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Ravulizumab-cwvz

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted

study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** for individuals one month of age and older for the treatment of either:

- Paroxysmal nocturnal hemoglobinuria (PNH); AND
    - Will not receive concurrently with other biologics used to treat paroxysmal nocturnal hemoglobinuria (PNH) (e.g., eculizumab [Soliris], iptacopan [Fabhalta], or pegcetacoplan [Empaveli]); OR
- Atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA); AND
    - Will not receive concurrently with other biologics used to treat atypical hemolytic uremic syndrome (aHUS) (e.g., eculizumab).

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** to treat individuals 18 years of age or older with generalized myasthenia gravis (gMG) who meet ALL the following criteria:

- Positive serologic test for anti-acetylcholine receptor;
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification II to IV;
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥6;
- Inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor (e.g., pyridostigmine, neostigmine);
- Inadequate treatment response or intolerance to at least ONE immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) or contraindication to all;
- Will not receive concurrently with other biologics used to treat myasthenia gravis (e.g., eculizumab, rituximab, immunoglobulin, efgartigimod alfa, rozanolixizumab-noli, zilucoplan).

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** to treat individuals 18 years of age or older with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

NOTE 1: Please refer to the Description Section for the MGFA Clinical Classification Guidelines and the MG-ADL profile.

Ravulizumab-cwvz (Ultomiris®) **is considered experimental, investigational and/or unproven** for all other indications including, but not limited to, Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

NOTE 2: Per the FDA label, life-threatening meningococcal infections have occurred in individuals treated with Ultomiris. The use of Ultomiris increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis) therefore, Ultomiris is contraindicated in patients with unresolved *Neisseria meningitidis* infection or are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying Ultomiris treatment outweigh the risks of developing a meningococcal infection.

Policy Guidelines

None.

Description

Paroxysmal nocturnal hemoglobinuria (PNH)
PNH is a chronic, progressive, debilitating, and life-threatening rare blood disorder that is characterized by the destruction of red blood cells. PNH is caused by a mutation in the X-linked *PIGA* gene, whose product is required for the first step in glycophosphatidylinositol (GPI) anchor synthesis. This acquired mutation occurs in a hematopoietic stem cell and leads to the expansion of stem cells with severely deficient or absent GPI. The absence of GPI-anchored proteins, CD55 and CD59, account for most of the clinical manifestations of PNH. CD55 and CD59 are regulatory proteins that normally bind to surface proteins and protect red blood cells from the complement system. The absence of these proteins leads to immune-mediated destruction of red blood cells. (1, 2)

Symptoms may vary widely and can include fatigue, difficulty swallowing, shortness of breath, abdominal pain, erectile dysfunction, hemoglobinuria, and anemia. Complications of PNH include bone marrow failure, renal failure, pulmonary hypertension, and thrombosis in blood vessels throughout the body which can result in organ damage or even death. (1, 2)

PNH is a rare disease with a worldwide incidence estimated at 1.3 cases per million population. The onset of PNH is typically in adults, with pediatric cases accounting for only 5-10% of reported cases. (3)

Atypical hemolytic uremic syndrome (aHUS)
Atypical HUS is a rare, life-threatening thrombotic microangiopathy (TMA) disorder characterized by hemolytic anemia, thrombocytopenia, and acute kidney injury. The development of aHUS is multifactorial. Production of *FH* autoantibodies and mutations in the *CFH, CFHR3, MCP, CFI, CFB,* and *C3* genes that encode complement regulatory proteins have been linked to the disorder. Episodes of aHUS are triggered by events such as pregnancy, viral infection, cancer, organ transplantation, and the use of certain medications. (4)

The annual incidence of aHUS is estimated to be two cases per million in the United States. Atypical HUS can present at any age.

Clinical manifestations of aHUS result from abnormalities in the alternative complement pathway resulting in endothelial cell dysfunction and formation of microvascular thrombi in the small blood vessels serving the kidneys and other organs. Severity of the disease depends upon the extent of microvascular injury and thrombosis, as well as ischemic injury to various organ systems. Patients typically present with hemolytic anemia, thrombocytopenia, and impaired renal function (proteinuria, hematuria, hypertension). Systemic symptoms can be observed in the central nervous system (irritability, convulsions, changes in vision), heart (cardiomyopathy, myocardial infarction, heart failure), extremities (gangrenous lesions), lungs (pulmonary hemorrhage, hypoxemia), GI system (pancreatitis, intestinal bleeding), and skeletal muscle (rhabdomyolysis).

The diagnosis of TMA must be made before aHUS can be distinguished. The diagnosis of TMA requires thrombocytopenia, microangiopathic hemolysis, and one or more of the following: neurological symptoms, renal impairment, or gastrointestinal symptoms. The diagnosis of aHUS is a diagnosis of exclusion. If the diagnosis of Shiga toxin or secondary HUS or TTP is not made clinically or confirmed by laboratory testing, then the diagnosis of aHUS may be considered.

Myasthenia Gravis

Myasthenia gravis is an acquired, autoimmune disorder that affects the neuromuscular junction of the skeletal muscles. Eighty to 90 percent of individuals with myasthenia gravis have autoantibodies against the acetylcholine receptor (AChR) detectable in serum, and these antibodies are believed to play a central role in disease pathomechanism. The AChR antibodies in myasthenia gravis are primarily immunoglobulin G1 (IgG1) and G3 (IgG3). In addition to blocking ACh binding to the AChR and cross-linking and internalizing the AChRs, these antibodies act through complement activation. (5) Some individuals with myasthenia gravis who are seronegative for AChR antibodies have antibodies directed against another target on the surface of the muscle membrane, muscle-specific receptor tyrosine kinase. (6) In contrast with AChR antibody-positive myasthenia gravis, in which complement-fixing immunoglobulin G1 (IgG1) and G3 (IgG3) subclasses predominate (7) muscle-specific kinase antibodies are mainly IgG4, (8) the IgG subtype that does not activate complement.

The clinical manifestations can vary from mild and focal weakness in some individuals to severe tetraparesis with respiratory failure in others. Symptom severity may also vary substantially in an individual patient throughout the day and over the course of the condition. Classification systems stratify individuals by symptoms or diagnostic findings to specify the severity of impairment and to aid with management. There are 2 clinical forms - ocular and generalized. In ocular from, weakness is limited to the eyelids and extraocular muscles while in generalized form, weakness involves a variable combination of ocular, bulbar, limb, and respiratory muscles. Myasthenia gravis may be categorized by symptom severity to guide treatment decisions, determine eligibility for clinical trials, and help with prognostication.

A widely used classification system from a task force of the Myasthenia Gravis Foundation of America stratifies individuals by the extent and severity of muscle weakness (9) and is

summarized below. Myasthenia gravis is a relatively uncommon disorder. Both incidence and prevalence have significant geographical variations. Reported prevalence rates range from 150 to 200 cases per million, and they have steadily increased over the past 50 years, at least partly due to improvements in recognition, diagnosis, treatment, and an overall increase in life expectancy. (10) More recent studies addressing incidence rates have been conducted in Europe and show a wide range from 4.1 to 30 cases per million person-years. (11, 12) The annual rate is lower in studies coming from North America and Japan, with the incidence ranging from 3 to 9.1 cases per million. (13)

The diagnosis is primarily based on clinical testing. Laboratory investigations and procedures can aid the clinician in confirming clinical findings. These may include serologic tests, electrophysiologic exams (e.g., repetitive nerve stimulation test and single-fiber electromyography), an edrophonium test, an ice-pack test, imaging, and laboratory testing for other coexisting autoimmune disorders (e.g., anti-nuclear antibodies, rheumatoid factor, and thyroid function). For most individuals with clinical features of myasthenia gravis, the diagnosis is confirmed by the presence of autoantibodies against the AChRs or against other muscle receptor-associated proteins. A positive anti-AChR antibody is present in 80% of individuals with gMG and confirms the diagnosis in an individual with classical clinical findings. About 5 to 10% of individuals will demonstrate anti-muscle specific kinase antibodies. Individuals who are seronegative for either of these antibodies will have anti-LRP4 antibodies.

Treatment

The goals of therapy are to render individuals minimally symptomatic or better while minimizing side effects from medications. The 4 basic therapies for myasthenia gravis include: 1) symptomatic therapy with an acetylcholinesterase inhibitor such as pyridostigmine and neostigmine; 2) chronic immunotherapies (such as glucocorticosteroids, eculizumab, rituximab, maintenance intravenous immunoglobulin [IVIG] or plasma exchange, and cyclophosphamide); 3) rapid but transient immunomodulatory therapies (plasma exchange and intravenous immune globulin); and 4) thymectomy. Approximately 10 percent of individuals with gMG have symptoms that are refractory or limited by specific toxicities of conventional immunomodulatory therapies (e.g., high-dose glucocorticoids). Therapeutic options for refractory disease include azathioprine, cyclosporine, eculizumab, efgartigimod, mycophenolate, ravulizumab, and tacrolimus.

In order to stabilize a patient with myasthenia gravis an operative procedure, IVIG or plasmapheresis may be utilized. These interventions are also the treatment of choice during a myasthenic crisis and in individuals who are resistant to immunosuppressive medications. Thymectomy may be employed as a therapeutic approach for certain individuals with myasthenia gravis.

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification

In 1997, the Medical Scientific Advisory Board of the MGFA formed a task force to address the need for universally accepted classifications, grading systems, and analytic methods for the management of individuals undergoing therapy and for use in therapeutic research trials. As a

result, the MGFA Clinical Classification was created. This classification divides myasthenia gravis (MG) into 5 main classes and several subclasses, as follows (14):

- Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
- Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.
    - IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
    - IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the individual in class IVb.

<u>The Myasthenia Gravis–Specific Activities of Daily Living Scale (MG-ADL)</u>

The Myasthenia Gravis–specific Activities of Daily Living scale (MG-ADL) was developed in the late 1990s to assess the status of symptoms and activities in MG. (15) It is an 8-item, patient reported questionnaire that can be completed in 2–3 minutes with no need for specialized equipment or training. See Table 1.

Table 1. MG Activities of Daily Living (MG-ADL) Profile

Grade	**0**	**1**	**2**	**3**	**Score (0, 1, 2, 3)**
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking	Gastric tube	

			necessitating changes in diet		
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependent	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Each activity is scored 0-3; and all scores are totaled to represent the overall MG-ADL score.

Neuromyelitis Optica Spectrum Disorder (16)
Neuromyelitis optica spectrum disorder (NMOSD; previously known as Devic disease or neuromyelitis optica [NMO]) is an inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and the spinal cord. Optic neuritis (inflammation of the optic nerve) can be caused by any inflammatory condition or may be idiopathic. Optic neuritis presents with varying degrees of vision loss and is almost always associated with eye pain that worsens with movement of the eye. Individual optic neuritis attacks in NMOSD may be similar to isolated syndromes of optic neuritis or those related to MS, though visual loss is generally more severe in NMOSD. While most optic neuritis attacks in NMOSD are unilateral, sequential optic neuritis in rapid succession or bilateral simultaneous optic neuritis is highly suggestive of NMOSD.

The prevalence of NMOSD in adults in various studies ranges from 0.37 to 10 per 100,000. The reported incidence of AQP4-antibody seropositive NMOSD in females is up to 10 times higher than in males whereas the female-to-male incidence with multiple sclerosis (MS) is approximately 2:1. The median age of onset for NMOSD is 32 to 41 years, but cases are described in children and older adults. Comparatively, the median age of onset for MS is 24 years.

Regulatory Status
Ravulizumab-cwvz (Ultomiris®) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria or with atypical hemolytic uremic syndrome (aHUS) to

inhibit complement-mediated thrombotic microangiopathy; and for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive. Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). Ravulizumab-cwvz (Ultomiris) is a monoclonal antibody that works through inhibition of the complement pathway. Ravulizumab-cwvz is administered as an intravenous infusion, with dosing based on the patient's body weight. Ravulizumab-cwvz is supplied in 300 mg/30 mL, 300 mg/3 mL, and 1100 mg/11 mL single-dose vials. Refer to <https://www.accessdata.fda.gov> for the recommended dosage regimen for adult and pediatric patients, 1 month of age or older weighing 5 kg or greater. (17)

In March 2024, the FDA expanded the use of Ravulizumab-cwvz (Ultomiris®) to include the treatment of adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

Boxed Warning

There is a boxed warning regarding the potential for serious life-threatening and fatal meningococcal infections. The warnings recommend that clinicians:

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in individuals with complement deficiencies.
- Immunize individuals with meningococcal vaccines at least 2 weeks prior to administering the first dose of ravulizumab-cwvz unless the risks of delaying therapy outweighs the risk of developing a meningococcal infection.
- Monitor individuals for early signs of meningococcal infections and evaluate immediately if infection is suspected.

Risk Evaluation and Mitigation Strategy

Due to the risk of meningococcal infections, Ravulizumab-cwvz is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Ultomiris REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patient with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines. (17)

Rationale

This policy was originally developed in February 2020 and is based on the U.S. Food and Drug Administration (FDA) labeled indications as of August 29, 2024.

Ravulizumab-cwvz (Ultomiris)

Paroxysmal Nocturnal Hemoglobinuria (PNH) - Adults

The safety and efficacy of ravulizumab in adult patients with PNH was assessed in two open-label randomized, active-controlled, non-inferiority Phase 3 studies (CHAMPION): study 301 and study 302. (17, 18, 19)

The CHAMPION-301 study involved 246 patients and consisted of a 4-week screening period, a 26-week randomized treatment period to evaluate the efficacy and safety of ravulizumab vs. eculizumab and an extension period of up to 2 years, during which all patients received ravulizumab. Patients were eligible to be enrolled if they were ≥18 years of age and had a documented diagnosis of PNH confirmed by a high-sensitivity flow cytometry of red and white blood cells with granulocyte or monocyte clone size of at least 5% and LDH level ≥1.5 upper limit of normal (ULN) at screening. All patients must have been vaccinated against meningococcal infections within 3 years before, or at the time of, initiating study drug. Patients who initiated study drug treatment <2 weeks after receiving a meningococcal vaccine were required to receive treatment with appropriate anaphylactic antibiotics until at least 2 weeks after vaccination. Within 3 months of screening, ≥ 1 of the following PNH-related signs or symptoms must have been present: fatigue, hemoglobinuria, abdominal pain, shortness of breath, anemia (Hgb <10 g/dL), or history of MAVEs (including thrombosis), dysphagia, dysphagia, erectile dysfunction, or history of packed red blood cell transfusion because of PNH. Key exclusion criteria included current or previous exposure to a complement inhibitor, weight <40 kg, history of bone marrow transplant, history of meningococcal or unexplained, recurrent infection, platelet count <30 x 10^9/L, or absolute neutrophil count <0.5 x 10^9/L at screening. (18)

Patients were randomly assigned in a 1:1 ratio to receive ravulizumab or eculizumab. Patients that participated in the trial were stratified into 6 groups based on transfusion history: 0, 1-14, or >14 units of packed red blood cells in the 1 year before the first dose of study drug and LDH screening level of 1.5 to <3 times the ULN or ≥3 ULN. The coprimary endpoints were transfusion avoidance (TA), defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through day 183 and hemolysis as measured by LDH normalization (ULN, 246 U/L) from days 29 through 183. Key secondary endpoints included percentage change from baseline to day 183 in LDH and change from baseline to day 183 in quality of life, as assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale; the proportion of patients with breakthrough hemolysis; proportion of patients with stabilized hemoglobin. (18)

The patient population had no noteworthy differences between treatment groups in demographics or baseline clinical characteristics. Study participants had a mean age of 45.5, 54.5% male, and 52.4% Asian. Baseline characteristics of the population included 86.2% with an LDH ratio ≥3 times ULN, a mean LDH of 1,606.4, and 63.8% received 1-14U of packed RBC within 1 year before study entry. (18)

Ravulizumab met the objective of noninferiority compared with eculizumab on both coprimary endpoints and point estimates for both coprimary end points favored ravulizumab. 73.6% of patients receiving ravulizumab and 66.1% receiving eculizumab avoided transfusion (p_{inf} < 0.0001). The adjusted prevalence of LDH normalization was 53.6% for the ravulizumab group and 49.4% for the eculizumab group (p_{inf} < .0001). Ravulizumab met its key secondary endpoints of noninferiority to eculizumab on percent change from baseline to day 183 in LDH, FACIT-Fatigue score, breakthrough hemolysis rate, and hemoglobin stabilization rate.

Ravulizumab met statistical significance for superiority over eculizumab for the proportion of patients with stabilized hemoglobin. (18)

The most common adverse event reported during the trial was headache, 36% and 33% in the ravulizumab and eculizumab groups, respectively. (18)

The CHAMPION-302 enrolled 195 patients and consisted of a 4-week screening period followed by a 26-week randomized treatment period and an extension period during which all patients received ravulizumab for 2 years. (19)

Enrolled patients were ≥18 years of age and had a documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation of red blood cells and white blood cells with granulocyte or monocyte clone size of ≥5% and who were clinically stable on eculizumab treatment. Eligible patients must have received eculizumab treatment ≥6 months before study entry, had an LDH level ≤1.5× the upper limit of normal (ULN; 246 U/L) at screening, and received the meningococcal vaccine within <3 years before dosing or at the time of study drug initiation. Key exclusion criteria included LDH value >2× the ULN in the 6 months before day 1, major adverse vascular event within 6 months before day 1, platelet count 30×10^9/L, absolute neutrophil count $<0.5 \times 10^9$/L, body weight <40 kg, history of bone marrow transplantation, and history of *N meningitidis* infection. (19)

Patients were stratified according to transfusion history and were randomly assigned (1:1) to 26 weeks of open-label treatment with IV ravulizumab or eculizumab. At the end of the 26-week treatment period, eculizumab treated patients were switched top open-label ravulizumab for the extension period. (19)

The primary efficacy endpoint was hemolysis as measured by percentage change in LDH levels from baseline to day 183. Key secondary endpoints were proportion of patients with breakthrough hemolysis, change from baseline in quality of life as assessed with the FACIT-Fatigue Scale, transfusion avoidance, and proportion of patients with stabilized hemoglobin. (19)

Patient demographics and baseline characteristics were well balanced between treatment groups. Patients were a mean age of 47.7; 50.3% male, and 56.9% white. Baseline characteristics of the population included a mean LDH of 231.6 and 25% received packed red blood cells/whole blood transfusions within 1 year before the first dose. (19)

Ravulizumab achieved noninferiority compared with eculizumab for the primary endpoint of percentage change in LDH, a decrease of 0.82% and an increase of 8.39% respectively (p_{inf} <0.0006). Treatment with ravulizumab achieved noninferiority compared with eculizumab for all 4 key secondary endpoints. No patients in the ravulizumab group experienced breakthrough hemolysis compared to 5 patients in the eculizumab group (p_{inf} <0.0004). Change in FACIT-Fatigue total score was 2.01 in the ravulizumab group and 0.54 in the eculizumab group (p_{inf} <0.0001). 87.6% of patients receiving ravulizumab and 82.7% of patients receiving eculilzumab

avoided transfusion (p_{inf} <0.0001). 76.3% of patients receiving ravulizumab and 75.5% receiving eculizumab achieved stabilized hemoglobin levels (p_{inf} <0.0005). Ravulizumab did not meet statistical significance for superiority in percentage change in LDH when compared to eculizumab (p=0.058). (19)

The most frequently reported adverse event occurring in 3% or more of patients in either treatment group was headache, which occurred in 26.8% of patients treated with ravulizumab and in 17.3% of patients treated with eculizumab. (19)

Paroxysmal Nocturnal Hemoglobinuria (PNH) – Pediatrics

The pediatric study, ALXN1210-PNH-304, was a multi-center, open-label Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment-naïve pediatric patients with PNH. A total of 13 pediatric patients with PNH completed Ultomiris treatment during the Primary Evaluation Period (26 weeks). Five of the 13 patients had never been treated with complement inhibitors and 8 patients were treated with eculizumab. Eleven of the thirteen patients were between 12 and 17 years of age at first infusion, with 2 patients under 12 years old (11 and 9 years old). (17)

Based on body weight, patients received a loading dose of Ultomiris on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on eculizumab therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of Soliris. The weight-based dose regimen of ravulizumab-cwvz provided inhibition of terminal complement in all patients throughout the entire 26-week treatment period regardless of prior experience with eculizumab. Following initiation of ravulizumab-cwvz treatment, steady-state therapeutic serum concentrations of ravulizumab-cwvz were achieved after the first dose and maintained throughout the primary evaluation period in both cohorts. Three of 5 complement inhibitor treatment-naïve patients and 6 out of 8 eculizumab-experienced patients achieved hemoglobin stabilization by Week 26, respectively. Transfusion avoidance was reached for 11 out of 13 of patients during the 26-week Primary Evaluation Period. One patient experienced breakthrough hemolysis during the extension period. (17)

A clinically relevant improvement from baseline in fatigue as assessed by Pediatric FACIT-Fatigue (i.e., mean improvement of > 3 units for Pediatric FACIT Fatigue scores) was sustained throughout the primary evaluation period in the 5-complement inhibitor treatment naïve patients. A slight improvement was also observed in eculizumab-experienced patients. However, patient-reported fatigue may be an under-or overestimation because patients were not blinded to treatment assignment. (17)

The efficacy of Ultomiris in pediatric patients with PNH is similar to that observed in adult patients with PNH enrolled in pivotal studies. (17)

Atypical Hemolytic Uremic Syndrome (aHUS) - Adults

The efficacy of ravulizumab in patients with aHUS was assessed in 2 open-label, single-arm studies. Study ALXN1210-aHUS-311 enrolled 56 patients who were naïve to complement inhibitor treatment prior to study entry. It consisted of a 26-week initial evaluation period and patients were allowed to enter an extension period for up to 4.5 years. Ninety-three percent of patients had extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. Forty patients (71.4%) had Stage 5 chronic kidney disease (CKD); and 14% had a medical history of kidney transplant. At study entry, 51.8% were on dialysis. Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period as shown in Table 2. (17)

Table 2. Efficacy Results in aHUS During the 26-week Initial Evaluation Period (ALXN1210-aHUS-311)

	Total	**Responder**	
		n	**Proportion (95% CI)[a]**
Complete TMA response	56	30	0.54 (0.40, 0.67)
Components of complete TMA response • Platelet count normalization • LDH normalization • ≥25% improvement in serum creatinine from baseline	 • 56 • 56 • 56	 • 47 • 43 • 33	 • 0.84 (0.72, 0.92) • 0.77 (0.64, 0.87) • 0.59 (0.45, 0.72)
Hematologic normalization	56	41	0.73 (0.60, 0.84)

CI: confidence interval; LDH: lactate dehydrogenase; TMA: thrombotic microangiography.
[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

One additional patient had a complete TMA response that was confirmed after the 26-week initial evaluation period. Complete TMA response was achieved at a median time of 86 days (range: 7 to 169 days). The median duration of complete TMA response was 7.97 months (range: 2.52 to 16.69 months). All responses were maintained through all available follow-up. Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). An increase in mean platelet count was observed after commencement of Ultomiris, increasing from 118.52 × 109/L

at baseline to 240.34 × 109/L at day 8 and remaining above 227 × 109/L at all subsequent visits in the initial evaluation period (26 weeks). Renal function, as measured by eGFR, was improved or maintained during Ultomiris therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with complete TMA response, renal function continued to improve after the complete TMA response was achieved. Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up and 6 of 27 (22%) patients were off dialysis at baseline were on dialysis at last available follow-up. (17)

Atypical Hemolytic Uremic Syndrome (aHUS) - Pediatrics

Pediatric study ALXN1210-aHUS-312 is a 26-week ongoing, multi-center, single-arm, study conducted in 16 pediatric patients. A total of 14 eculizumab-naïve patients with documented diagnosis of aHUS were enrolled and included in this interim analysis. The median age at the time of first infusion was 5.2 years (range 0.9, 17.3 years). The overall mean weight at baseline was 19.8 kg; half of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (71%) had pretreatment extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 35.7% (n = 5) of patients had a CKD Stage 5. Seven percent had history of prior kidney transplant and 35.7% were on dialysis at study entry. Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week evaluation period as shown in Table 3. (17)

Table 3. Efficacy Results in aHUS During the 26-week Initial Evaluation Period (ALXN1210-aHUS-312)

	Total	**Responder**	
		n	**Proportion (95% CI)[a]**
Complete TMA response	14	10	0.71 (0.42, 0.92)
Components of complete TMA response • Platelet count normalization • LDH normalization • ≥25% improvement in serum creatinine from baseline	 • 14 • 14 • 14	 • 13 • 12 • 11	 • 0.93 (0.66, 0.99) • 0.86 (0.57, 0.98) • 0.79 (0.49, 0.95)

Hematologic normalization	14	12	0.86 (0.57, 0.98)

Note: 1 patient withdrew from study after receiving 2 doses of ravulizumab.
CI: confidence interval; LDH: lactate dehydrogenase; TMA: thrombotic microangiography.
[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

Complete TMA response during the initial evaluation period was achieved at a median time of 30 days (range: 15 to 88 days). The median duration of complete TMA response was 5.08 months (range: 3.08 to 5.54 months). All responses were maintained through all available follow-up. Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR. An increase in mean platelet count was observed after commencement of Ultomiris, increasing from 60.50 × 109/L at baseline to 296.67 × 109/L at day 8 and remained above 296 × 109/L at all subsequent visits in the initial evaluation period (26 weeks). The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) by 26 weeks. Four of the 5 patients who required dialysis at study entry were able to discontinue dialysis after the first month in study and for the duration of Ultomiris treatment. No patient started dialysis during the study. (17)

Generalized Myasthenia Gravis (gMG) (17, 20)

The efficacy of Ultomiris for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306; NCT03920293). Patients were randomized 1:1 to either receive Ultomiris (n=86) or placebo (n=89) for 26 weeks. Ultomiris was administered intravenously according to the weight-based recommended dosage.

Patients with gMG with a positive serologic test for anti-AChR antibodies, Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥6 were enrolled. Baseline and disease characteristics were similar between treatment groups (including age at first dose [mean of 58 years for Ultomiris versus 53 years for placebo], gender [51% female for Ultomiris versus 51% female for placebo], race as White, Asian, and Black or African American [78%, 17%, and 2% for Ultomiris versus 69%, 18%, and 5% for placebo, respectively], and duration of MG since diagnosis [mean of 10 years, ranging from 0.5 to 39.5 years for Ultomiris versus mean of 10.0 years, ranging from 0.5 to 36.1 years for placebo].

Over 80% of patients were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants (ISTs) at study entry. Patients on concomitant medications to treat gMG were permitted to continue on therapy throughout the course of the study.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a

score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with the higher scores indicating more impairment.

The secondary endpoints, also assessed from baseline to Week 26, included the change in the Quantitative MG total score (QMG). The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total score ranges from 0 to 39, where higher scores indicate more severe impairment.

Other secondary endpoints included the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively.

Treatment with Ultomiris demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at Week 26 as compared to placebo (Table 4).

Table 4. Efficacy Results in Patients with gMG

Efficacy Endpoints: Change from Baseline at Week 26	**Placebo (n=89) LS Mean**	**Ultomiris (n=86) LS Mean**	**Treatment Effect (95% CI)**	**p-value[a]**
Primary Endpoint				
MG-ADL	-1.4	-3.1	-1.6 (-2.6, -0.7)	<0.001
Secondary Endpoint				
QMG	-0.8	-2.8	-2.0 (-3.2, -0.8)	<0.001

[a] p-value calculated using mixed effect model for repeated measures.
CI: confidence interval; LA: least squares; MG-ADL: Myasthenia Gravis Activities of Daily Living profile; QMG: Quantitative Myasthenia Gravis score for disease severity.

The proportion of QMG responders with at least a 5-point improvement at week 26 was greater for Ultomiris (30.0%) compared to placebo (11.3%) p = 0.005. The proportion of MG-ADL responders with at least a 3-point improvement at week 26 was also greater for Ultomiris (56.7%) compared to placebo (34.1%). The proportion of clinical responders at higher response thresholds (≥4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥6-, 7-, 8-, 9-, or 10-point improvement on QMG) was consistently greater for Ultomiris compared to placebo.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy and safety of Ultomiris for the treatment of NMOSD in adult patients with anti-AQP4 antibody positive NMOSD was assessed in an open-label multicenter study (Study

ALXN1210-NMO-307; NCT04291262). Patients participating in Study ALXN1210-NMO-307 received ULTOMIRIS in the Primary Treatment Period that ended when the last enrolled patient completed (or discontinued prior to) 50 weeks on study, representing a median study duration of 73.5 weeks (minimum 13.7, maximum 117.7). Efficacy assessments were based on a comparison of patients in Study ALXN1210-NMO-307 with an external placebo control group from another study (Study ECU-NMO-301, NCT01892345) composed of a comparable population of adult patients with anti-AQP4 antibody positive NMOSD. (17)

Study ALXN1210-NMO-307 enrolled 58 adult patients with NMOSD who had a positive serologic test for anti-AQP4 antibodies, at least 1 relapse in the last 12 months prior to the Screening Period, and an Expanded Disability Status Scale (EDSS) score ≤ 7. In the external placebo control group, eligibility criteria were similar except patients were required to have at least 2 relapses in last 12 months or 3 relapses in the last 24 months with at least 1 relapse in the 12 months prior to screening. Prior treatment with immunosuppressant therapies (ISTs) was not required for enrollment. However, patients on selected ISTs (i.e., corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus) were permitted to continue on therapy, with a requirement for stable dosing until they reached Week 106 in the Study. Similar IST use was permitted in the external placebo control group.

Ultomiris was administered intravenously according to the weight-based recommended dosage.

The demographics were similar between the Ultomiris treatment group from Study ALXN1210-NMO-307 and the placebo treatment group from Study ECU-NMO-301 (including age [median of 46.0 years for ULTOMIRIS versus 44.0 years for placebo] and sex [89.7% female for ULTOMIRIS versus 89.4% female for placebo]). The majority of patients were White or Asian. The median time from diagnosis to first dose was 0.9 years for Ultomiris and 2.0 years for placebo. The median annualized relapse rate (ARR) in the last 24 months was 1.4 for Ultomiris versus 1.9 for placebo, and the median number of historical relapses was 2 for Ultomiris versus 4 for placebo. The median baseline EDSS score was 3.3 for Ultomiris versus 4.0 for placebo. At baseline, 48% of patients in the Ultomiris group received concomitant IST, including corticosteroids, versus 72% of subjects in the placebo group.

The primary endpoint of Study ALXN1210-NMO-307 was the time to first adjudicated on-trial relapse as determined by an independent adjudication committee. No adjudicated on-trial relapses were observed in Ultomiris-treated patients during the Primary Treatment Period, representing a statistically significant difference between the Ultomiris and placebo treatment arms in time to first adjudicated on-trial relapse ($p < 0.0001$). The hazard ratio (95% confidence interval [CI]) for Ultomiris compared with placebo was 0.014 (0.000, 0.103), representing a 98.6% reduction in the risk of relapse. Ultomiris-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment.

Summary of Evidence

There is sufficient evidence to support the use of ravulizumab (Ultomiris) for the U.S. Food and Drug Administration (FDA) labeled indications for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, generalized myasthenia gravis and neuromyelitis optica spectrum disorder when criteria are met.

There is insufficient evidence to support the use of ravulizumab (Ultomiris) beyond the FDA labeled indications. For non-FDA approved indications, treatment with ravulizumab (Ultomiris) is considered experimental, investigational, and/or unproven.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J1303

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
02/01/2025	Document updated with literature review. The following changes were made in Coverage: 1) Modified criteria for generalized myasthenia gravis related to immunosuppressive therapy to state "Inadequate treatment response or intolerance to at least one immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) or contraindication to all."; 2) Added "Inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor (e.g., pyridostigmine, neostigmine)"; 3) Added "zilucoplan" as an example of other biologics used to treat myasthenia gravis; and 4) Added references 5-13, 15; others updated and/or removed.
08/01/2024	Document updated with literature review. The following changes were made to Coverage: 1) Modified conditional coverage criteria for generalized myasthenia gravis (gMG); 2) Added NOTE 2 regarding risk of life-threatening meningococcal infections; and 3) Added conditional coverage for neuromyelitis optica spectrum disorder when criteria are met. Reference 12 added; others updated.
10/01/2022	Document updated with literature review. The following changes were made to Coverage: Added "Will not receive concurrently with other biologics used to treat paroxysmal nocturnal hemoglobinuria (PNH) (e.g., eculizumab)" and "Will not receive concurrently with other biologics used to treat atypical hemolytic uremic syndrome (aHUS) (e.g., eculizumab)" to those coverage statements; added medically necessary indication for patients aged 18 and older with generalized Myasthenia Gravis. Updated reference 5; added references 8-11.
11/01/2021	Document updated with literature review. The following change was made to Coverage: Added medically necessary indication for pediatric patients one month of age and older for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Updated reference 5.
04/01/2021	Reviewed. No changes.
07/15/2020	New medical document. Ravulizumab-cwvz (Ultomiris™) may be considered medically necessary for adult patients for the treatment of paroxysmal nocturnal hemoglobinuria (PNH); OR atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Ravulizumab-cwvz (Ultomiris™) may be considered medically necessary for pediatric patients for the treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA). Ravulizumab-cwvz (Ultomiris™) is considered experimental, investigational

	and/or unproven for all other indications including, but not limited to, Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).