Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH054.1024	**HEMATOLOGICAL AGENTS COMPLEMENT INHIBITORS** See Table 2 for Applicable Medications
Effective Date: 01/1/2025	**Review/Revised Date**: 08/24 (KN)
Original Effective Date: 08/24	**P&T Committee Meeting Date**: 06/24, 10/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

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.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), NCCN, 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.

REQUIRED MEDICAL INFORMATION:
For ALL REQUESTS:
1. Dose and frequency must be in accordance with FDA-approved labeling
2. The requested agent must not be given concurrently with another Complement Inhibitor (for example Ultomiris® or Empaveli®), or neonatal Fc receptor blocker (for example, Rystiggo®, Vyvgart®, Vyvgart Hytrulo®)

For initiation of therapy (new starts), the following indication-specific criteria must be met:
1. **For Paroxysmal Nocturnal Hemoglobinuria (PNH),** Empaveli, Soliris, Ultomiris, or PiaSky may be covered if the following criteria are met:

a. Documented, confirmed diagnosis of PNH by Flow Cytometric Immunophenotyping (FCMI) using at least two independent flow cytometry reagents on at least two cell lineages (such as red blood cells [RBCs] and white blood cells [WBCs]) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (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 prior to initiating therapy with a complement inhibitor:
    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. For Soliris and PiaSky: Trial and failure, intolerance, or contraindication to ravulizumab-cwvz (Ultomiris®) and pegcetacoplan (Empaveli). Pegcetacoplan may be waived for PiaSky requests in patients less than 18 years of age

2. **For Complement-Mediated Hemolytic Uremic Syndrome (HUS),** Soliris or Ultomiris may be covered if the following criteria are met:
    a. Diagnosis of non-infectious HUS, meaning HUS is not due to infection with Shiga toxin-producing Escherichia coli
    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) prior to initiating therapy with a complement inhibitor
    c. For Soliris®: Trial and failure, intolerance, or contraindication to ravulizumab-cwvz (Ultomiris®)

3. **For Neuromyelitis Optica Spectrum Disorder (NMOSD)**, Soliris or Ultomiris may be covered if the following criteria are met:
    a. 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)
    b. Anti-AQP4 antibody positive

c. Documentation that other alternative diagnoses have been excluded (such as multiple sclerosis)
d. Trial and failure, intolerance (such as neutropenia, LFT elevation, hypogammaglobulinemia) or contraindication to rituximab
e. For Ultomiris®: Trial and failure, intolerance (such as neutropenia, LFT elevation, hypogammaglobulinemia), or contraindication to satralizumab (Enspryng®)
f. For Soliris®: Trial and failure, intolerance (such as neutropenia, LFT elevation, hypogammaglobulinemia), or contraindication to ravulizumab-cwvz (Ultomiris®) and satralizumab (Enspryng®)

4. **For Generalized Myasthenia Gravis (gMG)**, Soliris or Ultomiris may be covered if the following criteria are 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 at least four infusions/ year of either intravenous immunoglobulin (IVIg) OR plasma exchange (PE)
    e. For Soliris®: Trial and failure, intolerance, or contraindication to ravulizumab-cwvz (Ultomiris®)

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

1. For **PNH**, reduced LDH levels, reduced transfusion requirements, increase or stabilization of hemoglobin levels, or improvement in symptoms
2. For **HUS**, improvement in at least two thrombotic microangiopathy endpoints, such as:
    a. Maintenance of platelet counts (i.e., improvements or reductions less than 25%)
    b. Reductions in LDH
    c. Reduction in number of needed plasmapheresis or plasma infusion events
    d. Improvement in kidney function
3. For **NMOSD**, positive clinical response as defined by a reduction in relapses
4. For **MG,** documentation of sustained improvement in MG-ADL by at least two points from baseline

EXCLUSION CRITERIA: N/A

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

PRESCRIBER RESTRICTIONS:
- PNH or aHUS: 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:
The complement system is a system composed of over 50 proteins that is involved in the innate immune response. When unregulated, this system may lead to numerous diseases including paroxysmal nocturnal hemoglobinuria (PNH). Several drugs have been developed to target the complement system (see Table 1) and treat PNH as well as atypical hemolytic uremic syndrome, myasthenia gravis, and neuromyelitis optica spectrum disorder[13].

FDA APPROVED INDICATIONS:
Table 1. Complement Inhibitors and their respective FDA-approved ages and indications

Drug	Drug Class	aHUS	gMG	NMOSD	PNH
Empaveli (pegcetacoplan)	Complement (C3) Inhibitor				X (age 18+)

PiaSky (crovalimab-akkz)	HmAb Complement (C5) inhibitor				X (age 13+)
Soliris (eculizumab)	HmAb Complement (C5) inhibitor	X (age 2 months+)	X (age 18+)	X (age 18+)	X (age 18+)
Ultomiris (ravulizumab-cwvz)	HmAb Complement (C5) inhibitor	X (age 1 month+)	X (age 18+)	X (age 18+)	X (age 1 month+)

Abbreviations: aHUS = Atypical Hemolytic Uremic Syndrome, gMG = Generalized Myasthenia Gravis, NMOSD = Neuromyelitis Optica Spectrum Disorder, PNH = Paroxysmal Nocturnal Hemoglobinuria, HmAb = human monoclonal antibody

Limitation of Use: Soliris/Ultomiris 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 from a mutation in the phosphatidylinositol glycan class A (PIGA) gene of hematopoietic stem cells and is characterized by destruction of red blood cells by the complement system. Intravascular hemolysis results in the release of free hemoglobin, causing toxic effects including hypercoagulability. C3 fragments not destroyed by the membrane attack complex may also accumulate on the surface of cells causing extravascular hemolysis. C5 inhibitors block the final step of the complement pathways while Factor B, D, and C3 inhibitors exert their actions further up in the pathway.

Clinical symptoms associated with PNH include headache, fever, abdominal and back, and fatigue. Hemolytic anemia, venous thrombosis, and other cytopenias related to bone marrow failure syndrome are considered in the differential diagnosis of PNH. Although allogeneic hematopoietic stem cell transplantation is considered a curative treatment, it is typically only used for patients with life-threatening disease due to the significant morbidity and mortality associated with it.[2]

Eculizumab is a monoclonal antibody approved for PNH which blocks the terminal complement pathway by binding to the C5 protein. When compared to placebo, eculizumab treatment resulted in improved survival and was well-tolerated.[2]

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 which provided a moderate quality of evidence 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.[11,12]

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.

Hemolytic uremic syndrome (HUS)
Hemolytic uremic syndrome (HUS) is defined by hemolytic anemia, thrombocytopenia, 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 eligible 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.

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 8 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, ravulizumab 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 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.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

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. 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).[9] AQP4 autoantibodies are detected in approximately 80% of patients with NMOSD.[10]

Although off-label, azathioprine and mycophenolate mofetil have been utilized to effectively reduce NMOSD attacks for over 20 years in patients with both AQP4-IgG-positive and -negative patients. They are both considered inferior to rituximab.[10]

There are four monoclonal antibody immunotherapies approved for patients with AQP4-IgG-positive NMOSD which have shown efficacy in the treatment of AQP4-

IgG-positive NMOSD, eculizumab, inebilizumab, satralizumab, and ravulizumab. Their targets are as follows:

- Eculizumab: complement protein C5
- Inebilizumab: B cells through the CD19 antigen
- Ravulizumab: complement protein C5
- Satralizumab: Interleukin-6 (IL6)[10]

Of note, the efficacy of rituximab in reducing NMOSD attacks by over 80% has been demonstrated by multiple studies over the last 15 years with one of the most recent studies resulting in its approval for NMOSD in Japan.[10]

Due to the rarity of the condition, comparator trials would not be feasible as thousands of patients would need to be enrolled.[10]

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
Life-threatening and fatal meningococcal infections have occurred in patients treated with Soliris and Ultomiris. 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/Ultomiris, 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/Ultomiris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

REFERENCE/RESOURCES:

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5. 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.
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11. 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.
12. 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.
13. Gavriilaki E, Peffault de Latour R, Risitano AM. Advancing therapeutic complement inhibition in hematologic diseases: PNH and beyond. Blood 2022:139(25):3571-3582.

Table 2. HCPCS Codes

Brand Name	Generic Name	Drug Class	HCPCS Codes
Empaveli	pegcetacoplan	Complement (C3) inhibitor	J7799/C9399
PiaSky	crovalimab	HmAb Complement (C5) inhibitor	J3590/C9399
Soliris	eculizumab	HmAb Complement (C5) inhibitor	J1300
Ultomiris	ravulizumab-cwvz	HmAb Complement (C5) inhibitor	J1303