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Drug Class Update: Select Biologics for Rare Conditions

Date of Review: February 2023

Date of Last Review: December 2021
Dates of Literature Search: 01/01/2021 – 10/21/2022

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This review looks at new evidence for specialized medicines (eculizumab, inebilizumab, satralizumab, ravulizumab, efgartigimod alfa and pegcetacoplan) used to treat 4 rare diseases. These medicines work in different ways to block triggers that cause the immune system to attack itself.
- The Food and Drug Administration has approved these medicines to treat specific conditions:
    - Eculizumab to treat myasthenia gravis, parxoysmal nocturnal hemoglobinura, atypical hemolytic uremic syndrome, and neuromyelitis optica spectrum disorder.
    - Inebilzuamb and satralizumab to treat neuromyelitis optica spectrum disorder.
    - Ravlizumab to treat adults and children with atypical hemolytic uremic syndrome, parxoysmal nocturnal hemoglboinura and myasthenia gravis.
    - Efgartigimod alfa to treat myasthenia gravis.
    - Pegcetacoplan to treat adults with paroxysmal nocturnal hemoglobinura.
- Myasthenia gravis is a long-term condition which causes certain eye, arm, leg, and lung muscles to become weak and tired. This affects people's vision and their ability to talk, swallow, breathe, and walk.
- Ravulizumab recently received approval to treat myasthenia gravis. The study lasted 26 weeks and 175 adults with myasthenia gravis were included in this study. At 26 weeks, patients treated with ravulizumab had more improvement in the ability to conduct "activities of daily living" (i.e., talk, chew, brush teeth, get up from a chair) than those who received no medicine.
- Paroxysmal nocturnal hemoglobinuria is a rare condition in which red blood cells are attacked by the body's immune system and fall apart. Red blood cells carry oxygen to tissues inside the body. When the red blood cells fall apart, the hemoglobin inside the cells is released. When there are not enough red blood cells, also known as anemia, people can feel tired, out of breath, and tend to bruise or bleed easily. People with this condition need to get frequent blood transfusions to relieve pain, fatigue, and shortness of breath.
- Atypical hemolytic uremic syndrome occurs when red blood cells break apart and blood clots form in the small blood vessels, which can lead to kidney damage, high blood pressure, and anemia. Children and adults are both affected by this condition.
- Neuromyelitis optica spectrum disorder occurs when the immune system attacks the nerves in the eyes and central nervous system. This can lead to the nerves of the eyes or the spinal cord becoming inflamed. Inflammation of the nerves of the eyes causes pain when moving the eyes and loss of vision. Spinal

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cord inflammation can happen to different parts of the spinal cord and may cause muscle spasms and weakness leading to back pain, leg pain and bladder or bowel dysfunction. These symptoms are most severe during an attack or relapse of neuromyelitis optica spectrum disorder.

- Providers must explain to the Oregon Health Authority why someone needs eculizumab, inebilizumab, satralizumab, ravulizumab, efgartigimod alfa or pegcetacoplan before Medicaid will pay for it. This process is called prior authorization.

Purpose for Class Update:

Review evidence for the complement inhibitor, ravulizumab, which was recently Food and Drug Administration (FDA) approved for treatment of generalized myasthenia gravis (gMG), and assess new evidence for other biologic immunosuppressive agents used to treat rare conditions including gMG, paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic-uremic syndrome (aHUS), and neuromyelitis optica spectrum disorder (NMOSD).

Research Questions:

- What is the comparative efficacy or effectiveness of biologic immunosuppressants indicated for treating gMG, PNH, aHUS, and NMOSD?
- What are the comparative harms of biologic immunosuppressants in patients with gMG, PNH, aHUS, and NMOSD?
- Are there certain sub-populations (based on age, gender, race, ethnicity, comorbidities, disease duration or severity) in which eculizumab, ravulizumab inebilizumab, pegcetacoplan, efgartigimod alfa, or satralizumab may be more effective or cause more harm?

Conclusions:

- Since the last review of this class, one Cochrane review evaluated the safety and efficacy of eculizumab and ravulizumab in people with aHUS.[1] Four new guidelines were also recently published, with recommendations for treatment of NMOSD with satralizamb,[2] use of ravulizumab for treatment of aHUS,[3] and use of ravulizumab or pegcetacoplan for management of people with PNH.[4,5]
- A March 2021 Cochrane systematic review evaluated the benefits and harms of 2 treatments for aHUS.[1] After 26 weeks of eculizumab therapy, a 70% reduction in the number of patients requiring dialysis and complete thrombotic macroangiopathic response was observed in 60% of treated patients (4 studies; n=100 adults and children).[1] After 26 weeks of ravulizumab therapy, complete thrombotic macroangiopathic response was observed in 54% of patients and a 59% reduction in the number of patients requiring dialysis (1 study; n=58 adults).[1] All studies had a high risk of bias. Serious adverse events (SAEs) occurred in 37% of patients who received eculizumab, and meningococcal infection occurred in 2 patients. Serious adverse events occurred in 52% of patients treated with ravulizumab and no meningococcal infections were reported in this study.[1] When compared with historical data, treatment with eculizumab or ravulizumab appears to offer favorable outcomes in patients with aHUS, based upon very low-quality evidence.[1] Longer term follow-up data are needed to better understand treatment duration, adverse outcomes and risk of disease recurrence associated with these 2 therapies.[1]
- There is insufficient evidence to base conclusions on the comparative safety and efficacy of biologic agents approved to treat NMOSD, gMG, aHUS and PNH specific to demographic characteristics, socioeconomic status, concomitant medications, severity of disease, or co-morbidities, for individuals with these rare conditions.
- In April 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued recommendations for the use of satralizumab in people with NMOSD who are anti-aquaporin-4 (AQP4) positive.[2] Patients must have had at least 1 relapse of NMOSD in the 12 months before initiation despite an adequate trial of other accessible preventive treatments for NMOSD, or the patient cannot tolerate other preventive treatments for NMOSD (i.e., azathioprine, mycophenolate, rituximab).[2]
- In June 2021, the National Institute for Health and Care Excellence (NICE) published guidance for the use of ravulizumab as an option for treating aHUS in people weighing 10 kg or more or more who have not received a complement inhibitor before or who have responded to 3 months of eculizumab.[3]

- In March 2022, CADTH published recommendations for the use of ravulizumab in patients with PNH.[4] Only patients with adequate treatment response to eculizumab are eligible to switch directly to ravulizumab.[4]
- In March 2022, NICE issued guidance for the use of pegcetacoplan as an option for treating PNH. Adults who continue to have anemia after at least 3 months of treatment with a C5 inhibitor (i.e, eculizumab, ravulizumab) are eligible to switch to pegcetacoplan.[5]
- In April 2022, ravulizumab (ULTOMIRIS) received expanded FDA-approval for treatment of adult patients with anti-acetylcholine receptor (AChR) antibody positive gMG.[6]
- A new subcutaneous (SC) formulation of ravulizumab was approved in July 2022 for use in adults with PNH and aHUS after efficacy was demonstrated in adults weighing more than 40 kg with PNH.[6]

Recommendations:
- Recently published clinical evidence does not support any changes to the Preferred Drug List (PDL).
- Revise clinical prior authorization (PA) criteria for ravulizumab to include use in adults with generalized MG who are anti-AChR antibody positive and update dosing guidance for use in MG. Add SC dosing recommendations for adults with PNH and aHUS to ravulizumab PA criteria.
- Update select PA criteria to support individualized review for members younger than 21 years of age who have an unfunded diagnosis, to evaluate whether medically appropriate and necessary.
- After evaluation of costs in the executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy:
- In April 2021, the Pharmacy and Therapeutics (P&T) Committee reviewed evidence for eculizumab, inebilizumab, and satralizumab, which had received FDA approval for the treatment adults with NMOSD. The committee approved recommendations to: 1) create a new class of drugs on the PDL entitled "Biologics for Rare Diseases" and include eculizumab, inebilizumab, satralizumab in this new class; 2) implement clinical PA criteria for each monoclonal antibody to ensure appropriate utilization in FDA-approved indications funded by Oregon Health Plan (OHP); and 3) make eculizumab non-preferred and to add satralizumab and inebilizumab to the PDL.
- At the same April meeting, the evidence for the use eculizumab of in treating PNH, aHUS and gMG was reviewed and ravulizumab for PNH and aHUS in adults was reviewed. The P&T Committee approved to add ravulizumab to the "Biologics for Rare Diseases" drug class as a non-preferred agent with clinical PA criteria to ensure safe and appropriate use.
- In December 2021, the P&T Committee reviewed pegcetacoplan for treatment of adults with PNH. The Committee approved to add pegcetacoplan to the "Biologics for Rare Diseases" drug class with clinical PA criteria to ensure appropriate use and maintain pegcetacoplan as non-preferred. In addition, clinical PA criteria for ravulizumab were revised to reflect the expanded indication for use in pediatric patients aged 1 month and older with PNH or aHUS.
- In April 2022, the P&T Committee reviewed efgartigimod for treatment of gMG. The Committee approved to maintain efgartigimod as non-preferred in the "Biologics for Rare Diseases" drug class with clinical PA criteria to ensure safe and appropriate use.
- For the class of "Biologics for Rare Diseases" ravulizumab, inebilizumab, and satralizumab are preferred on the PDL (**Appendix 1)**, and all the other agents are non-preferred. All medications in this class require PA (**Appendix 3**).

Background:
Eculizumab is FDA-approved for 4 indications including: 1) reducing hemolysis in patients with PNH; 2) inhibiting complement-mediated thrombotic microangiopathy in patients with aHUS; 3) treatment of adults with anti-AChR antibody positive gMG; and 4) treatment of adults with anti-AQP4 antibody

positive NMOSD.[7] Inebilizumab and satralizumab are FDA-approved for the treatment of adults with anti-AQP4 antibody positive NMOSD.[8,9] Pegcetacoplan is FDA-approved for treatment of adults with PNH.[10] Ravulizumab, a C5 complement inhibitor engineered from eculizumab, is FDA-approved for treatment of PNH and aHUS, and was recently approved for treatment of gMG.[6] Efgartigimod is approved for treatment of adults with anti-AChR antibody positive gMG.[11] A summary of these medications, their mechanism of action, and their FDA-approved indications is presented in **Table 1**.

Table 1. FDA Indications of Biologics for Rare Diseases in Adults (Unless Otherwise Noted)[12]

Medication	Mechanism of Action	aHUS	gMG (ANTI-AChR antibody positive)	PNH	NMOSD (anti-AQP4 antibody positive)
Eculizumab (SOLIRIS)	C5 complement inhibitor	X	X	X	X
Efgartigimod alfa (VYVGART)	Neonatal Fc receptor blocker		X		
Inebilizumab (UPLINZA)	CD19 inhibitor (B-cell surface antigen)				X
Pegcetacoplan (EMPAVELI)	C3 complement inhibitor			X	
Ravulizumab (ULTOMIRIS)	C5 complement inhibitor	X (Patients 1 month of age and older)	X	X (Patients 1 month of age and older)	
Satralizumab (ENSPRYNG)	IL-6 inhibitor				X

Abbreviations: aHUS=atypical hemolytic uremic syndrome; AChR=acetylcholine receptor; AQP4=aquaporin-4; Fc=crystallizable fragment; FDA=Food and Drug Administration; gMG=generalized myasthenia gravis; IL=interleukin; NMOSD=neuromyelitis optica spectrum disorder; PNH=paroxysmal nocturnal hemoglobinuria

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder in which antibodies to acetylcholine receptors bind at the post-synaptic neuromuscular junction of skeletal muscles.[13] The thymus gland is thought to produce the anti-AChR antibodies which disrupt neuromuscular transmission.[13] The estimated prevalence of MG is 14 to 20 cases per 100,000 people, or approximately 36,000 to 60,000 cases in the United States.[13,14] Myasthenia gravis occurs at any age, but there tends to be a bimodal distribution to the age of onset, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decade (male predominance).[13] Myasthenia gravis presentation can be broadly classified as ocular or generalized MG. It characteristically presents with muscle weakness that worsens with repeated use (fatigable weakness), often initially involving the ocular muscles and manifesting as intermittent ptosis and diplopia.[15] Ultimately, the disease generalizes throughout the body in two-thirds of patients, leading to weakness of bulbar, neck, limb, and respiratory muscles.[15] In the most common type of MG, autoantibodies are produced that target the AChR, reducing the number of functional AChRs, and causing morphological damage to the endplate membrane, resulting in the clinical phenotype of fatigable muscle weakness.[16] Approximately 85% of people with MG test positive for AChR antibodies.[17] In AChR antibody-positive MG, the production of autoantibodies by pathogenic B cells is T cell-dependent.[16]

The Myasthenia Gravis Activities of Daily Living (MG-ADL) is a patient-reported, physician administered scoring tool.[18] Eight domains (talking, chewing, swallowing, breathing, ability to brush teeth, ability to arise from chair, vision and eyelid droop) are scored on a scale of 0 (normal) to 3 (severe).[18] A total score of 24 is possible; higher scores indicate more disability.[19] A 2-point reduction in the MG-ADL score is considered meaningful clinical improvement.[18] The Quantitative Myasthenia Gravis (QMG) score is a validated 13-item disease-severity physician-reported assessment tool.[20] This tool evaluates muscle strength based on quantitative testing of sentinel muscle groups: ocular (two items), facial (one item), bulbar (two items), gross motor (six items), axial (one item), and respiratory (one item).[20] The scores are not weighted, but each item is graded on a scale of 0 (no weakness) to 3 (severe weakness).[20] Total scores range from 0 to 39, higher scores represent greater disease burden.[20] A 3-point reduction in QMG total score considered clinically meaningful improvement.[21]

Novel biological agents offer selective, target-specific immunotherapy for MG refractory to initial therapy with anticholinesterase inhibitors (i.e., pyridostigmine) or systemic corticosteroids.[14] Complement inhibitors, anti-interleukin antibodies, and B-cell inhibitors are some of the immunomodulators currently being evaluated in clinical trials for MG treatment.[14] Neonatal Fc receptor inhibitors prevent immunoglobulin recycling and cause rapid reduction in pathogenic antibody levels.[22] In October 2019, the Myasthenia Gravis Foundation of America (MGFA) appointed a task force to update treatment guidance for MG.[23] The MGFA guidance recommends eculizumab be considered in the treatment of severe, refractory, anti-AchR antibody-positive gMG.[23] Until further data become available to allow comparisons of cost and efficacy with other treatments, eculizumab should be considered after trials of other immunotherapies (i.e., ravlizumab, efgartigimod) have been unsuccessful in meeting treatment goals.[23] The 3 FDA-approved biologic treatments for adults with gMG who are anti-AChR antibody-positive are presented in **Table 2**.

Table 2. FDA-Approved Biologic Treatments for Adults with Generalized Myasthenia Gravis[6,7,11]

	Eculizumab (SOLIRIS)	**Ravulizumab (ULTOMIRIS)**	**Efgartigimod Alfa (VYVGART)**
Administration Route	Intravenous Infusion	Intravenous Infusion	Intravenous Infusion
Recommended Dose	-Loading Dose: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 -Maintenance Dose: 1,200 mg every 2 weeks	-Loading Dose: 2,400 mg to 3,000 mg per weight-based recommendations as a single dose -Maintenance Dose: 3,000 mg to 3,600 mg per weight-based recommendations every 8 weeks 2 weeks after the loading dose.	10 mg/kg (maximum dose 1.2 g) once weekly for 4 weeks. Subsequent treatment cycles may be administered based on clinical evaluation and no sooner than 50 days from the start of the previous treatment cycle.
Primary Binding Target	Complement Protein C5		Neonatal Fc Receptor
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*		-Immunization with live vaccines during treatment
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections		None
Abbreviations: Fc = crystallizable fragment; g = grams; kg = kilograms; mg = milligrams; REMS = Risk Evaluation and Mitigation Strategies			

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare, complement-mediated hemolytic anemia, with occurrence estimated as high as 15.9 individuals per million worldwide.[24] This condition presents with a variety of symptoms, the most prevalent of which are aplastic anemia, hemoglobinuria, fatigue and shortness of breath.[25] Other findings associated with PNH include thrombosis, renal insufficiency, and in the later course of the disease, bone marrow failure.[25] The rarity of the disease and nonspecific symptoms can result in significant delays in diagnosis.[25] The condition is genetic, with the mutations occurring on the X-linked gene.[25] This mutation of the X-linked gene phosphatidylinositol glycan class A (PIGA) produces a deficiency in the glycosylphosphatidylinositol (GPI) protein,

which is responsible for anchoring other protein moieties to the surface of erythrocytes.[25] A chronic state of hemolysis ensues and can be exacerbated if the complement system is activated by stress due to surgery, trauma, or other triggers for inflammation.[25] Intravascular hemolysis with moderate to severe anemia, an elevated reticulocyte count, and up to a 10-fold increase in LDH levels are common in classic PNH.[26] Abdominal pain, esophageal spasm, dysphagia, and erectile dysfunction are common symptoms associated with classic PNH and are a direct consequence of intravascular hemolysis and the release of free hemoglobin.[26]

Complement inhibitor treatment can relieve PNH-associated symptoms, eliminate transfusion dependence, prevent thrombosis, and relieve pain, but it does not mitigate aplastic anemia. Allogeneic hematopoietic stem cell transplantation is the only curative treatment for PNH.[27] Pegcetacoplan can inhibit both intravascular and extravascular hemolysis; by contrast, ravulizumab and eculizumab target C5, which affects only intravascular hemolysis. National Institute for Health and Care Excellence guidance from 2021 recommends ravulizumab as an option for treating PNH in adults when hemolysis and clinical symptoms suggest high disease activity or disease is clinically stable after eculizumab treatment for at least 6 months.[28] A comparison of the 3 FDA-approved biologic agents to treat PNH is presented in **Table 3**.

Table 3. FDA-Approved Biologic Treatments for Paroxysmal Nocturnal Hemoglobinuria[6,7,10]

	Eculizumab (SOLIRIS)	**Ravulizumab (ULTOMIRIS)**	**Pegcetacoplan (EMPAVELI)**
Administration Route	Intravenous	Intravenous or Subcutaneous	Subcutaneous
Approved Age Range	Adults	Adults and pediatric patients 1 month of age and older	Adults
Recommended Dose	-Loading Dose: 600 mg at weeks 0, 1, 2, 3 and 900 mg at week 4 -Maintenance Dose: 900 mg every 2 weeks	<u>Adult</u> -Loading Dose: • 2,400 mg to 3,000 mg IV single dose per weight-based recommendations -Maintenance Dose: • 3,000 mg to 3,600 mg IV every 8 weeks per weight-based recommendations OR • 490 mg SC once a week starting 2 weeks after IV loading dose. Must weigh $\geq$ 40 kg <u>Pediatric</u> -Loading Dose: • 600 mg to 1,200 mg IV single dose per weight-based recommendations -Maintenance Dose: • 300 mg to 2,700 mg IV every 4 to 8 weeks per weight-based recommendations	1,080 mg SC twice weekly
Primary Binding Target	Complement Protein C5		Complement Protein C3
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*		-Unresolved serious infection caused by encapsulated bacteria

		-Not vaccinated against encapsulated bacteria
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	Mandatory REMS program due risk of life-threatening and fatal meningococcal infections and infections caused by encapsulated bacteria (i.e., *S. pneumoniae and H. influenzae*)
Abbreviations: IV = intravenous; REMS = Risk Evaluation and Mitigation Strategies; SC = subcutaneous		

Atypical Hemolytic-Uremic Syndrome

Atypical HUS can present at any age and is of acute onset in 20% of cases.[29] Approximately 35% to 42% of cases occur in children under the age of 18 years.[30] The clinical presentation depends upon the extent of microvascular injury and thrombosis, as well as ischemic injury to various organ systems.[29] Patients with aHUS present with hemolytic anemia, thrombocytopenia and impaired renal function. Renal impairment is frequent; the most common manifestations are proteinuria, hematuria, hypertension, and azotemia.[29] A majority of patients require chronic renal replacement therapy.[29] Hypertension is often moderate to severe, due to vascular disease and volume expansion.[29] Atypical HUS presents as a systemic disease, and extra-renal features are seen in 20% and a catastrophic presentation with multi-organ involvement in 5% of patients.[29]

This uncommon disorder is caused by a genetic abnormality in the complement alternative pathway resulting in over-activation of the complement system and formation of microvascular thrombi.[29] Abnormalities of the complement pathway may be in the form of mutations in key complement genes or autoantibodies against specific complement factors. By preventing membrane attack complex formation, eculizumab and ravulizumab inhibit the mechanism by which aHUS causes pathology, making these drugs effective treatments for people with aHUS.[29] Eculizumab is approved for treatment of aHUS in pediatric and adult patients.[7] Eculizumab dosing for aHUS in adults begins with a 900 mg loading dose every week for 4 weeks, followed by 1,200 mg for the fifth dose, and then 1,200 mg every 2 weeks thereafter.[7] Dosing for children weighing more than 5 kg is weight-based for induction and maintenance dosing.[7] Ravulizumab is approved for treatment of aHUS in adults and pediatric patients 1 month of age and older. Intravenous dosing of ravulizumab in patients with aHUS is the same as the recommended PNH dosing (**Table 3**). Subcutaneous dosing of ravulizumab is not approved for use in pediatric patients.[6]

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder is a rare, autoimmune, severe demyelinating disease of the CNS that predominantly involves inflammation of the optic nerve and spinal cord.[31] The pathogenesis is unknown, but it appears to be related to B-cell autoimmunity directed against aquaporin-4, the dominant water channel in the central nervous system.[31] Features of NMOSD include acute attacks of rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course.[31] Neuromyelitis optica had long been considered a subtype of multiple sclerosis (MS) due to the similarities between the clinical presentations of MS and NMOSD.[32] However, recent evidence indicates NMOSD is usually associated with a specific biomarker, AQP4-immunoglobulin-G (IgG) antibody, which differentiates NMOSD from MS.[33] The prevalence of NMOSD is estimated at around 0.1 to 10 persons per 100,000 individuals, affecting approximately 15,000 individuals in the United States.[33] A 2019 to 2020 review of medical claims in the Oregon Medicaid population shows approximately 0.4 persons per 100,000 individuals have a diagnosis of NMOSD. The reported incidence of NMOSD in women is up to 10 times higher than in men.[34] It is difficult to determine exact prevalence rates as many NMOSD cases are never diagnosed and many others are misdiagnosed as MS.[32]

The EDSS score is a quantitative measure of disability based on a standard neurological examination.[2] Validity of this tool has been established in patients with MS, but not NMOSD.[2] The EDSS is an ordinal scale that ranges from 0 points (normal exam) to 10 points (death) that increases in half-points increments once an EDSS of 1.0 has been reached.[2] An EDSS score of 1.0 to 4.5 refers to people who are fully ambulatory, with scores of 5.0 to 9.5 defined as impaired ambulation.[2] No minimal clinically important difference (MCID) has been defined for patients for NMOSD. In patients with MS with a baseline EDSS score of 1 to 5.5, the MICID is an increase of 1.0 points. When the baseline EDSS score is 6 or greater, a 0.5 increase in EDSS score is considered clinically important.[2] The 3 FDA-approved biologics for adults with NMOSD who are anti-AQP4 antibody positive are presented in **Table 4**.

Table 4. FDA-Approved Treatments for Adults with Neuromyelitis Optica Spectrum Disorder[7-9]

	Eculizumab (SOLIRIS)	**Inebilizumab-cdon (UPLIZNA)**	**Satralizumab-mwge (ENSPRYNG)**
Administration Route	Intravenous	Intravenous	Subcutaneous
Recommended Dose	-Loading Dose: 900 mg at weeks 0, 1, 2, 3 and 1200 mg at week 4 -Maintenance Dose: 1200 mg every 2 weeks	-Loading Dose: 300 mg at weeks 0, 2 -Maintenance Dose: 300 mg every 6 months	-Loading Dose: 120 mg at weeks 0, 2, 4 -Maintenance Dose: 120 mg every 4 weeks
Primary Binding Target	Complement Protein C5	CD19 on B cells	IL-6 Receptor
Contraindications	-Unresolved *Neisseria meningitides* infection -Not vaccinated against *Neisseria meningitides*	-Active Hepatitis B infection -Active or Untreated Tuberculosis	
Boxed Warning	Mandatory REMS program due to life-threatening and fatal meningococcal infections	None	
Abbreviations: IL=interleukin; mg=milligram; REMS = Risk Evaluation and Mitigation Strategies			

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane: Interventions for Atypical Hemolytic Uremic Syndrome

A March 2021 Cochrane systematic review evaluated the benefits and harms of 2 biologic treatments for aHUS.[1] Literature was searched through September 2020 for all RCTs and non-randomized clinical trials.[1] Given the rare incidence of aHUS, prospective single-arm studies were also included in the review.[1] Five single-arm studies which evaluated terminal complement inhibition for the treatment of aHUS met inclusion critieria.[1] All patients had evidence of renal

impairment, thrombocytopenia and hemolysis (LDH above the upper limit of normal).[1] Four studies evaluated eculizumab in children and adults (n=100) and one study evaluated ravulizumab in adults (n=58).[1] All included studies were of non-randomized, single-arm design with a high risk of bias.[1]

In the eculizuamb studies, 37/100 patients were undergoing dialysis at the initiation of eculizuamab therapy.[1] Of these patients, 26 discontinued regular dialysis after 26 weeks of eculizumab treatment which represents a 70% reduction in the number of patients requiring dialysis.[1] In the ravulizuamb study, dialysis was discontinued in 17/29 (59%) of patients who required dialysis at baseline.[1] Complete thrombotic macroangiopathic response was achieved in 60% of patients at 26 weeks and 65% of patients at two years after treatment with eculizumab.[1] After 26 weeks of ravulizumab therapy, complete thrombotic macroangiopathic response was achieved in 54% of patients and a 59% reduction in the number of patients requiring dialysis was observed.[1] Substantial improvements were seen in estimated glomerular filtration rate and health-related quality of life in both eculizumab and ravulizumab studies.[1] However, it is challenging to draw firm conclusions from this low-quality evidence.[1]

Serious adverse events occurred in 37% of patients treated with eculizumab. The types of SAEs were not[35] reported. The most commonly reported adverse events (AEs) included diarrhea (23%), fever (21%), headache (19%), upper respiratory tract infection (19%), cough (17%) and urinary tract infection (10%).[1] Meningococcal infection occurred in 2 patients (2%) treated with eculizumab.[1] Both patients had received meningococcal vaccination against serogroups A, C, W, and Y but had not been prescribed long-term antibiotics.[1] Serious adverse events occurred in 52% of patients treated with ravlizumab.[1] The most commonly reported SAEs with ravulizumab included malignant hypertension (3%) and infections including pneumonia (5%), and septic shock (3%).[1] The most commonly reported AEs included headache (36%), diarrhea (31%), vomiting (26), hypertension (22%), nausea (22%) and urinary tract infection (17%).[1] No patients treated with ravulizumab developed meningococcal infection.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria),[35] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[36-38]

New Guidelines:

Canadian Agency for Drugs and Technologies in Health: Satralizumab for Treating Neuromyelitis Optica Spectrum Disorder

In April 2021, CADTH issued recommendations for the use of satralizumab in NMOSD.[2] Evidence from 2 RCTs demonstrated that satralizumab, alone or in combination with immunosuppressants (i.e., corticosteroids, azathioprine, or mycophenolate), reduced the frequency of NMOSD relapses compared with placebo.[2] Only two-thirds of patients enrolled in these RCTs were AQP4 antibody-positive.[2] The trials did not report health-related quality of life or disability outcomes for the AQP4 antibody–positive subgroup.[2] Direct comparative efficacy and harms data for satralizumab versus immunosuppressants, eculizumab, or rituximab are presently unavailable.[2]

- CADTH Recommendation: Satralizumab should only be covered to treat patients who have NMOSD that is AQP4 positive.[2] Patients must have had at least 1 relapse of NMOSD in the 12 months before initiation despite an adequate trial of other accessible preventive treatments for NMOSD, or the patient cannot tolerate other preventive treatments for NMOSD (i.e., azathioprine, mycophenolate, rituximab). Patients must have an EDSS score of 6.5 points or less to begin treatment, as this was required in the 2 RCTs that showed improvement in reducing NMOSD replapses with satralizumab.[2]

National Institute for Health and Care Excellence: Ravulizumab for Treating Atypical Hemolytic Uremic Syndrome

In June 2021, NICE published guidance for the use of ravulizumab in treating aHUS in people weighing 10 kg or more.[3] Clinical trial evidence suggests that ravulizumab is effective for treating aHUS, but ravulizumab has not been compared directly with eculizumab.[3] The results of indirect comparisons are uncertain, but it is likely that ravulizumab and eculizumab are equally effective because they both inhibit complement C5.[3] Because ravulizumab is administered less

frequently than eculizumab (every 8 weeks versus every 2 weeks) it may improve quality of life and access to care.[3] Ravulizumab costs less than eculizumab and the cost-effectiveness estimates are within what NICE normally considers an acceptable use of National Health Service (NHS) resources.[3]

- NICE Recommendation: Ravulizumab is an option for treating aHUS in people weighing 10 kg or more who have not a complement inhibitor before or whose disease has responded to 3 months of eculizumab treatment.[3]

Canadian Agency for Drugs and Technologies in Health: Ravulizumab for Treating Paroxysmal Nocturnal Hemoglobinuria

In March 2022, CADTH published recommendations for the use of ravulizumab for PNH treatment.[4] Evidence from 2 open-label, active-controlled, noninferiority RCTs in adults with PNH showed that ravulizumab had a similar benefit as eculizumab in controlling hemolysis within blood vessels and removing the need for blood transfusions.[4] Although IV infusions of ravulizumab are less frequent than for eculizumab, there was not enough evidence to show that health-related quality of life is better with ravulizumab than with eculizumab due to the lack statistical testing for health-related quality of quality of life outcomes and the open-level study design of both studies.[4] There is no evidence to suggest ravulizumab is more effective than eculizumab in treating PNH.[4] There is insufficient evidence to demonstrate that patients who do not respond or lose response to treatment with eculizumab will benefit from ravulizumab treatment.[4]

- CADTH Recommendation: Only patients already receiving eculizumab treatment with adequate treatment response should be eligible to directly switch to ravulizumab treatment.[4]

National Institute for Health and Care Excellence: Pegcetacoplan for Treating Paroxysmal Nocturnal Hemoglobinuria

In March 2022, NICE issued guidance for the use of pegcetacoplan in treating adults with PNH.[5] Current treatments for PNH include C5 inhibitors such as eculizumab and ravulizumab. Some people still experience anemia and symptoms of PNH while receiving these treatments.[5] Clinical trial evidence suggests that pegcetacoplan improves hemoglobin levels and hematological symptoms of PNH for people who have anemia while taking eculizumab.[5] Pegcetacoplan is likely to have the same clinical benefits for people who have anemia while taking ravulizumab, because ravulizumab is very similar to eculizumab.[5]

- NICE Recommendation: Adults who continue to have anemia after at least 3 months of treatment with a C5 inhibitor (i.e, eculizumab, ravulizumab) are eligible to switch to pegcetacoplan.[5]

New Formulations and Indications:

In April 2022, ravulizumab (ULTOMIRIS) received expanded FDA approval for treatment of adult patients with generalized MG who are AchR antibody-positive.[6] In a double-blind, placebo-controlled, phase 3 RCT (CHAMPION-MG) of 175 adults with AChR antibody-positive MG, participants received ravulizumab infusions per protocol every 8 weeks after initial loading doses or placebo for 26 weeks.[39] Ravulizumab loading doses (2400, 2700, or 3000 mg) and maintenance doses (3000, 3300, or 3600 mg) were weight-based.[39] At baseline, patients had mild to moderate symptoms (median MG-ADL score 9) and most were taking glucocorticoids or other immunosuppressants.[39] The primary endpoint was change from baseline in MG-ADL total score, a patient-reported scale that assesses the ability to perform daily activities.[39] At 26 weeks, patients treated with ravulizumab had greater improvements in the MG-ADL score than those assigned to placebo (least squares mean reduction -3.1 versus -1.4, respectively; treatment difference, -1.6; $p < 0.001$).[39] Five-point improvement in the Quantitative Myasthenia Gravis score at 26 weeks (a secondary endpoint) was also greater in ravulizumab-treated adults compared with placebo (30.0% vs. 11.3%; $p=0.005$).[39] In additional secondary endpoints, improvements in quality of life and extent of fatigue, no differences between ravulizumab and placebo were observed.[39] The rate of AEs was similar between groups and the most frequently reported AEs were headache, diarrhea, and nausea.[39] On the basis of these results, ravulizumab was approved by the FDA for use in AChR antibody-positive patients with generalized MG.[6]

A new subcutaneous (SC) formulation of ravulizumab was approved in July 2022 for adults with PNH and aHUS.[6] The SC route of ravulizumab administration was studied in adults weighing more than 40 kg with PNH.[40] Subcutaneous ravulizumab was assessed in a multi-center, randomized, open-label, Phase 3 study

(ALXN1210-PNH-303) conducted in 136 adult patients with PNH who were clinically stable after having been treated with eculizumab for at least 3 months prior to study entry.[40] Patients were randomized 2:1 to receive SC dosing for the entire study period (3 years) or initiation with IV ravulizumab for 10 weeks followed by SC dosing for the rest of the study.[40] The primary endpoint was serum ravulizumab trough concentration at day 71.[40] Noninferiority was determined between IV and SC dosing regimens of ravulizumab. The FDA-approved SC dosing regimen of ravulizumab is 490 mg once a week administered via an on-body delivery system over 20 minutes.[6] The complete dose requires 2 pre-filled cartridges of 245 mg each.[6] The prescribing information provides instructions for switching from SC to IV administration of ravulizumab (or vice versa) or initiating ravulizumab after being treated with eculizumab.[6] The most frequently reported AEs in the adults with PNH who received SC ravulizumab included local injection site reactions (27%) diarrhea (13%) and headache (13%).[6]

New FDA Safety Alerts:

Table 4. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ravulizumab	ULTOMIRIS	4/2022	Warnings and Precautions	Infusion-Related Reactions[6] In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures. Adverse Reactions[6] The safety of ULTOMIRIS has been evaluated in 175 adult patients with generalized MG, including 169 patients who received at least one dose of ULTOMIRIS, 142 patients who were exposed for at least 6 months, and 95 who were exposed for at least 12 months. In a randomized, double-blind, placebo-controlled trial (ALXN1210-MG-306), the most frequent AEs (≥10%) with ULTOMIRIS were diarrhea and upper respiratory tract infection. Serious adverse reactions were reported in 20 (23%) patients with generalized MG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent SAEs were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

Randomized Controlled Trials:
A total of 87 citations were manually reviewed from the initial literature search. After further review, 867 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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9. ENSPRYNG (satralizumab) Subcutaneous Injection Prescribing Information. South San Francisco, CA; Genentech USA, Inc. August 2020.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
inebilizumab-cdon	UPLIZNA	VIAL	Y
ravulizumab-cwvz	ULTOMIRIS	VIAL	Y
satralizumab-mwge	ENSPRYNG	SYRINGE	Y
eculizumab	SOLIRIS	VIAL	N
efgartigimod alfa-fcab	VYVGART	VIAL	N
pegcetacoplan	EMPAVELI	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to October Week 4 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 26, 2022

1	exp Hemoglobinuria, Paroxysmal/	1995
2	exp Atypical Hemolytic Uremic Syndrome/	958
3	exp Myasthenia Gravis/	8139
4	eculizumab.mp.	1913
5	ravulizumab.mp.	77
6	Complement C3/ or pegcetacoplan.mp.	5113
7	efgartigimod.mp.	35
8	1 or 2 or 3	11049
9	4 or 5 or 6 or 7	6930
10	8 and 9	1081
11	limit 10 to (english language and humans and yr="2021 -Current")	190
12	limit 11 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	32

Ovid MEDLINE(R) 1996 to October Week 3 2022; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to October 26, 2022

1	exp Neuromyelitis Optica/	3873
2	inebilizumab.mp.	61
3	eculizumab.mp.	1915
4	satralizumab.mp.	52
5	2 or 3 or 4	1966
6	1 and 5	103
7	limit 6 to (english language and humans and yr="2021 -Current")	55

Inebilizumab-cdon (UPLINZA)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:

Up to 12 months

Requires PA:

- Inebilizumab-cdon (UPLINZA) pharmacy and physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4

Approval Criteria		
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6
6. Is the request for Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been screened for Hepatitis B and tuberculosis infection before starting treatment?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 4/21
Implementation: 5/1/21

Ravulizumab (ULTOMIRIS)

Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:

- Ravulizumab (ULTOMIRIS) pharmacy and physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.

Approval Criteria		
5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6
6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis for a patient with one of the following indications: • at least 1 month of age or older and weighs at least 5 kg with atypical Hemolytic Uremic Syndrome (aHUS) or Paroxysmal Nocturnal Hemoglobinuria (PNH) or • an adult with generalized myasthenia gravis (gMG) who is anti-acetylcholine receptor (AchR) antibody positive? Note: Ravulizumab is not indicated for the treatment of patients with Shiga toxin *E. coli* related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for intravenous dosing?	**Yes:** Go to # 9	**No:** Go to # 10
9. Does the requested intravenous dosing align with the FDA-approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Is the request for subcutaneous (SC) administration of ravlizumab 490 mg SC once a week in an adult weighing 40 kg or greater with PNH or aHUS? Note: Subcutaneous administration of ravulizumab is not approved for use in pediatric patients.	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Intravenous Weight-based Infusion Dosing for Ravulizumab in Adults and Pediatric Patients aged 1 month and older with PNH, aHUS, or gMG[1]

Body Weight	Indications	Loading Dose	Maintenance Dose (begins 2 weeks after loading dose)
5 to 9 kg	aHUS and PNH	600 mg	300 mg every 4 weeks
10 to 19 kg	aHUS and PNH	600 mg	600 mg every 4 weeks
20 to 29 kg	aHUS and PNH	900 mg	2,100 mg every 8 weeks
30 to 39 kg	aHUS and PNH	1,200 mg	2,700 mg every 8 weeks
40 to 59 kg	aHUS, gMG, and PNH	2,400 mg	3,000 mg every 8 weeks
60 to 99 kg	aHUS, gMG, and PNH	2,700 mg	3,300 mg every 8 weeks
100 kg or greater	aHUS, gMG, and PNH	3,000 mg	3,600 mg every 8 weeks
Abbreviations: aHUS = atypical hemolytic uremic syndrome; gMG = generalized myasthenia gravis; PNH = paroxysmal nocturnal hemoglobinuria			

1. ULTOMIRIS (Ravulizumab-cwvz) Solution for Intravenous Infusion Prescribing Information. Boston, MA: Alexion Pharmaceuticals Inc. 7/2022.

P&T/DUR Review 2/23 (DM); 12/21 (DM); 4/21 (DM)
Implementation: 4/1/23; 1/1/22; 5/1/21

Eculizumab (SOLIRIS)

Goal(s):
- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:
- Up to 12 months

Requires PA:
- Eculizumab (SOLIRIS) pharmacy and physician administered claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4

Approval Criteria		
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis one of the following: • Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive, • Paroxysmal Nocturnal Hemoglobinuria (PNH), • atypical Hemolytic Uremic Syndrome (aHUS)? (Note: Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	**Yes:** Go to #8	**No:** Go to #9

Approval Criteria		
8. Does the requested dosing align with FDA-approved dosing (**Table 1**)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for a diagnosis of myasthenia gravis in an adult patient who is Acytelcholine Receptor (AChR) antibody-positive?	**Yes:** Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient tried: • at least 2 or more immunosuppressant therapies (e.g., glucocorticoids in combination with azathioprine or mycophenolate mofetil or cyclosporine or tacrolimus or methotrexate or rituximab) for 12 months without symptom control OR • at least 1 or more nonsteroidal immunosuppressant with maintenance intravenous immunoglobulin once monthly or plasma exchange therapy (PLEX) over 12 months without symptom control?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score $\geq$ 6?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom control or improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. FDA-Approved Indications and Dosing for Eculizumab[1]

	Eculizumab		
FDA-approved Indications	• Neuromyelitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-AQP4-IgG-antibody • Reducing hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH) • Inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic uremic syndrome (aHUS) • Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive		
Recommended NMOSD dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended PNH dose in patients 18 yo and older	600 mg IV every week x 4 weeks, followed by 900 mg IV for the fifth dose 1 week later, then 900 mg IV every 2 weeks thereafter		
Recommended aHUS dose in patients less than 18 yo	**Body Weight** 5 kg to 9 kg 10 kg to 19 kg 20 kg to 29 kg 30 kg to 39 kg ≥ 40 kg	**Induction Dose** 300 mg weekly x 1 dose 600 mg weekly x 1 dose 600 mg weekly x 2 doses 600 mg weekly x 2 doses 900 mg weekly x 4 doses	**Maintenance Dose** 300 mg at week 2; then 300mg every 3 weeks 300 mg at week 2; then 300mg every 2 weeks 600 mg at week 3; then 600mg every 2 weeks 900 mg at week 3; then 900 mg every 2 weeks 1200 mg at week 5; then 1200 mg every 2 weeks
Recommended aHUS dose in patients 18 yo and older	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Recommended gMG dose	900 mg IV every week x 4 weeks, followed by 1200 mg IV for the fifth dose 1 week later, then 1200 mg IV every 2 weeks thereafter		
Dose Adjustment in Case of Plasmapheresis, Plasma Exchange, or Fresh Frozen Plasma Infusion	Dependent on most recent eculizumab dose: refer to prescribing information for appropriate dosing (300 mg to 600 mg)		

1. SOLIRIS (eculizumab) Solution for Injection Prescribing Information. Boston, MA: Alexion Pharmaceuticals, Inc. 11/2020.

P&T/DUR Review: 2/23 (DM); 12/21; 4/21
Implementation: 5/1/21

Satralizumab-mwge (ENSPRYNG)

Goal(s):

- Restrict use to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:
- Satralizumab-mwge (ENSPRYNG) pharmacy and physician administered claims

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is this an FDA approved indication?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6
6. Is the request for Neuromyelitis Optica Spectrum Disorder in an adult who is anti-aquaporin-4 (AQP4) antibody positive?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Has the patient been screened for Hepatitis B and tuberculosis infection prior to initiating treatment?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have active Hepatitis B or untreated latent tuberculosis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 4/21
Implementation: 5/1/21

Pegcetacoplan (EMPAVELI)

Goal(s):

- Restrict use to OHP-funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Restrict use to FDA-approved indications.

Length of Authorization:

- Up to 12 months

Requires PA:

- EMPAVELI (pegcetacoplan) pharmacy and physician administered claims

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is this request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 6

Approval Criteria		
6. Has the patient been vaccinated against *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Neisseria meningitidis serogroups A, C, W, and Y and serogroup B* according to current Advisory Committee on Immunization Practice (ACIP) recommendations for vaccination in patients with complement deficiencies*?* Note: Prescribing information recommends vaccination at least 2 weeks prior to starting therapy. If the risk of delaying therapy outweighs the risk of developing a serious infection, a 2-week course of antibiotic prophylaxis must be immediately initiated if vaccines are administered less than 2 weeks before starting complement therapy.	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis for an adult (age 18 years or older) with Paroxysmal Nocturnal Hemoglobinuria?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there objective documentation of treatment benefit from baseline? Appropriate measures will vary by indication (e.g., hemoglobin stabilization, decreased transfusions, symptom improvement, functional improvement, etc.).	**Yes:** Approve for 12 months Document baseline assessment and physician attestation received.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 12/21
Implementation: 1/1/22

Efgartigimod (VYVGART)

Goal(s):
- Restrict use to OHP-funded conditions.
- Promote use that is consistent with medical evidence.

Length of Authorization:
- Up to 12 months

Requires PA:
- VYVGART (efgartigimod) pharmacy and physician administered claims.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No: No:** For current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP For current age < 21 years: Go to #3.
3. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical necessity.
4. Is this an FDA approved indication?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Does the patient have an active infection?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically included hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella. Immunization with live vaccines is not recommended during efgartigimod treatment.	**Yes:** Go to #8. Document physician attestation of immunization history	**No:** Pass to RPh. Deny; medical appropriateness. Administer vaccines before initiation of a new treatment cycle of efgartigimod
8. Does the patient have a positive serological test for anti-acetylcholine receptor (AchR) antibodies?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Does the patient have a Myasthenia Gravis Foundation of America Clinical Classification of class II, III or IV?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Does the patient have a myasthenia gravis-specific activities of daily living scale (MG-ADL) total score of 5 points or more?	**Yes:** Go to #11 Record baseline MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Has the patient received or is currently receiving two immunosuppressant therapies (as monotherapy or in combination) for at least one year without adequate symptom control or do they have contraindications to these therapies? Example immunosuppressant therapies: - Azathioprine - Cyclosporine - Mycophenolate mofetil - Tacrolimus - Methotrexate - Cyclophosphamide	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of immunosuppressant therapy
12. Is the request for efgartigimod dosing that corresponds to FDA labeling? • 10 mg/kg once weekly for 4 weeks • For patients weighing 120 kg or more, the recommended dose is 1200 mg per infusion	**Yes:** Approve for up to two cycles. Each cycle is 1 dose/week for 4 weeks. The second cycle should not be administered sooner than 50 days from start of previous cycle.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has it been 50 days or more from the start of the previous efgartigimod treatment cycle?	**Yes**: Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is this request for the first renewal of efgartigimod?	**Yes**: Go to #3	**No:** Go to #4

Renewal Criteria		
3. Has the patient experienced a reduction in symptoms of at least 2 points from MG-ADL total baseline score?	**Yes**: Approve for up to 5 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient maintained a stable MG-ADL score over the last 12 months of efgartigimod therapy?	**Yes**: Approve for up to 7 cycles. Each cycle is 1 dose/week for 4 weeks. Additional cycles should not be administered sooner than 50 days from start of previous cycle. Record MG-ADL score	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 2/23 (DM); 4/22 (KS)
Implementation: 4/1/23; 5/1/22