Policy Number	**RX501.107**
Policy Effective Date	**01/01/2026**

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 generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. 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 generally accepted standards of medical care. 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

NOTE 1: 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.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** to reduce hemolysis for individuals one month of age and older who have paroxysmal nocturnal hemoglobinuria (PNH) AND meet the following criteria:

- Documentation of diagnosis of PNH through analysis by:
    - Flow cytometry of erythrocytes for CD59 deficiency; or
    - Granulocytes for either CD59 or CD55.

Atypical Hemolytic Uremic Syndrome

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** for individuals one month of age and older for the treatment of atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Generalized Myasthenia Gravis

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** to treat generalized myasthenia gravis (gMG) in individuals who meet ALL the following criteria:

- 18 years of age or older;
- Positive serologic test for anti-acetylcholine receptor;
- Myasthenia Gravis Foundation of America (MGFA) Clinical Classification II to IV (See Policy Guidelines);
- Myasthenia Gravis Activities of Daily Living (MG-ADL) total score ≥6 (See Policy Guidelines);
- Inadequate treatment response, intolerance, or contraindication to an acetylcholinesterase inhibitor (e.g., pyridostigmine, neostigmine); AND
- At least ONE immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) either in combination or as monotherapy.

Neuromyelitis Optica Spectrum Disorder

Ravulizumab-cwvz (Ultomiris®) **may be considered medically necessary** to treat individuals:

- 18 years of age or older; AND
- With a diagnosis of neuromyelitis optica spectrum disorder (NMOSD); AND
- That are anti-aquaporin-4 (AQP4) antibody positive.

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

Policy Guidelines

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 (17):

- 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.

The Myasthenia Gravis–Specific Activities of Daily Living Scale (MG-ADL)

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. (18) 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 PG1.

Table PG1. 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 necessitating changes in diet	Gastric tube	
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.

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. (2, 3)

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. (2, 3)

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. (4)

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. (5)

The annual incidence of aHUS is estimated to be two cases per million in the United States. Atypical HUS can present at any age. (6)

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). (5)

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. (5)

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. (7) 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. (8) In contrast with AChR antibody-positive myasthenia gravis, in which complement-fixing immunoglobulin G1 (IgG1) and G3 (IgG3) subclasses predominate (9) muscle-specific kinase antibodies are mainly IgG4, (10) 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 (11) and is summarized in the section of “Policy Guidelines.” 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. (12) 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. (13, 14) 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. (15)

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.

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/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. (1)

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. (1)

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for ravulizumab-cwvz (Ultomiris®) and a specialty society recommendation.

Paroxysmal Nocturnal Hemoglobinuria (PNH) (1)

The safety and efficacy of Ultomiris in adult patients with PNH was assessed in 2 open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 and PNH Study 302. Study 301 enrolled patients with PNH who were complement inhibitor-naïve and had

active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months. The safety and efficacy of Ultomiris in pediatric patients with PNH was assessed in PNH Study 304, an open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment-naïve pediatric patients with PNH.

In Study 301 and Study 302, adults with PNH were dosed with Ultomiris administered intravenously in accordance with the weight-based dosing (4 infusions of Ultomiris over 26 weeks) above. Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of the studies.

Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with Ultomiris or eculizumab or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Prophylactic treatment with appropriate antibiotics beyond 2 weeks after vaccination was at the discretion of the provider.

Study in Complement-Inhibitor Naïve Adult Patients with PNH
The Complement-Inhibitor Naïve Study [ALXN1210-PNH-301; NCT02946463] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.

Patients with PNH with flow cytometric confirmation of at least 5% PNH cells were randomized 1:1 to either intravenously administered Ultomiris or eculizumab. The mean total PNH granulocyte clone size was 85%, the mean total PNH monocyte clone size was 88%, and the mean total PNH RBC clone size was 39%. Ninety-eight percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy complications (3%), and other (16%). Major baseline characteristics were balanced between treatment groups.

Efficacy was established based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH [lactate dehydrogenase] levels. Transfusion avoidance was defined as patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline up to Day 183. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 × ULN [upper limits of normal], after prior LDH reduction to < 1.5 × ULN on therapy and the proportion of patients with stabilized hemoglobin. Non-inferiority of Ultomiris to eculizumab was demonstrated across endpoints in the complement-inhibitor naïve treatment population described in Table 1 below.

Table 1. Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

Abbreviations: LDH = lactate dehydrogenase; CI = confidence interval; N: number.
For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

There was no observable difference in fatigue between Ultomiris and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under- or over-estimation because patients were not blinded to treatment assignment.

Study in Eculizumab-Experienced Adult Patients with PNH
The study in eculizumab-experienced patients [ALXN1210-PNH-302; NCT03056040] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Patients who demonstrated clinically stable disease after being treated with eculizumab for at least the prior 6 months were randomized 1:1 to either continue eculizumab or to switch to Ultomiris administered intravenously. The mean total PNH granulocyte clone size was 83%, the mean total PNH monocyte clone size was 86%, and the mean total PNH RBC clone size was 60%. Ninety-five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment in the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%). Major baseline characteristics were balanced between the 2 treatment groups.

Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183 and supportive efficacy data was transfusion avoidance, proportion of patients with

stabilized hemoglobin, and the proportion of patients with breakthrough hemolysis through Day 183.

Non-inferiority of Ultomiris to eculizumab was demonstrated across endpoints in the patients with PNH previously treated with eculizumab described in Table 2 below.

Table 2. Efficacy Results in the Eculizumab-Experienced Adult Patients with PNH Eculizumab-Experienced Study

	ULTOMIRIS N = 97	**Eculizumab N = 98**	**Statistic for Comparison**	**Treatment Effect (95% CI)**
LDH percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)
Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6 %	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; N: number; PNH: Paroxysmal Nocturnal Hemoglobinuria.

There was no observable difference in fatigue between Ultomiris and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation because patients were not blinded to treatment assignment.

Study in Eculizumab-Experienced and Complement-Inhibitor Naïve Pediatric Patients with PNH
The pediatric study, ALXN1210-PNH-304 (NCT03406507), 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 intravenously administered 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).

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 eculizumab. 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. Table 3 presents secondary efficacy outcomes for the primary evaluation period.

Table 3. Efficacy Outcomes from the 26-Week Primary Evaluation Period of Pediatric Patient Study in PNH (ALXN1210-PNH-304)

Endpoint	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)
LDH percent change from baseline (%)[a]	-47.9 (-113.4, 17.5)	4.7 (-36.7, 46.0)
Transfusion avoidance (%)[b]	60.0 (14.7, 94.7)	100.0 (63.1, 100.0)
Change in FACIT-Fatigue[a]	3.4 (-4.2, 11.0)	1.3 (-3.1, 5.7)
Hemoglobin stabilization (%)[b]	60.0 (14.7, 94.7)	75.0 (34.9, 96.8)
Breakthrough hemolysis (%)	0	0[c]

FACIT: Functional Assessment of Chronic Illness Therapy; LDH: lactate dehydrogenase; N: number; PNH: Paroxysmal Nocturnal Hemoglobinuria.

[a] 95% CIs for the mean obtained from t-distribution were presented.

[b] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

[c] No patients experienced breakthrough hemolysis during the primary evaluation period. One patient experienced breakthrough hemolysis at 1.8 years during the extension period; however, at the time of the breakthrough hemolysis event the patient had adequate C5 inhibition (free C5 < 0.5 mcg/mL).

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 over-estimation because patients were not blinded to treatment assignment.

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

Atypical Hemolytic Uremic Syndrome (aHUS) (1)

The efficacy of Ultomiris administered intravenously in patients with aHUS was assessed in 2 open-label, single-arm studies. Study ALXN1210-aHUS-311 enrolled adult patients who displayed signs of TMA [thrombotic microangiopathy]. In order to qualify for enrollment, patients were required to have a platelet count ≤ 150 × 10^9/L, evidence of hemolysis such as an

elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis.

Study ALXN1210-aHUS-312 enrolled pediatric patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤ 150 × 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥ 97.5% percentile at screening or required dialysis. In both studies, enrollment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Patients with confirmed diagnosis of STEC-HUS after enrollment were excluded from the efficacy evaluation.

Study in Adult Patients with aHUS
The adult study [ALXN1210-aHUS-311; NCT02949128] was conducted in patients who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week Initial Evaluation Period and patients were allowed to enter an extension period for up to 4.5 years. All patients received Ultomiris administered intravenously according to their weight.

A total of 56 patients with aHUS were evaluated for efficacy. Ninety-three percent of patients had extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 71.4% (n = 40) of patients had Stage 5 chronic kidney disease (CKD). Fourteen percent had a medical history of kidney transplant and 51.8% were on dialysis at study entry. Eight patients entered the study with evidence of TMA for > 3 days after childbirth (i.e., postpartum).

The efficacy evaluation was based on Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period as shown in Table 4.

Table 4. 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	56	47	0.84 (0.72, 0.92)
LDH normalization	56	43	0.77 (0.64, 0.87)
≥ 25% improvement in serum creatine from baseline	56	33	0.59 (0.45, 0.72)
Hematologic normalization	56	41	0.73 (0.60, 0.84)

CI: confidence interval; LDH: lactate dehydrogenase; TMA: thrombotic Microangiopathy; n: number; aHUS: Atypical Hemolytic Uremic Syndrome.
[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-ups.

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 treatment, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/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.

Study in Pediatric Patients with aHUS
The Pediatric Study [ALXN1210-aHUS-312; NCT03131219] is a 26-week ongoing, multicenter, single-arm study conducted in 16 pediatric patients. All patients received Ultomiris administered intravenously according to their weight.

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.

Efficacy evaluation was based upon Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week Initial Evaluation Period as shown in Table 5.

Table 5. 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	14	13	0.93 (0.66, 0.99)
LDH normalization	14	12	0.86 (0.57, 0.98)
≥ 25% improvement in serum creatinine from baseline	14	11	0.79 (0.49, 0.95)
Hematologic normalization	14	12	0.86 (0.57, 0.98)

CI: confidence interval; LDH: lactate dehydrogenase; TMA: thrombotic Microangiopathy; n: number; aHUS: Atypical Hemolytic Uremic Syndrome.

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

Note: One patient withdrew from study after receiving 2 doses of ravulizumab-cwvz.

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 treatment, increasing from 60.50×10^9/L at baseline to 296.67×10^9/L at Day 8 and remained above 296×10^9/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.

Generalized Myasthenia Gravis (gMG) (1)

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 6).

Table 6. 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 *
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; gMG: Generalized Myasthenia Gravis; LS: 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) (1)

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.

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.

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

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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U.S. Food and Drug Administration Label:

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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
01/01/2026	Document updated. The following changes were made to the Coverage: 1) Revised coverage criteria for paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, generalized myasthenia gravis and neuromyelitis optica spectrum disorder; 2) Revised and added “non-Food and Drug Administration approved” to the experimental, investigational and/or unproven statement; and 3) Moved Myasthenia Gravis Foundation of America (MGFA) Clinical Classification and The Myasthenia Gravis-Specific Activities of Daily Living Scale (MG-ADL) to the Policy Guidelines section. Added references 5, 6 and 19; other updated, and some removed.
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).