Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
04-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
SOLIRIS® (eculizumab) Injection for intravenous use	Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis Treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy • Limitation of Use: SOLIRIS is not indicated for the treatment of patients with Shiga toxin E coli related hemolytic uremic syndrome (STEC-HUS) Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AchR) antibody positive Treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive		1
ULTOMIRIS® (ravulizumab-cwvz) Injection for intravenous use	Treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH) Treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) • Limitations of Use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) Treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive Treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive		2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Atypical Hemolytic Uremic Syndrome	Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. HUS typically develops in children, is preceded by bloody diarrhea, and responds well to supportive care. Typical HUS is caused by a bacterial infection associated with Shiga toxin-producing Escherichia coli (STEC) or other bacteria and is called STEC-HUS. However, atypical

	HUS (aHUS) can develop at any age; 5%-10% of cases do not have prodromal diarrhea and have a poor prognosis.(12) The major pathogenesis of aHUS involves dysregulation of the complement system such as genetic abnormalities or autoantibodies, which are responsible for 60%-70% of cases. Mutation in the complement Factor H(CFH), Factor 1 (F1) is the most frequent cause of aHUS, followed by membrane cofactor protein (MCP), complement factor I (CFI), complement 3 (C3), complement Factor B (CFB), thrombomodulin (THBD), and others. Autoantibodies against CFH are detected in 6%-10% of cases of aHUS. Recently, complement-independent forms of aHUS, such as mutations in diacylglycerol kinase Epsilon (DGKE) and plasminogen (PLG) have been reported.(12) The two important differential diagnoses of aHUS in adults include thrombotic thrombocytopenic purpura (TTP) and secondary HUS. TTP is characterized by persistent thrombocytopenia and a defect in ADAMTS13 activity, determined through fluorometric or chromogenic assay. ADAMTS13 assays are critical to differentiating between TTP and aHUS. Severe deficiency (less than 5-10% activity) is highly indicative of TTP. Secondary HUS may be considered in presence of autoimmune diseases, malignancies, hemopoietic stem cell or solid organ transplantation, malignant hypertension, or use of drugs such as calcineurin inhibitors, gemcitabine, mitomycin, interferon, quinine, and cocaine. The treatment of secondary HUS is withdrawal of offending drug or treating the triggering condition.(10) Since ADAMTS13 testing often takes several days to complete and severe end-organ damage may occur, more rapid methods of diagnosis have been proposed. Patients with a severe ADAMTS13 deficiency typically present with blood creatinine less than 2.26 mg/dL and a platelet count less than 30,000/mm3; approximately 50% also show antinuclear antibodies. Diagnostic testing using blood creatinine, platelet count, and presence of antinuclear antibodies had 98.1% specificity and 46.9% sensitivity.(10) Patients with aHUS require relatively comprehensive evaluation of the complement pathway. The evaluation should include:(10) • Estimation of blood levels of C3, Factor H, I, and B, and anti-factor H antibodies • Flow cytometry for MCP • Sequencing, using a next generation approach for the following CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR3, CFHR5, and DGKE Results of the above investigations might not be available immediately however, therapy should be initiated promptly. Therapy for aHUS is supportive, with attention to management of acute kidney injury and systemic complications. Although, plasma exchange and plasma infusions (PE/PI) have been the standard of care for aHUS, they do not address the underlying cause of complement dysfunction.(10) A multi-center audit of plasma therapy for aHUS showed significant complications of central venous catheterization in 31% of patients. The median time to hematological remission was 11.5 days; 11% of patients did not enter hematological remission and 17% were dialysis dependent by day 33.(11) Because of unsatisfactory recovery, experts in most developed countries do not recommend the empiric use of PE/PI for patients with aHUS.(10) Therapeutic strategies for aHUS have been based on resolution of dysregulation in the complement system. Previously, plasma therapy, including plasma infusion and exchange, was the first-line treatment option for patients with aHUS. However, the therapeutic efficiency of plasma therapy varies according to the causative genetic abnormalities of the alternative complement pathway or other pathways. Liver transplantation has been considered an alternative treatment option, although its utility is limited due to perioperative morbidities and donor shortage. Eculizumab, a monoclonal antibody to terminal C5, was introduced for the management of this debilitating disease and has shown superior outcomes; notably, it prevents organ

	damage and premature death more effectively than prior modalities. The long-acting C5 complement inhibitor, ravulizumab, received early approval by the Food and Drug Administration for the treatment of aHUS. These treatments improve the quality of life for aHUS patients.(12)
Generalized Myasthenia Gravis	Myasthenia gravis (MG) is a neuromuscular disorder primarily characterized by muscle weakness and muscle fatigue. Although the disorder usually becomes apparent during adulthood, symptom onset may occur at any age. The condition may be restricted to certain muscle groups, particularly those of the eyes (ocular myasthenia), or may become more generalized (generalized myasthenia gravis [gMG]), involving multiple muscle groups. Most individuals with MG develop weakness and drooping of the eyelids (ptosis); weakness of eye muscles, resulting in double vision (diplopia); and excessive muscle fatigue following activity. Additional features commonly include weakness of facial muscles; impaired speech (dysarthria); difficulties chewing and swallowing (dysphagia); and weakness of the upper arms and legs (proximal limb weakness). In addition, about 10% of affected patients may develop potentially life-threatening complications due to severe involvement of muscles used during breathing (myasthenic crisis). MG results from an abnormal immune reaction in which antibodies inappropriately attack and gradually injure certain receptors in muscles that receive nerve impulses (antibody-mediated autoimmune response).(13) The course of MG is highly variable. For example, the degree of muscle weakness may vary over hours, from day to day, or over weeks and months, tending to increase with repeated muscle use and to improve with rest. In addition, particularly during the first years after disease onset, some affected individuals may experience alternating periods in which symptoms temporarily subside or worsen. A short-term aggravation of symptoms may be triggered by a variety of factors, including infection, excessive physical activity, menstruation, and after delivery of a child.(13) Corticosteroids are a standard treatment for MG but may cause transient worsening within the first 2 weeks and patients should be monitored closely for this possibility. As a result, a MG consensus panel lists corticosteroids as one of many agents to avoid or use with caution in MG. A nonsteroidal immunosuppressive agent should be used initially in treating MG. Nonsteroidal immunosuppressive agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. For nonsteroidal immunosuppressive agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the immunosuppressive dose should be tapered slowly to the minimal effective amount. Patients must be monitored for potential adverse effects and complications from immunosuppressive drugs. Changing to an alternative immunosuppressive agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.(6) Plasma exchange and IVIg are appropriately used as short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom immunosuppressive agents are contraindicated. Refractory MG is defined as post-intervention status is unchanged or worse after corticosteroids and at least 2 other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by the patient and physician.(6) The time of onset and maximal effect varies between products. Azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus can take between 6 to 12 months to onset and up to 1 to 2 years to see maximal effect in MG. Rapid therapies such as plasmapheresis or IVIg therapy take approximately 1 week to onset and between 1 to 3 weeks to see maximal effect.(6) Certain medications have established pharmacologic adverse effects on neuromuscular transmission. Use of these medications in a patient with MG can further reduce the

	effectiveness of neuromuscular transmission and cause increased clinical weakness. However, reported associations do not necessarily mean these medications should never be prescribed in MG. Clinical judgment and the risk-to-benefit ratio of the drug should be considered when it is deemed important for a patient's treatment. Medications that can cause a significant increase in weakness in patients with MG include fluoroquinolones, botulinum toxin, ketolides (particularly telithromycin) and aminoglycoside antibiotics, beta blockers, macrolide antibiotics, procainamide, quinidine, quinine, and magnesium. A number of other medications may unmask or exacerbate MG, particularly the neuromuscular blocking agents used during anesthesia, which can lead to prolonged postoperative weakness and ventilator dependence.(6)
Paroxysmal Nocturnal Hemoglobinuria	Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, rare, multi-systemic disease developing as a result of a somatic mutation of hematopoietic stem cells, and characterized by clonal, complement-mediated intravascular hemolysis. PNH is mainly a disease of adults with a median age of onset in the thirties. High Precision Flow Cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH. Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH. Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., red blood cells [RBCs] and white blood cells [WBCs]) to establish a diagnosis of PNH.(7) The lack of the complement inhibitor CD59 on RBCs surface is mostly responsible for the clinical manifestations in PNH. These patients manifest with chronic intravascular hemolysis (IVH), paroxysmal flares of hemolysis, and a propensity for thrombosis. IVH leads to release of free hemoglobin (Hb) into the blood. Free Hb, in turn, can cause various toxic effects, including hypercoagulability, changes in vascular tone from reduction of circulating nitric oxide, and renal damage.(15) Extravascular hemolysis also occurs in patients with PNH because C3 fragments that are not destroyed by the membrane attack complex (MAC) intravascularly can accumulate on the GPI-negative red blood cell (lacking CD55) surface and these fragments opsonize the RBCs, causing reticuloendothelial destruction in the liver and spleen.(15) The main clinical situations or diseases that should be considered in the differential diagnosis of PNH are:(15) • Coombs-negative hemolytic anemia (e.g., hemoglobinopathies, hereditary spherocytosis), microangiopathic hemolytic anemias, drug- or toxin-induced hemolysis/anemias, disseminated intravascular coagulation, and autoimmune hemolysis • Venous thrombosis in atypical sites, including myeloproliferative disorders; solid tumors associated with hypercoagulability; extrinsic compression of vessels, and; inherited/acquired thrombophilias • Anemia and/or other cytopenias related to bone marrow failure syndrome (e.g., aplastic anemia, myelodysplastic syndrome [MDS]) PNH is classified into three different categories:(15) • Classic PNH (PNH with clinical and laboratory findings of intravascular hemolysis without any evidence of bone marrow deficiency) • PNH in the setting of another specified bone marrow disorder (evidence of hemolysis, as well as another specified bone marrow disorder [e.g., aplastic anemia, MDS])

	• Subclinical PNH (patients with a small population of PNH cells and no clinical or laboratory evidence of hemolysis or thrombosis) Historically, patients with PNH had a median survival of ten years after diagnosis however, since the development of complement inhibitors survival rates have improved to approximately 75%(16). The approach to therapy depends on the severity of symptoms and the degree of hemolysis. The treatment options for PNH are supportive care, allogenic hematopoietic stem cell transplantation (HSCT), and a complement blockade.(7,15)
Neuromyelitis Optica Spectrum Disorder	Neuromyelitis optica spectrum disorder (NMOSD), formerly known as Devic's disease, is a chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerve (optic neuritis) and inflammation of the spinal cord (myelitis). Initially, it was thought to be a monophasic illness, consisting of episodes of inflammation of one or both optic nerves and the spinal cord over a short period of time (days or weeks) but, after the initial episode, no recurrence. It is now recognized that most patients satisfying current criteria for NMOSD experience repeated attacks separated by periods of remission. The interval between attacks may be weeks, months, or years.(5) Early in the course of the disease, it may be difficult to distinguish between NMOSD and multiple sclerosis (MS) because both may cause optic neuritis and myelitis. However, the optic neuritis and myelitis tend to be more severe in NMOSD; the brain MRI is more commonly normal, and the spinal fluid analysis does not usually show oligoclonal bands in NMOSD, which are features that help distinguish it from MS.(5) NMOSD can be AQP4 antibody positive or negative. The diagnostic criteria for NMOSD with AQP4 positive diagnosis are: at least 1 core clinical characteristic, a positive test for AQP4-IgG, and exclusion of alternative diagnoses. The core clinical characteristics are:(8) • Optic neuritis • Acute myelitis • Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting • Acute brainstem syndrome • Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions • Symptomatic cerebral syndrome with NMOSD-typical brain lesions An international consensus panel reached several conclusions in addition to the above criteria to establish an NMOSD diagnosis. First, at least 1 discrete clinical attack of CNS symptoms must occur to establish NMOSD diagnosis. Although, asymptomatic AQP4-IgG seropositive status may exist for years before clinical NMOSD presentation, the natural history of asymptomatic seropositivity is poorly understood. Second, NMOSD diagnosis is not warranted in asymptomatic patients with NMOSD-compatible MRI lesions because the expected clinical course in such individuals is unknown. Third, no clinical characteristic is pathognomonic of NMOSD. Accordingly, a single clinical manifestation is not diagnostic when AQP4-IgG is not detected. Finally, no single characteristic is exclusionary, but some are considered red flags that signal the possibility of alternative diagnoses. The main clinical red flags concern the temporal course of the syndrome rather than the actual manifestations. Most notably, a gradually progressive course of neurologic worsening over months to years is very uncommon (1%–2%) in NMOSD. However, after thorough investigation for potential competing disorders, the weight of evidence may justify NMOSD diagnosis despite presence of 1 or more red flags.(8) Treatment strategies for attack prevention in NMOSD and MS differ. Some MS immunotherapies appear to aggravate NMOSD, indicating an imperative for early, accurate diagnosis. Patients with NMOSD who are AQP4-IgG seropositive should be assumed to be at risk for relapse indefinitely and preventative treatment should be considered.(8) Azathioprine and mycophenolate mofetil have been used off label to

	prevent NMOSD attacks for decades. Their efficacy in NMOSD has been demonstrated in several retrospective studies and case series. In recent years, their use in NMOSD has declined in favor of rituximab owing to their comparative lower efficacy as demonstrated in multiple retrospective studies.(14) Rituximab is a commonly used off-label preventative therapy in NMOSD. Rituximab is a monoclonal antibody (MAB) against CD20-positive B-Cells which include pre B-cell, immature B-cell, and memory B-cell lineage but not plasmablasts or plasma cells. Its exact mechanism of action in NMOSD is unknown, but it is hypothesized to involve reduction of pathogenic antibody production, dampening of pro-inflammatory cytokines, and decreasing B-cell dependent antigen presentation to T-cells.(14) There are currently 4 FDA labeled therapies for AQP4 antibody positive NMOSD; SOLIRIS, ULTOMIRIS, UPLIZNA, and ENSPRYNG.(14) Disability in NMOSD is a direct consequence of relapse. Spontaneous gradual progression of disability like in MS is very rare in NMOSD. Thus, NMOSD relapses are a clinically relevant measure. Amongst secondary end points, disability is very important. The main categories are spinal cord/ brainstem related, motor (weakness, spasticity), sensory (numbness and pain), bladder, bowel, sexual function, and vision. The expanded disability and status scale (EDSS) measure is a suitable and well validated in MS research, but cerebellar and cerebral functional scales are not really applicable in NMOSD, as cognitive and cerebellar dysfunction is limited in NMOSD. The optic spinal impairment scale is derived and modified from EDSS. There are no formal psychometrics supporting the scale and it is not widely used. There are numerous vision specific scales, but none are specific for optic neuritis. Despite the use of the EDSS in NMOSD clinical trials, current literature does not support its use as a measure of NMOSD disease severity.(9)
Soliris Efficacy	**aHUS(1)** SOLIRIS inhibits terminal complement-mediated IVH in patients with atypical hemolytic uremic syndrome (aHUS). The safety and efficacy of SOLIRIS for the treatment aHUS was evaluated in five single-arm studies (four prospective and one retrospective). Efficacy evaluations were based on thrombotic microangipathy (TMA) endpoints which included; platelet count change from baseline, hematologic normalization (maintenance of normal platelet counts and LDH levels for at least four weeks), complete TMA response (hematologic normalization plus at least a 25% reduction in serum creatinine for a minimum of four weeks), TMA-event free status (absence for at least 12 weeks of a decrease in platelet count of greater than 25% from baseline, plasma exchange or plasma infusion, and new dialysis requirement), and daily TMA intervention rate (number of plasma exchange or plasma infusion interventions and the number of new dialyses required per patient per day). Study 1 (C08-002A/B) enrolled 17 patients with aHUS who were resistant to plasma therapy (PE/PI). Patients were treated for a minimum of 26 weeks (mean was 38 weeks). SOLIRIS reduced signs of complement-mediated TMA activity, as shown by an increase in mean platelet counts from 109 +/- 32 x 10^9/L at baseline to 169 +/- 72 x 10^9/L by one week with the effect maintained through 26 weeks. Hematologic normalization (platelet counts and serum LDH concentrations) and complete TMA response were maintained by all responders. Renal function improved as indicated by increases in the eGFR from baseline and requirements for dialysis were reduced. Response to SOLIRIS was similar in patients with or without complement gene mutations. Study 2 (C08-003A/B) enrolled 20 patients with aHUS who were sensitive to PE/PI. Patients were treated for a minimum of 26 weeks (mean was 40 weeks). SOLIRIS reduced signs of complement-mediated TMA in this study as well. Platelet counts were maintained at normal levels despite elimination of PE/PI. The mean platelet count was 228 +/- 78 x 10^9/L at baseline and 233 +/- 69 x 10^9/L at week 26. Hematologic

	normalization (platelet counts and serum LDH concentrations) and complete TMA response were maintained by all responders. Renal function was maintained during SOLIRIS therapy. Study 3 (C09-001r; retrospective study) included 19 pediatric patients (2 months of age to 17 years). The median duration of SOLIRIS therapy was 16 to 38 weeks depending on the age of the patient. Efficacy results were consistent with the results of Study 1 and 2. SOLIRIS reduced signs of complement-mediated TMA, as shown by an increase in mean platelet counts of 171 +/- 83 x 10^9/L at baseline to 233 +/- 109 x 10^9/L one week after therapy with the effect maintained through 26 weeks (mean platelet count 254 +/- 79 x 10^9/L). Study 4 (C10-004) enrolled 41 adult patients who displayed signs of TMA. Patients were treated for a minimum of 26 weeks and efficacy results were similar to previous studies. SOLIRIS reduced signs of complement-mediated TMA, as shown by an increase in mean platelet counts of 119 +/- 66 x 10^9/L at baseline to 200 +/- 84 x 10^9/L one week after therapy with the effect maintained through 26 weeks (mean platelet count 252 +/- 70 x 10^9/L). Renal function was also improved during SOLIRIS therapy with mean eGFR increasing from 17 +/- 12 mL/min/1.73m2 to 47 +/- 24 mL/min/1.73m2. Study 5 (C10-003) enrolled 22 pediatric and adolescent patients (5 months of age to 17 years). Patients were treated for a minimum of 26 weeks and efficacy was similar to previous studies. SOLIRIS reduced signs of complement-mediated TMA, as shown by an increase in mean platelet counts of 88 +/- 42 x 10^9/L at baseline to 281 +/- 123 x 10^9/L one week after therapy with the effect maintained through 26 weeks (mean platelet count 293 +/- 106 x 10^9/L). Renal function was also improved during SOLIRIS therapy with mean eGFR increasing from 33 +/- 30 mL/min/1.73m2 to 98 +/- 44 mL/min/1.73m2. **PNH(1)** Similar to aHUS, SOLIRIS inhibits terminal complement-mediated IVH in PNH patients. SOLIRIS improves symptoms of PNH by reducing hemolysis, stabilizing Hb concentrations, and decreasing the need for RBC transfusions. The safety and efficacy of SOLIRIS for the treatment of PNH patients with hemolysis was evaluated in a double-blind, placebo-controlled 26-week study (Study 1; NCT00122330). Patients (n=87) with PNH who had received at least 4 RBC transfusions during the 12 months prior to study entry were randomized to receive SOLIRIS or placebo for 26 weeks. Patients were permitted to continue supportive therapies for PNH such as anticoagulants and systemic corticosteroids. Primary endpoints were stabilization of Hb above the level required for transfusion and number of packed RBCs transfused during the study period. Secondary efficacy measures included hemolysis, change in the level of fatigue as measured by FACIT-fatigue score, and proportion of patients with transfusion independence. Stabilization of Hb levels occurred in 49% of SOLIRIS treated patients compared to 0% in the placebo group (p less than 0.001). The median number of packed RBCs infused was zero in the SOLIRIS group compared to ten in the placebo group (p less than 0.001). Transfusion independence was achieved by 51% of patients treated with SOLIRIS compared to zero for placebo ($p < 0.001$). Fatigue scores were improved with SOLIRIS (+6.4 points) versus placebo (-4 points) (p less than 0.001). Hemolysis was also reduced with SOLIRIS therapy compared to placebo ($p < 0.001$). Additionally, (Study 2; NCT00122304) enrolled patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter. Patients received SOLIRIS treatment over a 52-week period. A reduction in intravascular hemolysis as measured by serum LDH levels was sustained for the treatment period and resulted in a reduced need for RBC transfusion and less fatigue. A long-term extension study

(NCT00122317) showed similar results over an exposure period ranging from 10 to 54 months.

gMG(1)

The precise mechanism by which SOLIRIS exerts its therapeutic effect in generalized myasthenia gravis (gMG) patients is unknown but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

A 26-week, phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicenter study (REGAIN; NCT01997229) was conducted to determine the safety and efficacy of SOLIRIS in anti-acetylcholine receptor antibody-positive refractory gMG. Eligible patients (N=125) were at least 18 years old; had a positive serological test for anti-acetylcholine receptor antibodies; had a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score of 6 or more; had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II-IV disease; had vaccination against Neisseria meningitides; and had previously failed treatment with at least 2 immunosuppressive therapies or one immunosuppressive therapy and chronic intravenous immunoglobulin or plasmapheresis/plasma exchange (given at least four times per year, for 12 months without symptom control). The primary efficacy endpoint was the change from baseline to week 26 in MG-ADL total score, as measured by the worst-rank ANCOVA. The primary analysis showed no significant difference between SOLIRIS and placebo (least squares mean rank 56.6 [SEM 4.5] vs 68.3 [4.5]; rank-based treatment difference -11.7, 95% CI -24.3 to 0.96; p=0.0698). However, there was a statistically significant difference in the change in MG-ADL score from baseline to week 26 between SOLIRIS and placebo in a pre-specified sensitivity repeated-measures model analysis with immunosuppressive treatments as covariates, (least squares mean -4.2 (SEM 0.49) vs. -2.3 (0.48); least squares mean difference of change in score with SOLIRIS relative to placebo -1.9, 95% CI -3.3 to -0.6; p=0.006).(1) The REGAIN trial discussion notes, "using the repeated-measures analyses, the benefit of SOLIRIS compared with placebo occurred within the first 4 weeks of treatment, with most of the effect achieved by 12 weeks."

The MGFA clinical classification divides MG into 5 main classes and several subclasses. It is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy.(4)

Class	Features
I	Any ocular muscle weakness; may have weakness of eye closure; All other muscles are normal
II	Mild weakness affecting muscles other than the 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.
III	Moderate weakness affecting muscles other than the 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.
IV	Severe weakness affecting muscles other than the 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.

	V | Intubation with or without mechanical ventilation (exception: intubation for routine perioperative management). The use of a feeding tube without intubation places a patient in class IVb. **NMOSD(1)** The efficacy of SOLIRIS for the treatment of NMOSD was established in NMOSD Study 1 (NCT01892345), a randomized, double-blind, placebo-controlled trial that enrolled 143 patients (96 patients were randomized to receive Solaris treatment and 47 were randomized to receive placebo) with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening: • History of 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 • EDSS score less than or equal to 7 (consistent with the presence of at least limited ambulation with aid) • If on immunosuppressive therapy, on a stable dose regimen • The use of concurrent corticosteroids was limited to 20 mg per day or less • Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIg within 3 weeks prior to screening The primary endpoint for NMOSD Study 1 was the time to the first adjudicated on-trial relapse. The time to the first adjudicated on-trial relapse was significantly longer in SOLIRIS-treated patients compared to placebo-treated patients (relative risk reduction 94%; hazard ratio 0.058; $p < 0.0001$). SOLIRIS-treated patients experienced similar improvement in time to first adjudicated on-trial relapse with or without concomitant treatment. SOLIRIS-treated patients had a 96% relative reduction in the adjudicated on-trial annualized relapse rate (ARR) compared to patients on placebo. Compared to placebo-treated patients, SOLIRIS-treated patients had reduced annualized rates of hospitalizations (0.04 for SOLIRIS versus 0.31 for placebo), of corticosteroid administrations to treat acute relapses (0.07 for SOLIRIS versus 0.42 for placebo), and of plasma exchange treatments (0.02 for SOLIRIS versus 0.19 for placebo).
ULTOMIRIS Efficacy	ULTOMIRIS (ravulizumab-cwvz), is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex.(2) **PNH(2)** The safety and efficacy of ULTOMIRIS in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 (NCT02946463) and PNH Study 302 (NCT03056040). 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. PNH Study 301 was a 26-week study that enrolled 246 patients. Efficacy was established based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was defined as patients who did not receive a transfusion and 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 greater than or equal to 2 × upper limit of normal (ULN), after prior LDH reduction to less than 1.5 × ULN on therapy and the proportion of patients with stabilized Hb. Non-inferiority of ULTOMIRIS to eculizumab was

	demonstrated across endpoints in the complement inhibitor naïve treatment population. PNH Study 302 was a 26-week study that enrolled 195 patients. 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 Hb, 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. The safety and efficacy of ULTOMIRIS was assessed in pediatric patients with PNH in an open-label Phase 3 trial: PNH Study 304 (NCT03406507). Study 304 was conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients. The pediatric study enrolled 13 patients who were treated over a 26-week period. Efficacy in pediatric patients with PNH is similar to that observed in adult patients. **aHUS(2)** The efficacy of ULTOMIRIS in patient with aHUS was assessed in 2 open-label, single-arm studies. Study ALXN1210-aHUS-311 enrolled adult patients who displayed signs of thrombotic microangiopathy (TMA) and Study ALXN1210-aHUS-312 enrolled pediatric patients who displayed signs of TMA. Study ALXN1210-aHUS-311 a total of 56 patients with aHUS were evaluated for efficacy. The efficacy evaluation was based on Complete TMS response during the 26-week initial evaluation period, as evidenced by normalization of hematological parameters (platelet count and LDH) and greater than or equal to 25% improvement in serum creatinine from baseline. Complete TMA response was observed in 30 of the 56 patients (34%) during the 26-week initial evaluation period. Study ALXN1210-aHUS-312 is a 26-week ongoing, multicenter, single-arm, study conducted in 14 patients with documented a-HUS. 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 LDA) and greater than or equal to 25% improvement in serum creatinine from baseline. Complete TMA response was observed in 10 of the 14 patients (71%) during the 26-week initial evaluation period. **gMG(2)** 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 with gMG with a positive serologic test for anti-AChr antibodies, MGFA clinical classification class II to IV, and MG-ADL total score greater than or equal to 6 were enrolled. 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 secondary endpoints, also assessed from baseline to Week 26, included the change in the Quantitative MG total score (QMG), 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. MG-ADL LS Mean was -1.4 for placebo group and -3.1 for the ULTOMIRIS group. QMG LS Mean was -0.8 for placebo group and -2.8 for the ULTOMIRIS group (both MG-ADL and QMG score changes has p value less than 0.001).

	NMOSD(2) The efficacy of ULTOMIRIS for the treatment of NMOSD was studied in 58 adult patients with anti-AQP4 antibody positive NMOSD (NCT04291262). This study was an open-label multicenter study comparing study participants with a placebo control group from another study (NCT01892345). Study individuals 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 less than or equal to 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. Study participants received ULTOMIRIS for a minimum of 50 weeks. The primary endpoint was the time to first adjudicated on-trial relapse. 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.
Safety	SOLIRIS (eculizumab) and ULTOMIRIS (ravulizumab-cwvz) contain the following boxed warnings:(1,2) SOLIRIS and ULTOMIRIS increase the risk of serious infections, caused by *Neisseria meningitidis*. Life-threatening and fatal meningococcal infections have occurred and these infections may become rapidly life-threatening or fatal if not recognized and treated early. • Vaccinate patients against meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to administering the first dose of Soliris or ULTOMIRIS unless risks of delaying therapy outweigh the risks of developing a serious infection • Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria • Patients receiving Soliris or ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected SOLIRIS (eculizumab) and ULTOMIRIS (ravulizumab-cwvz) are contraindicated in patients with unresolved serious *Neisseria meningitidis* infection.(1,2) SOLIRIS (eculizumab) discontinuation in PNH patients can cause serious hemolysis due to PNH and should be monitored by a healthcare provider for at least 8 weeks following SOLIRIS discontinuation.(1) SOLIRIS (eculizumab) and ULTOMIRIS (ravulizumab-cwvz) are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS and SOLIRIS REMS.(1,2)

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POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
J1300	Soliris	eculizumab iv soln	300 MG/30ML	M ; N ; O ; Y	N		
J1303	Ultomiris	ravulizumab-cwvz iv soln	300 MG/3ML	M ; N ; O ; Y	N		
J1303	Ultomiris	ravulizumab-cwvz iv soln	1100 MG/11ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Soliris	eculizumab iv soln	300 MG/30ML	Commercial ; HIM ; ResultsRx
Ultomiris	ravulizumab-cwvz iv soln	300 MG/3ML	Commercial ; HIM ; ResultsRx
Ultomiris	ravulizumab-cwvz iv soln	1100 MG/11ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Soliris	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of generalized Myasthenia Gravis (gMG) AND ALL of the following: 1. The patient has a positive serological test for anti-AChR antibodies (medical records required) **AND** 2. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IV **AND** 3. The patient has a MG-Activities of Daily Living total score of greater than or equal to 6 **AND** 4. ONE of the following: A. The patient's current medications have been assessed and any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides) have been discontinued **OR** B. Discontinuation of the offending agent is NOT clinically appropriate **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response after at least a 1-year total trial to at least TWO immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) (either combination or monotherapy) **OR** B. The patient has an intolerance or hypersensitivity to at least TWO immunosuppressive therapies **OR** C. The patient has tried and had an inadequate response after at least a 1-year total trial to treatment to at least ONE immunosuppressive therapy (e.g., azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) AND ONE of the following: 1. The patient required chronic intravenous immunoglobulin (IVIG) (i.e., at least every 3 months over 12 months without symptom control) **OR** 2. The patient required chronic plasmapheresis/plasma exchange (i.e., at least every 3 months over 12 months without symptom control) **OR** D. The patient has an intolerance or hypersensitivity to at least ONE immunosuppressant AND plasmapheresis/plasma exchange **OR** E. The patient has an FDA labeled contraindication to ALL immunosuppressive therapies and plasmapheresis/plasma exchange **AND** 6. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response to ULTOMIRIS (ravulizumab-cwvz), RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), or VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **OR** B. The patient has an intolerance or hypersensitivity to ULTOMIRIS (ravulizumab-cwvz), RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), or VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **OR** C. The patient has an FDA labeled contraindication to ALL of the following: 1. ULTOMIRIS (ravulizumab-cwvz) 2. RYSTIGGO (rozanolixizumab-noli) 3. VYVGART (efgartigimod) 4. VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **AND** 7. The patient will NOT be using the requested agent in combination with RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), or ZILBRYSQ (zilucoplan) for the requested indication **OR** B. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) AND ALL of the following: 1. The diagnosis was confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI)-linked proteins (lab tests required) **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to TWO of the following preferred agent(s); ULTOMIRIS (ravulizumab-cwvz), FABHALTA (iptacopan), EMPAVELI (pegcetacoplan) **OR** B. The patient has an intolerance or hypersensitivity to TWO of the following preferred agent(s); ULTOMIRIS (ravulizumab-cwvz), FABHALTA (iptacopan), EMPAVELI (pegcetacoplan) **OR** C. The patient has an FDA labeled contraindication to ALL of the following preferred agent(s); ULTOMIRIS (ravulizumab-cwvz), FABHALTA (iptacopan), EMPAVELI (pegcetacoplan) **OR** D. The patient is currently treated with the requested agent (medical records including last date of infusion required) **AND** 3. The patient will NOT be using the requested agent in combination with EMPAVELI (pegcetacoplan), FABHALTA (iptacopan), or PiaSky (crovalimab-akkz) for the requested indication **OR** C. The patient has a diagnosis of atypical Hemolytic Uremic Syndrome (aHUS) AND ALL of the following: 1. The diagnosis was confirmed by ONE of the following: (medical records required) A. Genetic mutation (e.g., *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR3, CFHR5*) **OR** B. Antibodies to complement factors **OR** C. A differential diagnosis of complement-mediated HUS has been demonstrated (i.e., screening for Shiga toxin-producing E. coli [STEC] for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 less than 10% activity for thrombotic thrombocytopenic purpura [TTP], screening for defective cobalamin metabolism) **AND** 2. The patient is negative for Shiga toxin-producing *E. coli* (STEC) **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to ULTOMIRIS (ravulizumab-cwvz) **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to ULTOMIRIS (ravulizumab-cwvz) **OR** C. The patient has an FDA labeled contraindication to ULTOMIRIS (ravulizumab-cwvz) **OR** D. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) AND ALL of the following: 1. The patient is anti-aquaporin-4 (AQP4) antibody positive (lab test required) **AND** 2. The diagnosis was confirmed by at least ONE of the following: A. Optic neuritis **OR** B. Acute myelitis **OR** C. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting **OR** D. Acute brainstem syndrome **OR** E. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions **OR** F. Symptomatic cerebral syndrome with NMOSD-typical brain lesions **AND** 3. The patient has had at least ONE discrete clinical attack of CNS symptoms **AND** 4. Alternative diagnoses (e.g., multiple sclerosis, ischemic optic neuropathy) have been ruled out **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response to ENSPRYNG (satralizumab-mwge), ULTOMIRIS (ravulizumab-cwvz), OR UPLIZNA (inebilizumab-cdon) **OR** B. The patient has an intolerance or hypersensitivity to ENSPRYNG (satralizumab-mwge), ULTOMIRIS (ravulizumab-cwvz), OR UPLIZNA (inebilizumab-cdon) **OR** C. The patient has an FDA labeled contraindication to ENSPRYNG (satralizumab-mwge), ULTOMIRIS (ravulizumab-cwvz), AND UPLIZNA (inebilizumab-cdon) **OR** D. The patient has severe disease, and it has been determined that ENSPRYNG (satralizumab-mwge), ULTOMIRIS (ravulizumab-cwvz), AND UPLIZNA (inebilizumab-cdon) would NOT be clinically appropriate for the patient **OR** E. The patient is currently using the requested agent (medical records including last date of infusion required) **AND** 6. The patient will NOT be using the requested agent in combination with ENSPRYNG, rituximab, or UPLIZNA for the requested indication **OR** E. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for the use of the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with ULTOMIRIS **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval**: 6 months **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient was previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent (e.g., decreased requirement for RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase [LDH]) (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with EMPAVELI (pegcetacoplan), FABHALTA (iptacopan), or PiaSky (crovalimab-akkz) for the requested indication **OR** B. The patient has a diagnosis of atypical hemolytic uremic syndrome (aHUS) AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent (e.g., improved platelet count, reduction of lactate dehydrogenase [LDH], stabilization/improvement of renal function) (medical records required) **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to ULTOMIRIS (ravulizumab-cwvz) **OR** B. The patient has an intolerance or hypersensitivity to ULTOMIRIS (ravulizumab-cwvz) **OR** C. The patient has an FDA labeled contraindication to ULTOMIRIS (ravulizumab-cwvz) **OR** C. The patient has a diagnosis of generalized myasthenia gravis (gMG) AND ALL of the following: 1. The patient has had improvements or stabilization with the requested agent (e.g., improved MG-ADL total score, improved quantitative myasthenia gravis total score) (medical records required) **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to ULTOMIRIS (ravulizumab-cwvz), RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), or VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **OR** B. The patient has an intolerance or hypersensitivity to ULTOMIRIS (ravulizumab-cwvz), RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), or VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **OR** C. The patient has an FDA labeled contraindication to ALL of the following: 1. ULTOMIRIS (ravulizumab-cwvz) 2. RYSTIGGO (rozanolixizumab-noli) 3. VYVGART (efgartigimod) 4. VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **AND** 3. The patient will NOT be using the requested agent in combination with RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), or ZILBRYSQ (zilucoplan) for the requested indication **OR** D. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) AND BOTH of the following: 1. The patient has had stabilization or improvement with the requested agent (e.g., decreased relapses, improvement or stabilization of vision or paralysis) (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with ENSPRYNG, rituximab, or UPLIZNA for the requested indication **OR**

Module	Clinical Criteria for Approval
	E. The patient has a diagnosis other than PNH, aHUS, gMG, or NMOSD AND the patient has had improvements or stabilization with the requested agent (e.g., improvement or stabilization of symptoms) (medical records required) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with ULTOMIRIS **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months
Ultomiris	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) AND BOTH of the following: 1. The diagnosis was confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI)-linked proteins (lab tests required) **AND** 2. The patient will NOT be using the requested agent in combination with EMPAVELI (pegcetacoplan), FABHALTA (iptacopan), or PiaSky (crovalimab-akkz) for the requested indication **OR** B. The patient has a diagnosis of atypical Hemolytic Uremic Syndrome (aHUS) AND BOTH of the following: 1. The diagnosis has been confirmed by ONE of the following: (medical records required) A. Genetic mutation (e.g., *CFH, CD46, CFI, C3, CFB, THBD, CFHR1, CFHR3, CFHR5*) **OR** B. Antibodies to complement factors **OR** C. A differential diagnosis of complement-mediated HUS has been demonstrated (i.e., screening for Shiga toxin-producing E. coli [STEC] for STEC-HUS, pneumococcal culture of blood/sputum/cerebrospinal or pleural fluid for pneumococcal-associated HUS, ADAMTS13 less than 10% activity for thrombotic thrombocytopenic purpura [TTP], screening for defective cobalamin metabolism) **AND** 2. The patient is negative for Shiga toxin-producing *E. coli* (STEC) **OR** C. The patient has a diagnosis of generalized Myasthenia Gravis (gMG) AND ALL of the following: 1. The patient has a positive serological test for anti-AChR antibodies (medical records required) **AND** 2. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IV **AND** 3. The patient has a MG-Activities of Daily Living total score of greater than or equal to 6 **AND** 4. ONE of the following: A. The patient's current medications have been assessed and any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides) have been discontinued **OR** B. Discontinuation of the offending agent is NOT clinically appropriate **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE conventional agent used for the treatment of myasthenia

Module	Clinical Criteria for Approval
	gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR** B. The patient has an intolerance or hypersensitivity to ONE conventional agent used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR** C. The patient has an FDA labeled contraindication to ALL conventional agents used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR** D. The patient required chronic intravenous immunoglobulin (IVIG) **OR** E. The patient required chronic plasmapheresis/plasma exchange **OR** 6. The patient will NOT be using the requested agent in combination with RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), or ZILBRYSQ (zilucoplan) for the requested indication **OR** D. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) AND ALL of the following: 1. The patient is anti-aquaporin-4 (AQP4) antibody positive (lab test required) **AND** 2. The diagnosis was confirmed by at least ONE of the following: 1. Optic neuritis **OR** 2. Acute myelitis **OR** 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting **OR** 4. Acute brainstem syndrome **OR** 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions **OR** 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions **AND** 3. The patient has had at least ONE discrete clinical attack of CNS symptoms **AND** 4. Alternative diagnoses (e.g., multiple sclerosis, ischemic optic neuropathy) have been ruled out **AND** 5. The patient will NOT be using the requested agent in combination with ENSPRYNG, rituximab, or UPLIZNA for the requested indication **OR** E. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with SOLIRIS **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 6 months **Renewal Evaluation:** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient was previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent (e.g., decreased requirement for RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH), stabilization/improvement of symptoms (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with EMPAVELI (pegcetacoplan), FABHALTA (iptacopan), or PiaSky (crovalimab-akkz) for the requested indication **OR** B. The patient has a diagnosis of Atypical Hemolytic Uremic Syndrome (aHUS) AND the patient has had improvements or stabilization with the requested agent (e.g., improved platelet count, reduction of lactate dehydrogenase (LDH), stabilization/improvement of renal function) (medical records required) **OR** C. The patient has a diagnosis of generalized myasthenia gravis (gMG) AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent (e.g., improved MG-ADL total score, improved quantitative myasthenia gravis total score) (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with RYSTIGGO (rozanolixizumab-noli), VYVGART (efgartigimod), VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), or ZILBRYSQ (zilucoplan) for the requested indication **OR** D. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) AND BOTH of the following: 1. The patient has had stabilization or improvement with the requested agent (e.g., decreased relapses, improvement or stabilization of vision or paralysis) (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with ENSPRYNG, rituximab, or UPLIZNA for the requested indication **OR** E. The patient has a diagnosis other than PNH, aHUS, gMG, or NMOSD AND the patient has had improvement or stabilization with the requested agent (e.g., improvement or stabilization of symptoms) (medical records required) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with SOLIRIS **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months