ravulizumab (Ultomiris™), eculizumab (Soliris®, biosimilars)

Medicare Advantage Medical Policy # MA-108
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Based on review of available data, the Health Plan may consider ravulizumab (Ultomiris™)‡ or eculizumab (Soliris®, biosimilars)‡ for the treatment of paroxysmal nocturnal hemoglobinuria to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of paroxysmal nocturnal hemoglobinuria will be considered when the following criteria are met for the requested drug:

- Initial authorization:
    - Patient has received meningococcal vaccination according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations in patients receiving a complement inhibitor; AND
    - If the drug is initiated < 2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics; AND
    - Documentation is provided of peripheral blood high sensitivity flow cytometry results showing a granulocyte or monocyte clone size of ≥ 5%; AND
    - Patient has at least ONE of the following significant disease manifestations caused by hemolysis:
        - Documented history of a major adverse vascular event (MAVE) from thromboembolism; OR
        - Presence of organ damage secondary to chronic hemolysis (e.g. worsening renal insufficiency); OR
        - Patient is pregnant and potential benefit outweighs potential fetal risk; OR
        - Patient is transfusion-dependent as evidenced by 2 or more transfusions in the 12 months prior to initiation of treatment; OR
        - Patient has high lactate dehydrogenase (LDH) activity (defined as ≥ 1.5 x ULN) with clinical symptoms (e.g., severe fatigue, dyspnea, jaundice, abdominal or chest pain, discolored urine, dysphagia, pulmonary hypertension); AND

- Patient meets ONE of the following:
  - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks following loading dose that does not exceed 3,000 mg; OR
  - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 900 mg every 2 weeks after a loading dose of 600 mg weekly for 4 weeks.

- Continuation request:
  - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
  - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
    - Decreased serum lactate dehydrogenase (LDH) compared to pretreatment baseline; OR
    - Decreased need for blood transfusion compared to pretreatment baseline; OR
    - Stabilization of hemoglobin; AND
  - Patient meets ONE of the following:
    - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks; OR
    - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 900 mg every 2 weeks.

Atypical Hemolytic Uremic Syndrome (aHUS)

Based on review of available data, the Health Plan may consider ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of atypical hemolytic uremic syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of atypical hemolytic uremic syndrome will be considered when the following criteria are met:

- Initial authorization:
  - Patient has received meningococcal vaccination according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations in patients receiving a complement inhibitor; AND
  - If the drug is initiated < 2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics; AND
  - Patient has a diagnosis of atypical hemolytic uremic syndrome (aHUS); AND
  - Other causes of hemolytic uremic syndrome (e.g. Shiga toxin-producing *E. coli* infection) have been ruled out; AND
  - Patient meets ONE of the following:
    - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks after an initial loading dose of 3,000 mg; OR

        - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks after a loading dose of 900 mg weekly for 4 weeks.
- Continuation request:
    - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
    - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
        - Increased platelet count from pretreatment baseline; OR
        - Stabilization or improvement in estimated Glomerular Filtration Rate (eGFR) from pretreatment baseline; OR
        - Decreased serum lactate dehydrogenase (LDH) compared to pretreatment baseline; AND
    - Patient meets ONE of the following:
        - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks; OR
        - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks.

Generalized Myasthenia Gravis (gMG)

Based on review of available data, the Health Plan may consider ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of generalized myasthenia gravis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of generalized myasthenia gravis will be considered when the following criteria are met:

- Initial authorization:
    - Patient is greater than or equal to 18 years of age; AND
    - Patient has a diagnosis of generalized myasthenia gravis; AND
    - Patient has an anti-acetylcholine receptor autoantibody positive serologic test; AND
    - Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV; AND
    - Patient has received or is currently receiving pyridostigmine unless there is clinical evidence or patient history that suggests the use of pyridostigmine will cause an adverse effect or inadequate response to the patient; AND
    - Patient has received or is currently receiving at least one nonsteroidal immunosuppressive therapy (NSIST) for at least 1 year unless there is clinical evidence or patient history that suggests NSISTs will be ineffective or cause an adverse reaction to the patient. Examples of NSISTs include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide; AND

  - Patient has evidence of unresolved symptoms of generalized myasthenia gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND
  - Patient meets ONE of the following:
    - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks after an initial loading dose of 3,000 mg; OR
    - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks after a loading dose of 900 mg weekly for 4 weeks.
- Continuation request:
  - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
  - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
    - Improvement in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score; OR
    - Improvement in Quantitative Myasthenia Gravis (QMG) total score; AND
  - Patient meets ONE of the following:
    - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks after an initial loading dose of 3,000 mg; OR
    - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Based on review of available data, the Health Plan may consider ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) will be considered when the following criteria are met:

- Initial authorization:
  - Patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) as evidenced by at least ONE of the following core clinical characteristics:
    - Optic neuritis; OR
    - Acute myelitis; OR
    - Area postrema syndrome (i.e., episode of otherwise unexplained hiccups or nausea and vomiting); OR
    - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD typical brain lesions; OR

        - Symptomatic cerebral syndrome with NMOSD-typical brain lesions; AND
    - Patient is 18 years of age or older; AND
    - Patient has a positive anti-aquaporin-4 antibody (AQP4-IgG) serologic test; AND
    - Diagnosis of multiple sclerosis has been ruled out; AND
    - Patient is NOT receiving a disease modifying multiple sclerosis medication (see policy background information for examples); AND
    - Patient has a history of one or more relapses that required rescue therapy during the previous 12 months OR patient has a history of two or more relapses that required rescue therapy during the previous 24 months; AND
    - Patient has received meningococcal vaccination according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations in patients receiving a complement inhibitor; OR if the drug is initiated < 2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics; AND
    - Requested medication is NOT used in combination with other biologics such as inebilizumab-cdon (Uplizna™)‡ or satralizumab-mwge (Enspryng™)‡; AND
    - Patient meets ONE of the following:
        - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks after an initial loading dose of 3,000 mg; OR
        - For eculizumab (Solris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks after a loading dose of 900 mg weekly for 4 weeks.
- Continuation request:
    - Patient has received an initial authorization for the requested drug from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
    - Patient is NOT receiving a disease modifying multiple sclerosis medication (see policy background information for examples); AND
    - Requested medication is NOT used in combination with other biologics such as inebilizumab-cdon (Uplizna) or satralizumab-mwge (Enspryng); AND
    - Patient has experienced a positive clinical response (e.g., reduction in the frequency of relapse) as attested to by the treating provider; AND
    - Patient meets ONE of the following:
        - For Ultomiris requests: Dose does not exceed 3,600 mg every 8 weeks; OR
        - For eculizumab (Soliris, biosimilars) requests: Dose does not exceed 1,200 mg every 2 weeks.

When Services Are Considered Not Medically Necessary

Based on review of available data, the use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for PNH when the patient does not have a manifestation of significant disease is considered to be **not medically necessary.****

Based on review of available data, the continued use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) when the patient has not demonstrated improvement in PNH or aHUS disease manifestations while on therapy is considered to be **not medically necessary.****
Based on review of available data, the use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for gMG when the disease is not MGFA class II to IV, when the patient hast not tried and failed pyridostigmine in addition to at least one NSIST, or does not have evidence of unresolved symptoms of gMG is considered to be **not medically necessary.****

Based on review of available data, the continued use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for gMG or NMOSD when the patient has not experienced improvement while on therapy is considered to be **not medically necessary.****

Based on review of available data, the Health Plan considers the use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) for NMOSD when the patient does not have a history of one or more relapses that required rescue therapy during the previous 12 months OR does not have a history of two or more relapses that required rescue therapy during the previous 24 months to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of ravulizumab (Ultomiris) or eculizumab (Soliris, biosimilars) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Policy Guidelines

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification

Class	***Description***
I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
IIa	Mild weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIb	Mild weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IIIa	Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

IVa	Severe weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IVb	Severe weakness affecting muscles other than ocular muscles. 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 except when employed during routine postoperative management.

Myasthenia Gravis Activities of Daily Living (MG-ADL) profile

Grade	***0***	***1***	***2***	***3***	***Score***
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. 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	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL score total (items 1-8)=	

Quantitative Myasthenia Gravis (QMG) Score

Test Item	***None***	***Mild***	***Moderate***	***Severe***	***Score***
Grade	***0***	***1***	***2***	***3***	

Double vision on lateral gaze (secs)	61	11-60	1-10	Spontaneous	
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete without resistance	Incomplete	
Swallowing 4 oz water	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal congestion	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Forced Vital Capacity	≥80	65-79	50-64	≤50	
Rt-hand grip, kg Men Women	 ≥45 ≥30	 15-44 10-29	 5-14 5-9	 0-4 0-4	
Lt-hand grip, kg Men Women	 ≥35 ≥25	 15-34 10-24	 5-14 5-9	 0-4 0-4	
Head lifted (45 degrees supine), seconds	120	30-119	1-29	0	
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0	
Left leg outstretched (45	100	31-99	1-30	0	

degrees supine), seconds					
				Total QMG Score:	

Background/Overview

Ultomiris and Soliris are monoclonal antibodies that inhibit the conversion of the complement protein C5a to C5b and prevents the generation of the terminal complement complex C5b-9. As a result, they inhibit terminal complement-mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH). They are also approved for the treatment of atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD). Ultomiris is structurally similar to (Soliris®)‡, but with a targeted substitution in the molecule's backbone that causes it to have an increased duration of action. This allows Ultomiris to be given at a longer dosing interval than Soliris. Prior to initiation of either product, the patient must receive meningococcal vaccination because these drugs carry a risk of serious infection. If vaccination cannot be given at least 2 weeks prior to the start of therapy, the patient should be given antibacterial drug prophylaxis. In addition, the Advisory Committee on Immunization Practices (ACIP) recommends a booster dose of meningococcal vaccine every 5 years. Both drugs require the prescriber to be enrolled in a risk evaluation and mitigation strategy (REMS) program. For all indications, Ultomiris requires a weight-based loading dose followed by a weight-based maintenance dose every 4 or 8 weeks beginning 2 weeks after the loading dose. The dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (except for the first maintenance dose); but subsequent doses should be administered according to the original schedule. The recommended dosage regimens for Soliris vary depending on indication. For PNH, patients should receive 600mg of Soliris weekly for the first 4 weeks, followed by 900 mg for the fifth dose 1 week later, then 900 mg every 2 weeks thereafter. In adult patients with aHUS, Soliris should be dosed as 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. For patients less than 18 years of age, Soliris dosing is based upon body weight. In gMG and NMOSD patients, Soliris should be administered as 4 weekly 900 mg doses followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Soliris should be administered at the recommended dosage regimen time points, or within two days of the time points.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is an acquired hematopoietic stem cell disorder associated with an acquired somatic mutation of the phosphatidylinositol glycan class A (PIGA) gene. Mutations disrupt the first step in glycophosphatidylinositol (GPI) synthesis, which causes an absence of the GPI anchor and a deficiency of GPI proteins. The absence of GPI proteins on erythrocytes makes them susceptible to attack by complement and intravascular hemolysis. Intravascular hemolysis associated with PNH leads to release of free hemoglobin, leading to anemia, hemoglobinuria, thrombosis, dysphagia, abdominal pain, pulmonary hypertension, renal impairment, and erectile dysfunction. The prevalence of PNH is estimated to be between 0.5-1.5 per million people in the general population,

with an approximately equal male to female distribution. Although PNH can affect any age group, the median age at diagnosis is during the fourth decade of life. The primary clinical finding is hemolysis of red blood cells by complement, which leads to hemoglobinuria that is most prominent in the morning. Those with PNH are also susceptible to repeated, potentially life-threatening thromboses. Underlying bone marrow dysfunction may also be present and those who are severely affected may have pancytopenia. Many patients also have acquired aplastic anemia. Although less common, some patients have concomitant myelodysplasia. For unknown reasons, PNH may rarely develop into acute leukemia.

Signs and symptoms of PNH may vary, with some patients exhibiting mild and stable disease for many years while other patients have severe symptoms that rapidly progress to life-threatening. However, chronic hemolysis is central to all of the symptoms and physical findings associated with PNH. Fatigue, rapid heartbeat, headaches, and chest pain and difficulty breathing while exercising can result from mild hemolysis. With severe hemolysis, disabling fatigue, dysphagia, and painful contractions of the abdomen and esophagus may occur. It is estimated that 15-30% of patients with PNH develop blood clots, particularly venous thrombosis. Diagnosis of PNH is suspected in those with unexplained hemoglobinuria or abnormally high serum lactate dehydrogenase (LDH) levels. However, flow cytometry is the main diagnostic test for the identification of PNH cells.

There are no formal guidelines for treatment of PNH. However, there is an expert opinion for management of PNH published in a journal supported by the American Society of Hematology. Diagnosis of PNH is straightforward based on flow cytometry and specific treatment is recommended based on classification by the PNH interest group. Soliris is recommended for patients with classic PNH characterized by > 50% of GPI-AP-deficient PMNs as well as patients with PNH in the setting of another bone marrow failure syndrome with large PNH clones. No specific PNH therapy is recommended for patients with subclinical PNH with no clinical or biochemical evidence of intravascular hemolysis. This review was published before the approval of Ultomiris.

Atypical Hemolytic Uremic Syndrome (aHUS)
Hemolytic Uremic Syndrome (HUS) is defined as the triad of non-immune hemolytic anemia, thrombocytopenia, and acute renal failure, in which the underlying lesions are mediated by systemic thrombotic microangiopathy (TMA). Atypical HUS (aHUS) is a subtype of HUS in which TMA is caused by dysregulation of the activity of the complement system. Various aHUS-related mutations have been identified in genes of the complement system, which can explain approximately 60% of the aHUS cases, and a number of mutations and polymorphisms have been functionally characterized. aHUS should be distinguished from a more common condition referred to as typical HUS. The two disorders have different causes and different signs and symptoms. Unlike aHUS, the typical form is caused by infection with certain strains of *Escherichia coli* bacteria that produce toxic substances called Shiga-like toxins. The typical form is characterized by severe diarrhea and most often affects children < 10 years of age. It is less likely than aHUS to involve recurrent attacks of kidney damage that lead to end stage renal disease. The incidence of aHUS is estimated to be 1:500,000 people per year in the US, approximately 10 times less common than typical HUS. Soliris

is considered a first line treatment for aHUS and should be started as soon as possible within the first 48 hours of hospital admission. Recently, Ultomiris has also gained approval for aHUS and has the advantage of less frequent dosing compared to Soliris.

Generalized Myasthenia Gravis (gMG)
Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles. The hallmark of the condition is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder, however, the muscles that control breathing and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR). However, antibodies to other proteins, such as the muscle-specific kinase (MuSK) protein, can also lead to impaired transmission at the neuromuscular junction. Myasthenia gravis most commonly occurs in young adult women (< 40 years of age) and older men (> 60 years of age), but it can occur at any age, including childhood. The incidence ranges from 0.3 to 2.8 per 100,000, and it is estimated to affect more than 700,000 people worldwide. Various clinical scoring systems are available to assess the severity of disease and include the Myasthenia Gravis Foundation of America (MGFA) clinical classification system, Myasthenia Gravis Activities of Daily Living (MG-ADL), and Quantitative Myasthenia Gravis (QMG) test.

Medications to treat myasthenia gravis include anticholinesterase agents (e.g., pyridostigmine), which slow the breakdown of acetylcholine at the neuromuscular junction and thereby improve neuromuscular transmission and increase muscle strength. Immunosuppressive drugs improve muscle strength by suppressing the production of abnormal antibodies and may include prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and rituximab. Plasmapheresis and intravenous immunoglobulin (IVIG) may be options in severe cases to remove the destructive antibodies; however, their effectiveness frequently lasts only a few weeks to months. Additionally, the Food and Drug Administration (FDA) recently approved eculizumab (Soliris) and zilucoplan (Zilbrysq®)‡, both complement inhibitors, as well as rozanolixizumab (Rystiggo®)‡ and efgartigimod alfa products (Vyvgart®, Vyvgart® Hytrulo)‡ which contain an IgG monoclonal antibody that binds to the neonatal Fc receptor for the treatment of generalized myasthenia gravis. Although Soliris, Ultomiris, Zilbrysq, Rystiggo, Vyvgart and Vyvgart Hytrulo are the only agents with FDA approval for the condition, the other agents have been used off-label and are still recommended as first-line therapy in clinical practice guidelines.

Neuromyelitis Optica Spectrum Disorder (NMOSD)
Previously thought to be a subtype of multiple sclerosis, NMOSD is a rare, chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerve and spinal cord. Multiple sclerosis should be ruled out prior to diagnosing NMOSD. Disease modifying multiple sclerosis

drugs should not be used concurrently with Ultomiris. Disease modifying drugs for the treatment of relapsing forms of multiple sclerosis include oral products such as Gilenya®‡, Mayzent®‡, Tecfidera®‡, Vumerity®‡, Zeposia®‡, Bafiertam™‡, and Aubagio®‡. Other disease modifying medications include Copaxone®‡, Avonex®‡, Rebif®‡, Extavia®‡, Betaseron®‡, Plegridy®‡, Tysabri®‡, Mavenclad®‡, Kesimpta®‡, and Lemtrada®‡. NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility. Most patients with NMOSD experience repeated attacks separated by periods of remission that may last for weeks, months, or years. Over 70% of patients with this disorder produce anti-AQP4 antibodies, which can be a diagnostic factor and may be prognostic of more severe disease. Treatment of acute attacks is typically high-dose intravenous corticosteroids with plasma exchange as a rescue treatment for patients who do not respond adequately to the corticosteroids. The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are satralizumab-mwge (Enspryng), eculizumab (Soliris), ravulizumab (Ultomiris), inebilizumab-cdon (Uplizna), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, effect on autoimmune and other comorbidities, frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ultomiris is approved for the treatment of adult and pediatric patients 1 month of age and older with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome, and adults with generalized myasthenia gravis who are anti-acetylcholine receptor antibody-positive or neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

Soliris is approved for the treatment of patients with paroxysmal nocturnal hemoglobinuria or atypical hemolytic uremic syndrome, and adults with generalized myasthenia gravis who are anti-acetylcholine receptor antibody-positive or neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Ultomiris

Paroxysmal Nocturnal Hemoglobinuria

The safety and efficacy of Ultomiris in adults was evaluated in patients with PNH in two 26-week, open-label, non-inferiority, phase III studies. Study 301 enrolled patients who were complement inhibitor naïve and had active hemolysis. Study 302 included adults who were clinically stable after having been treated with Soliris for at least the past 6 months. In both studies, Ultomiris was dosed according to the dosing provided in the FDA-approved package insert. The safety and efficacy of Ultomiris in pediatric patients with PNH was assessed in PNH Study 304, an open-label, phase III study conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients with PNH.

Study 301 included 246 patients naïve to complement inhibitor treatment prior to study entry. Patients had a flow cytometric confirmation of at least 5% PNH cells and were randomized 1:1 to either Ultomiris or Soliris. 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. Non-inferiority of Ultomiris to Soliris was demonstrated across endpoints in this population. The transfusion avoidance rate in the Ultomiris group was 73.6% vs 66.1% in the Soliris group leading to a treatment effect of 6.8 (95% CI -4.66, 18.14). LDH normalization occurred in 53.6% and 49.4% of the Ultomiris and Soliris patients, respectively. This corresponded to a treatment effect of 1.19 (95% CI, 0.8, 1.77).

Study 302 included 195 patients with PNH who were clinically stable after having been treated with Soliris for at least the previous 6 months. Patients were randomized 1:1 to either continue Soliris or to switch to Ultomiris. 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 Soliris was demonstrated across endpoints in this population. The LDH percent change was -0.82% in the Ultomiris group and 8.4% in the Soliris group corresponding to a treatment effect of 9.2 (95% CI -0.42, 18.8).

Study 304 included 13 pediatric patients aged 9- 17 years with PNH. Of these patients, 5 had never been treated with complement inhibitors and 8 had been treated with Soliris. 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 thereafter for patients weighing $\geq$ 20 kg, or once every 4 weeks for patients weighing < 20 kg. For patients who entered the study on Soliris therapy, day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of Soliris. Following initiation of Ultomiris, steady-state therapeutic serum concentrations were achieved after the first dose and maintained throughout the primary evaluation period in both cohorts. Three of the 5 complement

inhibitor-naïve patients and 6 of the 8 Soliris-experienced patients achieved hemoglobin stabilization by week 26. Transfusion avoidance was reached for 11 of the 13 patients during the 26-week primary evaluation period. The efficacy seen in pediatric patients with PNH was similar to that observed in adult patients with PNH enrolled in pivotal studies.

Atypical Hemolytic Uremic Syndrome
The efficacy of Ultomiris in patients with aHUS was assessed in 2 open-label, single-arm studies, one in adults and one in pediatric patients. Both studies were restricted to patients displaying signs of TMA defined as a platelet count $\leq$ 150x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine elevated or requiring dialysis. Enrollment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motive, member 13 (ADAMTS13) deficiency, Shiga toxin related hemolytic uremic syndrome, and genetic defect in cobalamin C metabolism.

The adult study was conducted in 56 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. 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 $\geq$ 25% improvement in serum creatinine from baseline. Patients had to meet each complete TMA response criterion at 2 separate assessments obtained at least 4 weeks apart, and any measurement in between. This complete TMA response was observed in 30 of the 56 patients (54%) during 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.

The pediatric study is a 26-week ongoing, multicenter, single-arm study conducted in 16 pediatric patients. 14 eculizumab-naïve patients were included in the interim analysis that was used to demonstrate efficacy prior to FDA approval. 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 $\geq$ 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 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. Response 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-ups.

Generalized Myasthenia Gravis
The efficacy of Ultomiris for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study. 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, MGFA clinical classification class II to IV, and MG-ADL total score ≥ 6 were enrolled. Over 80% of patients were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants (NSISTs) 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 higher scores indicating more impairment. Treatment with Ultomiris demonstrated a statistically significant change in the MG-ADL scores compared to placebo. The mean change from baseline in the placebo group was -1.4, and the mean change from baseline in the Ultomiris group was -3.1 ($p < 0.001$).

Neuromyelitis Optica Spectrum Disorder (NMOSD)
The efficacy and safety of Ultomiris in adult patients with anti-AQP4 antibody positive NMOSD was assessed in an open-label multicenter study. Study participants received Ultomiris intravenously 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 made based on the comparison of study participants to an external placebo control group from another study composed of a comparable population of adult patients with anti-AQP4 antibody positive NMOSD.

The Ultomiris study 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.

The primary endpoint 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.

Soliris

Paroxysmal Nocturnal Hemoglobinuria

The safety and efficacy of Soliris in PNH patients with hemolysis were assessed in a randomized, double-blind, placebo-controlled 26 week study (PNH Study 1); PNH patients were also treated with Soliris in a single arm 52 week study (PNH Study 2) and in a long-term extension study (E05-001). In all studies, the dose of Soliris was 600 mg study drug every 7 ± 2 days for 4 weeks, followed by 900 mg 7 ± 2 days later, then 900 mg every 14 ± 2 days for the study duration.

Study 1 included PNH patients with at least four transfusions in the prior 12 months, flow cytometric confirmation of at least 10% PNH cells and platelet counts of at least 100,000/microliter who were randomized to receive either Soliris (n = 43) or placebo (n = 44). Prior to randomization, all patients underwent an initial observation period to confirm the need for RBC transfusion and to identify the hemoglobin concentration (the "set-point") which would define each patient's hemoglobin stabilization and transfusion outcomes. The hemoglobin set-point was less than or equal to 9 g/dL in patients with symptoms and was less than or equal to 7 g/dL in patients without symptoms. Endpoints related to hemolysis included the numbers of patients achieving hemoglobin stabilization, the number of RBC units transfused, fatigue, and health-related quality of life. To achieve a designation of hemoglobin stabilization, a patient had to maintain a hemoglobin concentration above the hemoglobin set-point and avoid any RBC transfusion for the entire 26-week period. Hemolysis was monitored mainly by the measurement of serum LDH levels, and the proportion of PNH RBCs was monitored by flow cytometry. Patients receiving anticoagulants and systemic corticosteroids at baseline continued these medications. Patients treated with Soliris had significantly reduced ($p < 0.001$) hemolysis resulting in improvements in anemia as indicated by increased hemoglobin stabilization and reduced need for RBC transfusions compared to placebo treated patients. After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life.

In Study 2 and Extension Study, PNH patients with at least one transfusion in the prior 24 months and at least 30,000 platelets/microliter received Soliris over a 52-week period. Concomitant medications included anti-thrombotic agents in 63% of the patients and systemic corticosteroids in 40% of the patients. Overall, 96 of the 97 enrolled patients completed the study (one patient died following a thrombotic event). 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 total of 187 Soliris-treated PNH patients were enrolled in a long-term extension study. All patients sustained a reduction in intravascular hemolysis over a total Soliris exposure time ranging from 10 to 54 months. There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment.

Atypical Hemolytic Uremic Syndrome

The efficacy of eculizumab in the treatment of aHUS was evaluated in four prospective single-arm studies, which were published as two abstracts. One abstract describes subjects with plasma therapy resistant aHUS (n = 17 aged 12 years or older) treated with eculizumab for 26 weeks. The comparator was baseline levels at the start of therapy. Outcomes of interest included the reduction in the signs of thrombotic microangiopathy (TMA; e.g., reduction of serum LDH levels, increased platelet count, improvements in creatinine clearance [CrCl]). These subjects experienced a mean platelet count (primary endpoint) increase from 109,000±32,000 at baseline to 210,000±68,000 after 26 weeks of therapy. The second abstract reported subjects with plasma therapy-sensitive aHUS (n = 20 aged 12 years or older), also treated with eculizumab for 26 weeks. The comparator in this study was a baseline measure recorded over an 8-week observation period. The outcome of interest was reduction in the signs of TMA, but in subjects already stabilized on plasma therapy and where eculizumab was substituted, outcomes of interest were maintaining the corrected levels of TMA indicators already achieved with plasma therapy (platelet count and serum LDH levels remain stable compared to baseline). The primary endpoint for the cohort with plasma therapy sensitive aHUS was TMA event free status, defined as 12 weeks or more of stable platelet count, no plasma therapy and no new dialysis. The primary endpoint was achieved in 80% (95% CI 0.56-0.94) of the cohort.

Generalized Myasthenia Gravis

The efficacy of Soliris for the treatment of gMG was established in gMG Study 1, a 26-week randomized, double-blind, parallel-group, placebo-controlled, multicenter trial that enrolled patients who met the following criteria at screening: 1. Positive serologic test for anti-AChR antibodies, 2. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV, 3. MG-Activities of Daily Living (MG-ADL) total score ≥ 6, 4. Failed treatment over 1 year or more with 2 or more immunosuppressive therapies (ISTs) either in combination or as monotherapy, or failed at least 1 IST and required chronic plasmapheresis or plasma exchange (PE) or intravenous immunoglobulin (IVIg). A total of 62 patients were randomized to receive Soliris treatment and 63 were randomized to receive placebo. Soliris was administered according to the recommended dosage regimen. The primary efficacy endpoint for gMG Study 1 was a comparison of the change from baseline between treatment groups in the Myasthenia Gravis-Specific Activities of Daily Living scale (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 (total score 0-24). A statistically significant difference favoring Soliris was observed in the mean change from baseline to Week 26 in MG-ADL total scores [-4.2 points in the Soliris-treated group compared with -2.3 points in the placebo-treated group (p = 0.006)].

Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1, a randomized, double-blind, placebo-controlled trial that enrolled 143 patients with NMOSD who were anti-AQP4 antibody positive and met the following criteria at screening: 1. 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, 2. Expanded Disability Status Scale (EDSS) score ≤ 7 (consistent with the presence of at least limited ambulation with aid), 3. If on immunosuppressive therapy (IST), on a stable dose regimen, 4. The use of concurrent corticosteroids was limited to 20 mg per day or less, 5. Patients were excluded if they had been treated with rituximab or mitoxantrone within 3 months or with IVIG within 3 weeks prior to screening. A total of 96 patients were randomized to receive Soliris treatment and 47 were randomized to receive placebo. Soliris was administered according to the recommended dosage regimen. 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; $p < 0.0001$).

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Policy History

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04/15/2025 UM Committee review and approval. New policy.
Next Scheduled Review Date: 04/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1303, J1299, Q5151, Q5152
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

ravulizumab (Ultomiris™), eculizumab (Soliris®, biosimilars)

Medicare Advantage Medical Policy #MA-108
Original Effective Date: 07/01/2025
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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

ravulizumab (Ultomiris™), eculizumab (Soliris®, biosimilars)

Medicare Advantage Medical Policy #MA-108
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When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.