60	1.2×10^9	0.6

*For wound area over 60 cm^2, recommend calculating the total dose based on this table until the maximum weekly dose is reached.

REFERENCE/RESOURCES:

1. Vyjuvek package insert. Krystal Biotech, Inc. Pittsburgh, PA: May 2023
2. Beremagene geperpavec In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed June 21, 2023
3. Beremagene geperpavec In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed June 21, 2023
4. Guide SV, Gonzalez ME, Bağcı IS, *et al*. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. N Engl J Med. 2022 Dec 15;387(24):2211-2219.
5. Food and Drug Administration. Center for Drug Evaluation and Research. BLA Clinical Review Memorandum STN 125774/0. Available at https://www.fda.gov/media/169435/download (Accessed June 21, 2023)
6. Fine, JD. Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. *JAMA Dermatol*. 2016 Nov;152(11):1231-1238.
7. National Organization for Rare Disorders (NORD). Epidermolysis Bullosa. Available at https://rarediseases.org/rare-diseases/epidermolysis-bullosa/#disease-overview-main (Accessed July 9, 2023).
8. Mellerio, J.E., El Hachem, M., Bellon, N. *et al*. Emergency management in epidermolysis bullosa: consensus clinical recommendations from the European reference network for rare skin diseases. *Orphanet J Rare Dis* 15, 142 (2020).
9. debra of America. About EB. Available at https://www.debra.org/about-eb (accessed July 24, 2023)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCOTH031.1023	**MISCELLANEOUS AGENTS** **XIAFLEX®** (collagenase clostridium histolyticum kit)
Effective Date: 1/1/2024 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 03/20, 07/20, 11/20, 08/21, 09/22, 09/23 (CJD) P&T Committee Meeting Date: 04/20, 08/20, 12/20, 10/21, 10/22, 10/23 Original Effective Date: 07/20 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
Dupuytren's contracture and Peyronie's disease, subject to criteria below

For Medicaid: Peyronie's disease is considered "below the line". Therefore, coverage is dependent on whether the condition adversely affects, or is secondary to, a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

REQUIRED MEDICAL INFORMATION:

Initial Authorization Criteria:

For **Dupuytren's contracture (DC)**:
1. Both of the following diagnostic criteria:
    a. Finger flexion contracture of at least 20° with a palpable cord in a metacarpophalangeal (MP) joint or proximal interphalangeal (PIP) joint
    b. Documentation of a positive "table top test," defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top

2. Documentation that affected joint has not had surgical intervention within the previous 90 days

For **Peyronie's disease (PD):**
1. Patient's disease is stable, defined as unchanged degree of curvature for at least three months
2. Patient has a curvature of the penis that is between 30 and 90 degrees with a palpable cord, or a cord that is documented through ultrasound
3. Patient has intact erectile function, with or without the use of medications
4. Documentation of a functional impairment that is expected to improve with treatment (e.g., inability to have intercourse despite intact erectile function, due to curvature)
5. Documentation showing the patient does **not** have any of the following:
    a. Significant pain with palpation of the plaque
    b. Lack of full erectile response to prostaglandin E1 during curvature measurement
    c. Ventral curvature
    d. Calcified plaque
    e. Plaque located proximal to the base of the penis
6. Documentation that the patient has been counseled on expectations of treatment (e.g., expected average curvature reduction is 17 degrees without reduction in pain or erectile dysfunction, potential for adverse effects)

Reauthorization Criteria:
For **DC**:
1. Documentation of fewer than three total injections in affected cord.

For **PD**
1. Documentation that the curvature of the penis remains greater than 15 degrees. Limited to eight total injections per lifetime.

EXCLUSION CRITERIA:
- PD involving the urethra.
- More than three total injections per affected cord for DC
- More than eight total injections per lifetime for PD.

AGE RESTRICTIONS:
Approved for 18 years and older

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:

For **DC**:

Initial authorization will be approved for three months for a maximum of three treatment courses. Reauthorization will be approved for three months, not to exceed three injections per affected cord.

For **PD**:

Initial authorization will be approved for three months, not to exceed four injections. Reauthorization will be approved for six months, not to exceed eight injections per lifetime.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Xiaflex® contains purified collagenase clostridium histolyticum, consisting of two microbial collagenases in a defined mass ratio. Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions, resulting in lysis of collagen deposits. Dupuytren's contracture (DC) cords are typically comprised of collagen and Peyronie's disease (PD) is caused by the buildup of collagen plaques in the penis that causes a curvature.

FDA APPROVED INDICATIONS:

- Treatment of adult patients with DC (ICD-10 M72.0) with a palpable cord
- Treatment of adult men with PD (ICD-10 N48.6) with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

POSITION STATEMENT:

DC is a condition that affects the fascia in the palm and fingers. It is characterized by fascial thickening that can progress to longitudinal bands, referred to as cords, that can limit mobility and function of the hand and fingers. It causes flexion of the metacarpophalangeal (MCP) joint, proximal interphalangeal (PIP) joint, or both. Treatment can involve steroid injections, surgery (most common for advanced disease), or injection of collagenase clostridium histolyticum.

PD is characterized by a buildup of collagen plaques that can cause a curvature deformity of the penis. This can be associated with penile pain, erectile dysfunction, and negative impact on quality of life (e.g., emotional distress, depressive symptoms, and relationship difficulties). Other symptoms (e.g., difficulty urinating) may point to a different diagnosis, and are not considered to be a problem associated with Peyronie's disease directly. Patients' symptoms may be self-resolving and may not require treatment. While this disease may compromise sexual function and, therefore, quality of life, it does not impact overall mortality. Treatment with collagenase clostridium histolyticum helps break up the plaques and resolve the deformity.

The American Urological Association (AUA) 2015 guidelines for the management of Peyronie's disease recommends treatment with intraregional collagenase clostridium histolyticum in combination with modeling in patients with stable PD (symptoms have not changed for at least three months), penile curvature >30° and <90°, and intact erectile function (with or without the use of medications), as this is the patient population in which clinical controls were studied . The AUA specifically states that this agent should not be used solely for the treatment of pain or erectile dysfunction due to PD, as this treatment is not without risk (e.g., penile ecchymosis, swelling, pain, and corporal rupture). In addition, the AUA recommends that the expected results of the treatment be thoroughly discussed with the patients, as typically only a 17 degree curvature reduction is seen, a modest benefit over placebo. There is also no information available regarding the duration of response and long-term effects. The AUA states studies have not been performed in patient populations with hourglass deformity, ventral curvature, calcified plaque, or plaque proximal to the base of the penis. The AUA guidelines include reference to additional exclusion criteria from the IMPRESS trial utilized for FDA approval of Xiaflex for PD. These include curvature less than 30° or greater than 90°, lack of full erectile response to prostaglandin E1 during curvature measurement, and further specifies exclusion criteria of isolated hourglass deformity without curvature.

Xiaflex® has a REMS program due to the risk of corporal rupture. Required components of the program include the following:

- Prescribers must be certified with the program by enrolling and completing training in the administration of treatment for PD.

- Healthcare sites must be certified with the program and ensure that the medication is only dispensed for use by certified prescribers.

REFERENCE/RESOURCES:

1. Xiaflex package insert. Malvern, PA: Auxilium Pharmaceuticals, LLC; 2022 Aug.
2. John's Hopkins Medicine. Dupuytren's Contracture. Available at https://www.hopkinsmedicine.org/health/conditions-and-diseases/dupuytrens-contracture (Accessed September 9, 2022)
3. American Urological Association (AUA). Peyronie's Disease: AUA Guideline, published 2015. Available at https://www.auanet.org/guidelines-and-quality/guidelines/peyronies-disease-guideline (Accessed September 9, 2022).
4. Gliptin D, Coleman S, Hall S, et al. Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. https://pubmed.ncbi.nlm.nih.gov/21134613/ (Accessed September 9, 2022).

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES017.0823	**RESPIRATORY AGENTS** **XOLAIR®** (Omalizumab injection)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 12/03, 12/04, 04/06, 02/07, 06/07RR, 02/08, 04/08, 08/09, 08/10, 12/11, 02/12, 06/13, 06/14, 05/15, 06/15, 05/16, 09/16, 05/17, 05/18, 11/18, 05/19, 05/20, 10/20, 04/21, 07/21, 05/22, 04/23, 08/23 (snm) P&T Committee Meeting Date: 12/03, 12/04, 04/06, 02/07, 06/07, 02/08, 08/09, 08/10, 12/11, 02/12, 06/13, 06/14, 05/15, 06/15, 06/16, 12/16, 06/17, 06/18, 12/18, 06/19, 06/20, 10/20 (off-cycle), 06/21, 08/21, 6/22, 06/23, 08/23 Original Effective Date: 12/03 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 8

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. For initiation of therapy (new starts), must meet indication-specific criteria below:
    a. For **asthma**, must meet all of the following criteria:
        i. Diagnosis of moderate to severe persistent allergic asthma
        ii. IgE baseline levels greater than 30 IU/ml
        iii. Positive skin test to a common perennial aeroallergens
        iv. In the past three months, patient is adherent to treatment with maximally tolerated doses of both of the following, unless patient has an intolerance or contraindication to all therapies (This may be verified by pharmacy claims information):
            1) Inhaled corticosteroid
            2) One of the following:
                a. A long-acting inhaled beta 2-agonist (LABA)
                b. A leukotriene receptor antagonist (LTRA)
                c. A long-acting muscarinic antagonist (LAMA)
        v. Inadequate asthma control despite above therapy, defined as one of the following:

1) Asthma Control Test (ACT) score less than 20 or Asthma Control Questionnaire (ACQ) score greater than or equal to 1.5
2) At least two exacerbations requiring oral systemic corticosteroids in the last 12 months
3) At least one exacerbation requiring hospitalization, emergency room or urgent care visit in the last 12 months
4) Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered
5) Baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted

b. For **chronic idiopathic urticaria**, must meet all the following criteria:
   i. Patient has had over six weeks of hives and itching
   ii. Condition is idiopathic and that secondary causes of urticaria (such as offending allergens, physical contact, etc.) have been ruled out
   iii. Trial and failure of a second-generation non-sedating H1 antihistamine (such as levocetirizine, loratadine, cetirizine, fexofenadine)
   iv. Trial and failure of one additional medication from one of the following classes:
      1) leukotriene receptor antagonists (such as montelukast),
      2) first generation H1 antihistamine (such as diphenhydramine), or
      3) histamine H2-receptor antagonist (such as famotidine, ranitidine)

c. For **nasal polyps**, must meet all of the following criteria:
   i. Evidence of bilateral nasal polyposis by direct examination, endoscopy or sinus CT scan
   ii. Patient had an inadequate response to a three month trial of intranasal corticosteroids (such as fluticasone) or has an intolerance or contraindication to ALL intranasal corticosteroids
   iii. Patient will continue standard maintenance therapy (such as intranasal corticosteroids, nasal saline irrigation) in combination with omalizumab

2. For <u>patients established</u> on the requested therapy within the previous year, response to therapy indicating improvement or stabilization of condition

EXCLUSION CRITERIA:

Concurrent use with anti-IL5 (such as mepolizumab, reslizumab, benralizumab), anti-IgE, anti-TSLP (such as tezepelumab), or anti-IL4 (such as dupilumab) monoclonal antibodies

AGE RESTRICTIONS:
For all indications, the patient's age must be within FDA labeling for the requested indication

PRESCRIBER RESTRICTIONS:
Asthma: Must be prescribed by, or in consultation with an asthma specialist (such as a pulmonologist, immunologist, or allergist)

Urticaria: Must be prescribed by, or in consultation with, a dermatologist, allergist or immunologist

Nasal polyps: Must be prescribed by, or in consultation with, an otolaryngologist, allergist, pulmonologist, or immunologist

COVERAGE DURATION:
Asthma: Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

Urticaria and nasal polyps: Initial authorization will be for one year and reauthorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Omalizumab (Xolair®) is an injectable medication for patients with moderate to severe persistent allergic asthma, chronic idiopathic urticaria (CIU) not controlled with other conventional therapies, and chronic rhinosinusitis with nasal polyps.

Omalizumab is a monoclonal antibody that binds to and blocks immunoglobulin E (IgE) which is responsible for causing the release of histamine and other inflammatory mediators from mast cells and basophils.

Omalizumab is given via a subcutaneous injection. The doses and dosing frequency in treating allergic asthma and nasal polyps is determined by total serum IgE level at baseline, and body weight. The dose in CIU is between 150 to 300 mg every four weeks and is independent of serum IgE level or body weight.

FDA APPROVED INDICATIONS:

- Moderate to severe persistent asthma in patients (six years of age and above) with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids
- Chronic idiopathic urticaria in adults and adolescents (12 years of age and above) who remain symptomatic despite H1 antihistamine treatment
- Nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment

POSITION STATEMENT:

Concomitant Asthma and Allergic Rhinitis

- According to the asthma management guidelines of the National Heart, Lung and Blood Institute (NHLBI), for individuals with moderate to severe persistent asthma already taking low- or medium dose ICS, the preferred treatment is a single inhaler with ICS-formoterol (referred to as single maintenance and reliever therapy, or “SMART”) used both daily and as needed.[16]
- The Global Initiative for Asthma (GINA) 2023 update utilizes a five step treatment approach separated in two tracks (a preferred controller and reliever track and an alternative controller and reliever track) . If asthma remains uncontrolled despite good adherence and inhaler technique a step up in treatment is recommended. Add on therapy with omalizumab is an option for adults and children six years of age or older with moderate to severe allergic asthma if asthma is persistently uncontrolled despite step 4 or 5 treatments. Medium to high dose ICS-LABA is the recommended treatment in step 4.[15]
- Vignola and colleagues evaluated the efficacy of omalizumab in a randomized, double-blind, placebo-controlled trial involving 405 adults and adolescents with concomitant allergic asthma and PAR. Enrollment criteria included an IgE concentration of 30–1300 IU/mL, a positive skin-prick test to an indoor allergen, a history of moderate-to-severe PAR for at least two years, asthma requiring ICS therapy, and a history of 2–3 unscheduled medical visits for asthma over the prior 1–2 years. Patients were also required

to have quality of life testing scores that indicate greater than mild symptoms. Patients were randomized to subcutaneous omalizumab (at least 0.016 mg/kg per IU of IgE/mL per four weeks) or placebo for 28 weeks. End-of-trial comparisons to placebo revealed that fewer omalizumab recipients had experienced an asthma exacerbation (30.1% vs 20.6%, *P* = .02), and the mean rate of exacerbations was lower. Additionally, more omalizumab recipients reported clinically relevant changes and large improvements in quality of life.[6]

Numerical asthma control tools for assessment of asthma symptom control:[14]

- Asthma Control Test (ACT): Scores range from 5 to 24 (higher is better controlled symptoms). Scores of 20 to 25 is classified as well-controlled asthma; 16 to 19 as not well-controlled, and 5 to 15 as very poorly controlled asthma. The ACT includes a patient self-assessed level of asthma control, frequency of shortness of breath, use of rescue medications, and the effect on daily function due to asthma. The minimum clinically important difference is 3 points
- Asthma Control Questionnaire (ACQ): Scores range from 0 to 6 (higher score is worse control). A score of 0.0 to 0.75 is classified as well-controlled asthma; 0.75 to 1.5 is a “gray zone,” and 1.5 or greater as poorly controlled asthma. ACQ score is calculated as the average of 5 to 7 items that includes five symptom questions. ACQ-7 includes a score for pre-bronchodilator FEV1, in addition to questions on symptoms and use of rescue medications. The minimum clinically important difference is 0.5 points.

Chronic Idiopathic Urticaria

- For the treatment of CIU, omalizumab has been approved based on two similarly designed Phase III randomized, double-blind, placebo-controlled studies (ASTERIA I and ASTERIA II). Patients (n=319 and n=322 respectively) with CIU were randomized to either Xolair 75, 150, or 300 mg or placebo by SC injection every four weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks. In both studies, patients receiving 150 mg and 300 mg had greater decreases in UAS7 (Weekly Urticarial Activity Score) from baseline compared to placebo. These results were not consistently demonstrated in the patients receiving the 75 mg dose.[1]
- Guidelines created by the American Academy of Allergy , Asthma & Immunology (AAAAI); American College of Allergy , Asthma &Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI) recommended a step wise approach for the management of chronic urticaria. Step 1 includes the use of monotherapy with second-generation antihistamines and the avoidance of triggers as first-line therapy. Step 2 may

include one or more of the following measures, higher doses of second-generation antihistamines used in step 1 with or without the addition of another second-generation antihistamine, a H2-antagonist, a leukotriene receptor antagonist, or a first-generation antihistamine (at bedtime). Step 3 involves the dose advancement of potent antihistamines (e.g., hydroxyzine or doxepin) as tolerated. Step 4 recommends the addition of alternative agents such as omalizumab, cyclosporine, other anti-inflammatory agents, or immunosuppressants.[8]

- Efficacy and dosing of omalizumab in patients with IgE levels greater than 30 IU/ml has been established for individuals with concomitant allergic asthma and allergic rhinitis.[1]
- Beneficial effects may not be seen with omalizumab for 6-12 weeks.[1]

Nasal Polyps

- Omalizumab was assessed as add-on maintenance therapy for patients with nasal polyps, with an inadequate response to nasal corticosteroids, in two double-blind, placebo-controlled trials. Patients received either omalizumab or placebo every two to four weeks for 24 weeks. Dosing was based on pretreatment serum IgE and bodyweight. All patients received background nasal mometasone. Primary endpoints were changes in baseline bilateral Nasal Polyp Score (NPS) and Nasal Congestion Score (NCS). NPS was scored (range 0-4 per nostril: 0= no polyps; 1=small polyps in the middle meatus; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps; 4=large polyps causing complete obstruction of the inferior nasal cavity) for a total NPS (range 0-8). Nasal congestion was measured by a daily assessment on a 0 to 3 point severity scale (0=none, 1=mild, 2=moderate, 3=severe). The co-primary endpoint showed statistically significant improvement with omalizumab.
- The 2023 Joint Task Force, consisting of members from the American Academy of Allergy, Asthma & Immunology, American College of Allergy, Asthma, and Immunology, recommend the following: (1) In people with CRSwNP, the guideline panel suggests INCS rather than no INCS (conditional recommendation, low certainty of evidence). (2) In people with CRSwNP, the guideline panel suggests biologics rather than no biologics (conditional recommendation, moderate certainty of evidence). [16]

Black Box Warning[1]: Anaphylaxis

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported to occur after administration of Xolair®. Anaphylaxis has occurred as early as after the first dose of Xolair®, but also has occurred beyond one year after beginning regularly administered treatment.

Omalizumab should be initiated under the guidance of a healthcare provider with possible patient self-administration after assessment of anaphylaxis risk and mitigation strategies. Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after Xolair® administration, and health care providers administering Xolair® should be prepared to manage anaphylaxis that can be life-threatening. Patients should be informed of the signs and symptoms of anaphylaxis and now how to treat anaphylaxis appropriately.

Malignancy Warning

- Malignancies were observed in 20/4127 (0.5%) omalizumab and 5/2236 (0.2%) placebo in clinical studies
- 18 of the 20 cancers occurred within 12 months of starting therapy and 60% were within six months
- Several patients had premalignant conditions or risk factors for malignancy development
- Risk vs. benefit discussion should be held between patient and physician; no direct correlation has been established between use of omalizumab and development of malignancies

REFERENCES:

1. Xolair® (omalizumab) for injection prescribing information. South San Francisco, CA: Genentech Inc. March 2023.
2. FDA Advisory Pulmonary-Allergy Subcommittee May 15, 2003.
3. Busse W, Corren J, Lanier Q. et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001;108:184-190.
4. Soler M. Matz J. Townley R. et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001;18:254-261.
5. Holgate S et al. Omalizumab, reduces inhaled corticosteroid use in patients with severe allergic asthma receiving high dose inhaled corticosteroid therapy compared with placebo. Abstract 2001.
6. Vingola AM, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy, 2004 Jul;59(7):709-17.
7. Bernstein JA, Saini SS, Maurer M, et al. Efficacy Of Omalizumab In Patients With Chronic Idiopathic/Spontaneous Urticaria With Different Background Therapy: Post Hoc Analysis Of Asteria I, Asteria II, and Glacial Studies. Presented at: American Academy of Allergy, Asthma & Immunology Annual Meeting; March 2, 2014; San Diego, CA.

8. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277.
9. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy. 2018 Jul;73(7):1393-1414. doi: 10.1111/all.13397. PMID: 29336054.
10. DeConde AS, Soler ZM. Chronic rhinosinusitis: Epidemiology and burden of disease. *Am J Rhinol Allergy*. 2016; 30:134-139
11. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. 2015; 152(2 suppl): S1-S39
12. Bachert C, Gevaert P, Hellings P. Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps. *J Allergy Clin Immunol Pract*. 2017 Nov-Dec;5(6):1512-1516.
13. Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic Agents for the Treatment of Chronic Rhinosinusitis With Nasal Polyps. *Am J Rhinol Allergy*. 2019 Mar;33(2):203-211.
14. Global Initiative for Asthma. Global initiative for asthma management and prevention (2023 update). Available at: http://www.ginasthma.org. Accessed on May 9, 2023.
15. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPPCC), Cloutier MM, Baptist AP, et al. 2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. J Allergy Clin Immunol 2020; 146:1217.
16. Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. J Allergy Clin Immunol. 2023;151(2):386-398. doi:10.1016/j.jaci.2022.10.026
17. Orlandi, RR, Kingdom, TT, Smith, TL, et al. International consensus statement on rhinology and allergy: rhinosinusitis. Int Forum Allergy Rhinol. 2021; 11: 213– 739. https://doi.org/10.1002/alr.22741

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCBIO010.0823	**BIOLOGICAL** **ZINPLAVA®** (bezlotoxumab injection)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 04/17, 11/17, 10/18, 11/10, 10/20, 04/21, 04/22, 04/23, 08/23 (BS) P&T Committee Meeting Date: 04/17, 12/17, 12/18, 12/19, 12/20, 06/21, 06/22, 06/23, 08/23 Original Effective Date: 06/17 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 4

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
All the following criteria must be met for *Clostridioides difficile* infection (CDI):

1. Previous trial of standard-of-care antibiotic regimen for recurrent CDI (such as oral vancomycin, fidaxomicin)
2. Bezlotoxumab (Zinplava®) must be used in combination with standard-of-care antibiotics for treatment (such as oral vancomycin, fidaxomicin)
3. Dosing is within Food and Drug Administration's approved labeling
4. **For Commercial/Medicare Part B only:** Patient has at least one risk factor for higher likelihood of recurrent CDI [for example, age of 65 years or older, history of CDI in the previous six months, compromised immunity, clinically severe CDI (defined as a Zar score greater than or equal to 2; scores range from 1 to 8, with higher scores indicating more severe infection)]

Reauthorization requires all the following criteria to be met:

1. Previous dose was at least 12 months prior

2. Patient must have had documented benefit from previous infusion, defined as reduction in frequency of recurrences of CDI from baseline
3. Bezlotoxumab (Zinplava®) is used in combination with standard-of-care antibiotics for treatment (such as oral vancomycin, fidaxomicin)
4. Dosing is within Food and Drug Administration's approved labeling

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: Approved for 1 years of age and older

PRESCRIBER RESTRICTIONS: Must be prescribed by or in consultation with an infectious disease specialist or gastroenterology specialist

COVERAGE DURATION: Initial authorization and reauthorization will be approved for a one-time intravenous

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Bezlotoxumab (Zinplava®) is a human monoclonal antibody that binds to and neutralizes *Clostridioides difficile* toxin B. Bezlotoxumab is given as a one-time 10 mg/kg dose, infused intravenously over 60 minutes. It has no antimicrobial effects and therefore must be used as an adjunctive treatment with a standard-of-care antibiotic for *C. difficile* infection.

FDA APPROVED INDICATIONS:

Prophylaxis for recurrent *Clostridioides difficile* infection (CDI) in patients who are receiving antibacterial drug treatment for CDI and are at high risk of CDI recurrence

POSITION STATEMENT:
Per the 2021 International Disease Society of America's guidelines on *Clostridioides difficile,* treatment for a first recurrence of CDI includes oral vancomycin or fidaxomicin. Antibiotic treatment options for patients with more than one recurrence of CDI include oral vancomycin therapy using a tapered and pulsed regimen, a standard course of oral vancomycin followed by rifaximin, or fidaxomicin. Fecal microbiota transplantation is recommended for patients with multiple recurrences of CDI (rCDI) who have failed appropriate antibiotic treatments.[5]

Bezlotoxumab (Zinplava®) was studied in two pivotal randomized, double-blind, placebo-controlled phase 3 trials, MODIFY I (N=807) and MODIFY II (N=806). Patients age 18 years and older with primary or recurrent CDI were randomized to receive a one-time dose of bezlotoxumab or placebo, along with the standard-of-care antibacterial therapy (metronidazole, vancomycin, or fidaxomicin for 10 to 14 days). The primary endpoint was the number of patients with recurrent infection within 12 weeks after bezlotoxumab infusion in the modified intention-to-treat population. Data from both trials were pooled for final analysis. Rate of recurrence within 12 weeks was 129/781 (17%) patients in the bezlotoxumab group vs 206/773 (27%) patients in the placebo group ($p<0.01$). The rate of initial clinical cure was 80% (625/781) in the bezlotoxumab group and 80% (621/773) in the placebo group. In a post-hoc analysis of participants with one or more risk factors for recurrence, recurrent infection occurred in 17% of the participants (100/592) in the bezlotoxumab group and in 30% of the participants (174/583) in the placebo group. Risk factors for the subgroup analysis included age 65 years and older, history of CDI in the previous six months, immunocompromised, clinically severe CDI (i.e., Zar score of at least 2) and hypervirulent strains (ribotypes 027, 078, 244). Limitations of the clinical trial included heavy sponsor involvement, no standardization of antibacterial therapy which was chosen by the treating physician, and the study duration may not be sufficient to really assess the rate of recurrence.[7]

Common adverse events in clinical trials included infusion-specific reactions (10.3%), nausea (7.0%), and heart failure exacerbation (13%) in patients with heart failure. A higher mortality rate due to cardiac failure, infection, and respiratory failure was observed in patients with a history of heart failure who received bezlotoxumab.

Per the package insert, the safety and efficacy of repeat administration of Zinplava® in patients with CDI have not been studied. A recent follow-up study from Modify II was done looking at relapse risk for bezlotoxumab use in patients that had a sustained clinical cure (SCC), defined as achieving an initial clinical cure and having no rCDI through Week 12. "Among bezlotoxumab-treated participants, there were no cases of rCDI in the 9-month extension period. This suggests that the efficacy of bezlotoxumab seen in the core study was due to rCDI prevention rather than a delay

in rCDI onset after antibody concentrations were diminished. Bezlotoxumab has an elimination half-life of ~19 days and was detectable in serum at clinically important concentrations up to six months after treatment. As low levels of antibodies against toxins A and/or B are associated with an increased recurrence risk, the concentration of bezlotoxumab remaining in serum at six months after a single dose may be sufficiently high to neutralize *C. difficile* toxin B for ≥6 months."[8]

Overall, the role of bezlotoxumab for the treatment of CDI is unclear, especially when fecal microbiota transplant is emerging as a treatment of choice for recurrent infections. There is low quality of evidence to support bezlotoxumab, a non-antibiotic, human monoclonal antibody for adjunctive treatment for CDI to prevent recurrence. The 2021 International Disease Society of America's guidelines on *Clostridioides difficile* has updated their recommendations to include bezlotoxumab in addition to standard of care antibiotics in patients with a recurrent CDI episode within the last six months.

REFERENCES:

1. Bezlotoxumab (Zinplava™) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc; March 2023.
2. Zinplava (bezlotoxumab) In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed April 17, 2023.
3. Zinplava (bezlotoxumab) In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed April 17, 2023.
4. Formulary Dossier for ZINPLAVA® (bezlotoxumab); Merck & Co., Inc; 2016.
5. Johnson S, Lavergne V, Skinner AM et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. *Clinical Infectious Disease*. 2021; 73(5):e1029-e1044
6. Kim, Kami MD. Clostridioides difficile, C.diff. *The Sanford Guide to Antimicrobial Therapy.* Sperryville, VA, USA: Antimicrobial Therapy, Inc; 2020.
7. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. N Engl J Med. 2017;376(4):305–317. doi:10.1056/NEJMoa1602615.
8. Goldstein EJC et al. Bezlotoxumab for the prevention of recurrent Clostridioides difficile infection: 12-month observational data from the randomized phase III trial, MODIFY II. *Clin Infect Dis.* 2020; 71(4):1102-1105

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU031.0823	**NEUROMUSCULAR DRUGS** **ZOLGENSMA®** (onasemnogene abeparvovec-xioi kit)
Effective Date: 10/1/2023 **Robert Gluckman, M.D.** **Chief Medical Officer**	Review/Revised Date: 06/19, 07/19, 06/20, 06/21, 06/22, 07/23 (MTW) P&T Committee Meeting Date: 06/19, 08/19, 08/20, 08/21, 08/22, 08/23 Original Effective Date: 09/19 Approved by: Oregon Region Pharmacy and Therapeutics Committee Page: 1 of 10

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
1. Confirmed genetic diagnosis of spinal muscular atrophy (SMA) with documentation of bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and less than or equal to three copies of SMN2
2. Documentation that premedication with prednisolone 1 mg/kg/day (or equivalent) will be started 24 hours prior to infusion and continue for at least 30 days
3. Documentation of baseline anti-AAV9 antibody titers of less than or equal to 1:50
4. Documentation of baseline tests for liver function, platelet count, and troponin-I

EXCLUSION CRITERIA:
- Use in combination with nusinersen (Spinraza®) or risdiplam (Evrysdi®) therapy
- Repeat infusion of onasemnogene abeparvovec
- Advanced symptoms of SMA (such as, complete paralysis of limbs, tracheostomy or ongoing invasive ventilator support in the absence of an acute reversible illness)

AGE RESTRICTIONS:
May be covered for patients two years of age and under

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist

COVERAGE DURATION:
Authorization will be approved for a one-time infusion

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Zolgensma® is a gene therapy designed to treat patients with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene. Other currently available treatments include nusinersen (Spinraza®), an antisense oligonucleotide, and Evrysdi®, a splicing modifier, and first oral treatment available for SMA.

FDA APPROVED INDICATIONS:
An adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than two years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene.

- Limitation of Use:
    - The safety and effectiveness of repeat administration have not been evaluated.
    - The use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated

POSITION STATEMENT:
Spinal muscular atrophy (SMA) is a progressive and severe neurodegenerative disease.

- Incidence ~1 in 10,000 live births
- Characterized by mutations in the survival motor neuron 1 (SMN1) gene and insufficient production of functional SMN protein, causing degeneration and loss of motor neurons
- Classified into four subtypes (SMA types 1–4) based on the severity of symptoms and the age of onset.

SMA Type	Age of Onset	Highest Achieved Motor Function	Natural Age of Death	Typical Number of *SMN2* Copies
0	Prenatal/fetal	None	<6 months	1
I	<6 months	Sit with support only	<2 years	1-3
II	6–18 months	Sit independently	>2 years	2-3
III	>18 months	Walk independently	Adulthood	3-4
IV	Adult (20s-30s)	Walk through adulthood	Adult	≥4

Adapted from Table 1 of Verhaart et al. 2017.[9]
Number of *SMN2* copies based on Calucho et al. 2018.[16]

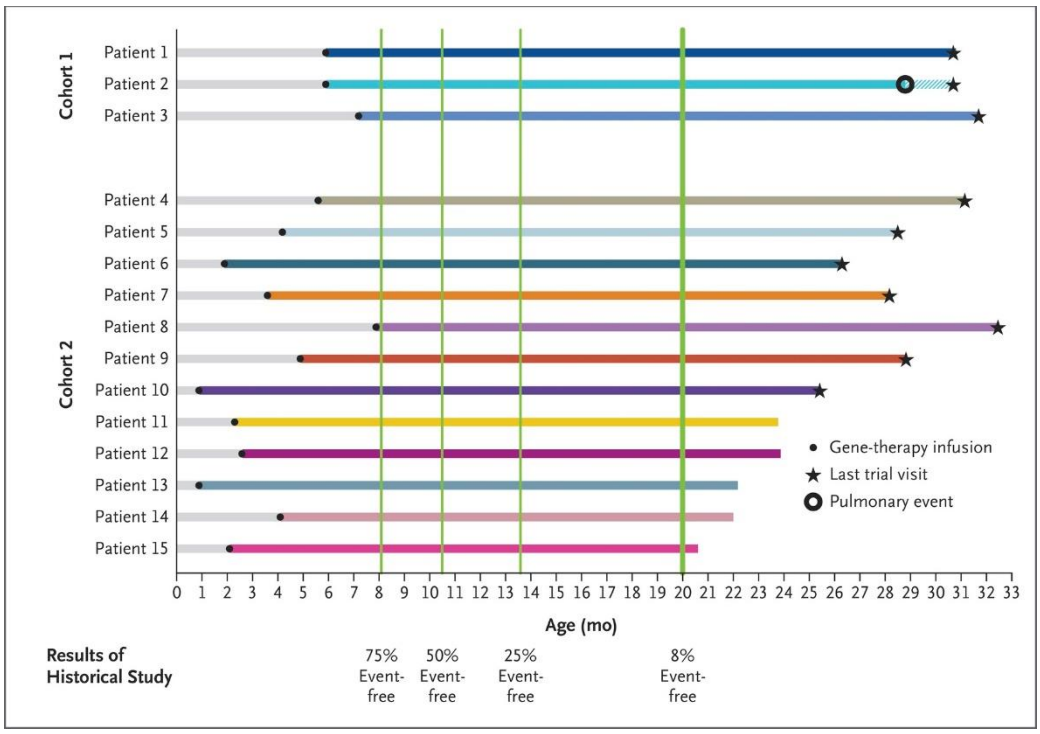
- SMA Type 1 – most common and most severe; often symptomatic within first months of life and fail to reach basic motor milestones, resulting in 8% survival to 20 months
- The phenotypic expression of the mutation is dependent on multiple variables, including the number of copies of survival of motor neuron 2 (SMN). Disease severity in SMA correlates inversely with *SMN2* copy number
- Goal of therapy is to maintain mobility and function as long as possible
    - Multidisciplinary, supportive care including respiratory, nutritional, gastrointestinal, orthopedic, and other support is needed
- CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scale is used to measure motor function in patients with SMA
    - Scores range from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but one of the patients did not reach a score of at least 40 after 6 months of age. In another study, CHOP INTEND scores decreased by a mean of 10.7 points from six months to 12 months of age

CLINICAL EVIDENCE SUMMATION

Clinical Trials:
Mendell et al.; AVXS-CL-101 (PubMed ID #29091557)
ClinicalTrials.gov Identifier: NCT02122952

- **Study Design**: Single-arm, two cohort Phase 1 trial
- **Study Duration**: single-dose followed by on-going monitoring; Median age at their last pulmonary assessment was 30.8 months in cohort 1 and 25.7 months in cohort 2
- **Patient population**: Patients (N=15) with clinically and genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2.
    - Other key inclusion criteria: age at dosing <9 months for the first nine patients and <6 months for the last six patients, disease onset prior to 6 months, and the presence of hypotonia by clinical evaluation with a delay in motor skills, poor head control, round shoulder posture, and hypermobility of the joints.
    - Key exclusion criteria: Patients with the c.859G→C disease modifier in exon 7 of SMN2; active viral infection; use of invasive ventilator support; concomitant use of drugs for the treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the trial; and signs of aspiration based on a swallowing test or are unwilling to use an alternative method to oral feeding.
- **Intervention**: two cohorts, according to the dose of gene therapy that was administered.
    - Cohort 1 (N=3): low dose (6.7×10^{13} vg per kilogram)
    - Cohort 2 (N=12): high dose (2.0×10^{14} vg per kilogram)
        - As a result of serum aminotransferase elevations in Patient 1 in cohort 1, patients 2 through 15 received oral prednisolone 1 mg/kg/day for ~30 days, starting 24 hours before the administration of gene vector.
- **Primary endpoint**: determination of safety based on any treatment-related adverse events of grade 3 or higher.
- **Secondary outcome**: time until death or the need for permanent ventilatory assistance, defined as at least 16 hours of respiratory assistance per day continuously for at least 14 days in the absence of an acute, reversible illness or a perioperative state
- **Results**:
    - Safety: 56 serious adverse events were observed in 13 patients in the two cohorts.
        - Investigators determined that two events were treatment-related grade 4 events
            - Patient 1 (cohort 1) had elevations in alanine aminotransferase [ALT] [31 times the upper limit of the

normal (ULN)] and in aspartate aminotransferase (AST) (14 times ULN). No other liver-function abnormalities or clinical manifestations.
    - Patient 2 (cohort 2) required additional prednisolone to attenuate elevated serum ALT and AST levels (35 times the upper limit of the normal range for ALT and 37 times for AST)
  - 3 non-serious treatment-related events: asymptomatic elevations in serum aminotransferase levels in 2 patients (ALT and AST, both less than 10 times the upper limit of the normal range), which were resolved without additional prednisolone treatment
- Efficacy:
  - 100% of patients reached an age of at least 20 months and did not require permanent mechanical ventilation (compared to 8% in historical cohort)
  - All patients achieved improvements in their motor function
    - 100% had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study.
    - 11 patients attained and sustained scores of more than 40 points.
  - Most patients achieved motor milestones that historical cohort did not achieve
    - 9 of 12 patients in cohort 2 were able to sit unassisted for at 30 seconds
    - 11 patients achieved head control, 9 could roll over, and 2 were able to crawl, pull to stand, stand independently, and walk independently.
    - 11 patients attained the ability to speak. Patients in historical cohort rarely had achieved the ability to speak.



- **GRADE evidence rating**: C
    - Strengths: unmet clinical need; high magnitude of positive clinical effect
    - Limitations: small study size, single-arm, Phase 1 study designed to evaluate safety, qualitative analysis of efficacy results

START - Long-term follow-up from AVXS-101-CL-101 (PubMed ID # N/A; information gathered from poster presentation)
ClinicalTrials.gov Identifier: NCT03421977

- Study Design: observational safety follow-up
- Study Duration: patients rolled over from AVXS-101-CL-101 into this trial for continuous safety monitoring up to 15 years (N=13)
- Patient population: Same as AVXS-101-CL-101
- Intervention: annual in-person follow up study visits for five (5) years, then phone follow-ups annually for ten (10) years
- Primary endpoint: incidence of serious adverse events (SAEs) and Adverse Events of Special Interest
- Results: (from poster, data through 12/31/19)
    - Safety

        - SAEs reported in 8 of 13 patients; most frequent: acute respiratory failure (n=4), pneumonia (n=4), dehydration (n=3), respiratory distress (n=2), bronchiolitis (n=2)
        - All SAEs considered unrelated to treatment, no fatal AEs
    - Efficacy
        - No previously achieved motor milestones have been lost; two patients gained motor milestone of standing with assistance
        - No new initiation of mechanical respiratory support; 6 of 10 (60%) patients required no regular, daily respiratory support more than 4 years after dosing

STR1VE (PubMed ID # N/A)
ClinicalTrials.gov Identifier NCT03306277

- Study Design: Phase 3, open-label, single-arm, single-dose
- Study Duration:
- Patient population: Patients (N=22) with SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 1 or 2 copies of SMN2 (inclusive of the known SMN2 gene modifier mutation (c.859G>C))
    - Other key inclusion criteria: Age <6 months at the time of infusion; swallowing evaluation test performed prior to infusion,
    - Key exclusion criteria: active or acute infection; previous, planned or expected scoliosis repair surgery/procedure during the study assessment period; tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥ 6 hours daily over the 7 days prior to the screening visit; or ≥ 6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing; anti-AAV9 antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay; gestational age at birth < 35 weeks (245 days)
- Intervention: one-time infusion of 1.1×10^{14} vg/kg
- Primary endpoints
    1. Achievement of independent sitting for at least 30 seconds
    2. Event-free survival, defined as the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation
- Secondary outcomes:

1. Ability to thrive, defined as does not receive nutrition through mechanical support or other non-oral method. Ability to tolerate thin liquids as demonstrated through a formal swallowing test. Maintains weight
2. Ventilatory support independence

- Results (per FDA label):
  - Mean age of treatment: 3.9 months
  - Efficacy as of data cutoff
    - 10 of 21 patients (47.6%) achieved the ability to sit without support for ≥30 seconds between 9.2 and 16.9 months of age (mean age was 12.1 months)
    - As of data cut-off, 19 patients achieved event-free survival (age range 9.4-18.5 months), one patient died due to disease progression (age 7.8 months), and one patient withdrew (age 11.9 months)
    - 13 of 19 patients reached age 14 months without permanent ventilation
- GRADE evidence rating: D
  - Strengths: unmet need, large magnitude of effect
  - Limitations: small study size, single-arm, unpublished

SPR1NT (PubMed ID # N/A; information gathered from poster presentation) ClinicalTrials.gov Identifier NCT03505099

- Study Design: Phase 3, open-label, single-arm, single-dose
- Study Duration:
- Patient population: Patients (N=29) divided into two cohorts: 2 or 3 copies of SMN2
- Intervention: one-time infusion of 1.1×10^{14} vg/kg (first patient dosed 4/10/18)
- Primary endpoints
  - Independent sitting for ≥30 seconds at any visit up to 18 months of age
  - Independent standing for ≥3 seconds up to 24 months of age
- Secondary outcomes:
  - Survival at age 14 months
  - Ability to maintain weight without need for feeding support at any visit up to 18 months of age
  - Independent walking for ≥5 steps at any visit up to 24 months
  - Event-free survival, defined as avoidance of death or the need for permanent ventilation
- Results (through 12/31/19): All patients alive and did not use ventilator support of any kind
  - Patients with 2 copies of SMN2

        - Eight patients have achieved independent sitting; other 6 are still within World Health Organization (WHO) developmental window
        - Four patients have achieved independent walking; other 10 are still within WHO developmental window
    - Patients with 3 copies of SMN2
        - Four patients have achieved independent sitting; other 11 are still within WHO developmental window
        - Three patients have achieved independent walking; other 12 are still within WHO developmental window
- GRADE evidence rating: D
    - Strengths: unmet need, large magnitude of effect
    - Limitations: small study size, results only available vis poster (not peer reviewed), single-arm trial and no comparison to historical cohort (some patients with 3 copies of SMN2 would reach these milestones without intervention)

Zolgensma® carries a boxed warning for acute serious liver injury. Liver function should be assessed before initiating therapy and monitored for at least three months after infusion. Systemic steroids need to be administered to all patients before and after infusion with Zolgensma®.

REFERENCE/RESOURCES:

1. Zolgensma package insert. Bannockburn, IL; AveXis, Inc; 2023 March.
2. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713–22.
3. U.S. National Library of Medicine. Long-Term Follow-up Study for Patients From AVXS-101-CL-101 (START). Available at https://clinicaltrials.gov/ct2/show/record/NCT03421977 (Accessed June 24, 2020)
4. Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value Final Evidence Report. Available at https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf (Accessed July 6, 2023)
5. Strauss KA, Swoboda KJ, Farrar MA, et al. AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update. Poster presented at 71st American Academy of Neurology Annual Meeting (AAN). 2019 May 4-10. Philadelphia, PA.
6. Finkel RS, Day JW, Darras BT, et al. Phase 1/2a Study of Intrathecal

Administration of AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 2 (STRONG). Poster presented at 71st American Academy of Neurology Annual Meeting (AAN). 2019 May 4-10. Philadelphia, PA.

7. Day JW, Chiriboga CA, Crawford TO, et al. AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1: Phase 3 Study (STR1VE) Update. Poster presented at 71st American Academy of Neurology Annual Meeting (AAN). 2019 May 4-10. Philadelphia, PA.
8. Strauss KA, Farrar MA, Swoboda KJ et al. Onasemnogene Abeparvovec-xioi in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update as of 31 Dec 2019. 2020 Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, Virtual Poster Session. Available at https://avexis.medicalcongressposters.com/FileUpload/QRPDF/Strauss_1137543%20MDA20%20SPR1NT%20Update%20Poster_4.20.20_A_Final.pdf (Accessed June 24, 2020)
9. Mendell JR, Shell R, Lehman KJ et al. Gene Therapy in Spinal Muscular Atrophy Type 1: Long-Term Follow-Up From the Onasemnogene Abeparvovec Phase 1 Clinical Trial. 2020 Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, Virtual Poster Session, April 2020. Available at https://avexis.medicalcongressposters.com/FileUpload/QRPDF/Mendell_1137550_AveXis_%20MDA%20LTFU%20Poster_4.22.20a_Final.pdf (Accessed June 24, 2020)

Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCHEM036.1223	**HEMATOLOGICAL AGENTS** **ZYNTEGLO®** (betibeglogene autotemcel suspension)
Effective Date: 2/1/2024	**Review/Revised Date**: 11/23 (JCN)
Original Effective Date: 02/23	**P&T Committee Meeting Date**: 12/22, 12/23
Approved by: Oregon Region Pharmacy and Therapeutics Committee Page 1 of 5	

SCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For beta-thalassemia, Zynteglo® may be approved when all the following criteria are met:

1. Documented diagnosis of beta-thalassemia confirmed by genetic testing
2. Patient has transfusion-dependent disease defined as one of the following:
    a. History of transfusions of at least 100 mL/kg/year of packed red blood cells (pRBCs)
    b. Eight or more transfusions of pRBCs per year in the two years preceding therapy
3. Patient is clinically stable and eligible to undergo the pre-conditioning regimen and infusion regimen
4. Patient does not have any of the following:
    a. Prior history of receiving a hematopoietic stem-cell transplant
    b. Prior history of receiving gene therapy for the requested indication
    c. Advanced liver disease (such as evidence of cirrhosis and/or persistent alanine aminotransferase, aspartate transferase or direct bilirubin values greater than three times the upper limit of normal)

d. Evidence of severe iron overload (such as T2* less than 10 ms by magnetic resonance imaging (MRI) or other evidence of severe iron overload in the opinion of treating physician)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
May be approved for patients aged four years and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a hematologist

COVERAGE DURATION:
Authorization will be limited to one treatment course per lifetime

---

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Betibeglogene autotemcel (beti-cel) is the first cell-based gene therapy for the treatment of patients with β-thalassemia who require regular red blood cell (RBC) transfusions. Beti-cel works via a lentiviral vector by adding functional copies of a modified form of the beta-globin gene into a patient's own hematopoietic (blood) stem cells to enable the production of a modified functional adult hemoglobin.[4]

FDA APPROVED INDICATIONS:
Treatment of adult and pediatric patients with β-thalassemia who require regular red blood cell (RBC) transfusions.

POSITION STATEMENT:

- Current standard of care is blood transfusions and iron chelation therapy to manage iron overload. In addition, luspatercept, an erythroid maturation agent, is approved to reduce the number of required transfusions and its efficacy is based on low quality evidence from one phase 3 trial that showed at least a 33% reduction in blood transfusions in adult patients receiving chronic blood transfusions.[1]
- Hematopoietic stem cell transplant (HSCT) is the only other available curative treatment for transfusion dependent β-thalassemia. HSCT requires a matched donor and carries its own risks such as mortality, graft failure/rejection, younger patients have better outcomes.[1]
- Moderate quality evidence based on two phase 3 trials (Northstar-2[2], Northstar-3[3]) and one long-term follow-up trial (LTF 303) that beti-cel may achieve transfusion independence in adult and pediatric patients with beta-thalassemia who require regular red blood cell transfusions.
    - Phase 3 trials and long-term results show up to 7 years of treatment effect with beti-cel; however, the true duration of response remains unclear.
    - Northstar-2 was conducted in 23 patients with beta-thalassemia requiring regular transfusions and with a non-β0/β0 genotype. Northstar-3 was conducted in 18 patients whom had β0 /β0 or non-β0 /β0 genotype. The trials enrolled patients 50 years of age and younger and they were required to be transfusion dependent which was defined as those who had received transfusions of ≥100 ml per kilogram of body weight of packed red cells per year or those who had ≥eight transfusions per year in the 2 years before enrollment. Key exclusion criteria included any evidence of severe iron overload warranting exclusion, a known and available HLA-matched family donor, prior receipt of gene therapy, prior HSCT, and advanced liver disease.
    - Warnings and precautions associated with beti-cel include delayed platelet engraftment, risk of neutrophil engraftment failure, risk of insertional oncogenesis, drug interaction with anti-retroviral and hydroxyurea use, interference with serology testing.[4]
    - Most common adverse reactions (≥ 20%): mucositis, febrile neutropenia, vomiting, pyrexia (fever), alopecia (hair loss), epistaxis (nosebleed), abdominal pain, musculoskeletal pain, cough, headache, diarrhea, rash, constipation, nausea, decreased appetite, pigmentation disorder, and pruritus (itch).[4]
    - Overall, the safety profile is consistent with that of the mobilization and conditioning agents.
    - Thus far, there have been no reports of malignancies or cases of insertional oncogenesis. There were no deaths reported.[4]

REFERENCE/RESOURCES:

1. Farmakis D, Porter J, Taher A, Domenica Cappellini M, Angastiniotis M, Eleftheriou A. 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia. *Hemasphere*. 2022;6(8):e732. doi:10.1097/HS9.0000000000000732
2. Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene Autotemcel Gene Therapy for Non-β0/β0 Genotype β-Thalassemia. *N Engl J Med*. 2022;386(5):415-427. doi:10.1056/NEJMoa2113206
3. bluebird bio. *A Phase 3 Single Arm Study Evaluating the Efficacy and Safety of Gene Therapy in Subjects With Transfusion-Dependent β-Thalassemia by Transplantation of Autologous CD34+ Stem Cells Transduced Ex Vivo With a Lentiviral BA-T87Q-Globin Vector in Subjects ≤50 Years of Age*. clinicaltrials.gov; 2022. Accessed December 15, 2022. https://clinicaltrials.gov/ct2/show/NCT03207009
4. Zynteglo® package insert. Somerville, MA: bluebird bio, Inc.; 2022 Aug.
5. Zynteglo® name In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed September 22, 2022.
6. Zynteglo® In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed November 9, 2023.
7. National Organization for Rare Disorders (NORD). Beta Thalassemia. https://rarediseases.org/rare-diseases/thalassemia-major/#affected-populations (Accessed September 29, 2022).
8. Magrin E, Semeraro M, Hebert N, et al. Long-term outcomes of lentiviral gene therapy for the β-hemoglobinopathies: the HGB-205 trial. Nat Med. 2022 Jan;28(1):81-88. doi: 10.1038/s41591-021-01650-w. Epub 2022 Jan 24. PMID: 35075288.
9. Institute for Clinical and Economic Review. Betibeglogene Autotemcel for Beta Thalassemia: Effectiveness and Value, Final Evidence Report. July 19, 2022.
10. Matthes-Martin S, Pötschger U, Barr R, et al. Costs and Cost-Effectiveness of Allogeneic Stem Cell Transplantation in Children Are Predictable. Biology of Blood and Marrow Transplantation. 2012 Oct;18 (10): 1533-1539.
11. Origa R. Beta-Thalassemia. 2000 Sep 28 [Updated 2021 Feb 4]. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1426/. Accessed November 17, 2022.
12. U.S. Food and Drug Administration Cellular, Tissue, and Gene Therapies Advisory Committee Meeting. June 10, 2022. Accessed November 17, 2022. https://www.fda.gov/advisorycommittees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisorycommittee-june-9-10-2022-meeting-announcement-0609202

13. Taher A, et al. B-Thalassemias.N Engl J Med. 2021;25;384(8):727-743.