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