Soliris_Ultomiris (eculizumab_ravulizumab)
Policy Number: C4867-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DATE
06/2010	07/2019	07/2020
J CODE		**LAST P&T APPROVAL/VERSION**
J1300- Injection, eculizumab, 10 mg C9052 Injection, ravulizumab-cwvz, 10 mg (ultomiris) J3590- Unclassified biologics (ultomiris)	RxPA	Q3 2019 20190828C4867-A

PRODUCTS AFFECTED:
Soliris (eculizumab), Ultomiris (ravulizumab)

DRUG CLASS:
Complement Inhibitor

ROUTE OF ADMINISTRATION:
Intravenous Infusion

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill (IV), Provider-administered

AVAILABLE DOSAGE FORMS:
Soliris SOLN 300MG/30ML, Ultomiris SOLN 300MG/30ML

FDA-APPROVED USES:
For the treatment of patients with Paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis

Soliris (eculizumab) ONLY: For the treatment patients with Atypical Hemolytic Uremic Syndrome (aHUS) to prevent complement-mediated thrombotic microangiopathy and treatment of generalized myasthenia gravis(gMG) in adults 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

COMPENDIAL APPROVED OFF-LABELED USES: None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
Paroxysmal nocturnal hemoglobinuria (PNH), Soliris (eculizumab) ONLY: Atypical Hemolytic Uremic Syndrome (aHUS), Generalized Myasthenia Gravis (gMG)

D59.3 Hemolytic-uremic syndrome, D59.5 Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli], G70.00 Myasthenia gravis without (acute) exacerbation, G36.0 Neuromyelitis optica [Devic]

REQUIRED MEDICAL INFORMATION:

ALL INDCATIONS:

1. Member has been vaccinated against meningococcal infection (at least 2 weeks prior to eculizumab treatment, if not previously vaccinated). Documentation of meningococcal vaccine date required.

A. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA:

1. Documented diagnosis of PNH as established by flow cytometry (Documentation of flow cytometry required)
   AND
2. Documentation of meningococcal vaccine at least two weeks before starting treatment
   AND
3. Documentation of baseline Serum lactate dehydrogenase (LDH), hemoglobin level, and packed RBC transfusion requirement
   AND
4. Lactate dehydrogenase (LDH) level of 1.5 times the upper limit of the normal range (within the last 30 days). Submit laboratory results with reference range
   AND
5. Transfusion-dependent, defined by having a transfusion within the last 12 months and ONE (1) of the following: Transfusion dependent as defined as hemoglobin level less than 9g/dL in the presence of symptoms, or Hemoglobin less than 7g/dL without symptoms (*Lab should be drawn before transfusion or at least one (1) month since last transfusion)
   AND
6. Member meets ONE of the following criteria: Thrombotic event event(s) attributable to PNH (i.e. arterial/venous thrombosis, hepatic vein thrombosis, etc.) or major adverse vascular events from thromboembolism, Symptoms of PNH that inhibit the patient's quality of life (i.e. anemia, fatigue, difficulty swallowing, thromboses, frequent paroxysms of pain, recurrent abdominal pain, erectile dysfunction, chronic kidney disease, organ damage secondary to chronic hemolysis) OR Pregnant and potential benefit outweighs potential fetal risk

B. ATYPICAL HEMOLYTIC UREMIC SYNDROME (SOLIRIS ONLY):

1. Documentation of a definitive diagnosis of atypical Hemolytic Uremic Syndrome (aHUS)
   AND
2. Documentation of baseline Serum LDH, serum creatinine/eGFR, platelet count, and plasma exchange/infusion requirement
   AND
3. Documentation of meningococcal vaccine at least two weeks before starting treatment

C. GENERALIZED MYASTHENIA GRAVIS (SOLIRIS ONLY):

1. Documentation of diagnosis of myasthenia gravis with a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of class II, III, or IV
   AND
2. Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) total score of greater than or equal to 6
   AND
3. Positive serologic test for binding anti-acetylcholine receptor antibodies (AChR-ab)
   AND
4. (a) Documentation of inadequate response to, is intolerant of, or has a labeled contraindication to TWO or more immunosuppressive drug agents used alone or in combination for at least 12 months one year [i.e. azathioprine (Imuran), mycophenolate

mofetil (Cellcept), cyclosporine (Sandimmune), cyclophosphamide, methotrexate, tacrolimus, rituximab (Rituxan)]
OR
(b) Documentation of inadequate response to, is intolerant of, or has a labeled contraindication to ONE or more immunosuppressive drug agents as monotherapy or in combination therapy AND requires chronic plasma exchange, plasmapheresis or intravenous immunoglobulin therapy

D. NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) (SOLIRIS ONLY):
1. (a)Documenation of positive for blood AQP4-IgG AND at least one core clinical characteristic must be identified from among the following: ON, acute myelitis, acute postrema syndrome (APS, characterized by unexplained hiccups or nausea and vomiting), acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions.
   AND
2. Prescriber attests all other alternative diagnoses have been excluded

DURATION OF APPROVAL:
Initial authorization: 3 months; Continuation of therapy: 6 months

QUANTITY:
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA: Soliris (eculizumab), 90 HCPCS units (10 mg per unit) per date of service OR 6 vials/180ml per 28 day supply. Ultomiris (raulizumab), up to 3,000mg for loading dose then up to 3,600mg per 56 days maintenance dose (to start 2 weeks after loading dose)
ATYPICAL HEMOLYTIC UREMIC SYNDROME (SOLIRIS ONLY): 120 HCPCS units (10 mg per unit) per date of service OR 4 vials/120ml per 28 day supply

GENERALIZED MYASTHENIA GRAVIS (SOLIRIS ONLY): 120 HCPCS units
(10 mg per unit) per date of service OR 4 vials/120ml per 28 day supply

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) (SOLIRIS ONLY): 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

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified hematologist, oncologist, immunologist,genetic specialist or neurologist. Prescriber must be enrolled in Soliris or Ultomiris REMS program. Submit consultation notes if applicable.

NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

AGE RESTRICTIONS:
ATYPICAL HEMOLYTIC UREMIC SYNDROME: 2 months of age and older.
ALL OTHER INDICATIONS: 18 years of age and older

GENDER:
Male and female

CONTINUATION OF THERAPY:

A. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA:
1. Documentation of disease improvement or stabilization by any of the following: decrease in serum LDH, hemoglobin level above baseline or reduction in the need for blood transfusions

B. ATYPICAL HEMOLYTIC UREMIC SYNDROME (SOLIRIS ONLY):
1. Documentation of disease improvement or stabilization by any of the following: decrease in serum LDH, Increase or improvement in serum creatinine/Egfr, Increase or normalization of platelet counts, Decrease in plasma exchange/infusion requirement

C. GENERALIZED MYASTHENIA GRAVIS (SOLIRIS ONLY):
1. Documentation of disease improvement or stabilization by all of the following: Improvement of at least 3 points (reduction in score) from pre-treatment baseline on the Myasthenia Gravis-Specific Activities of Daily Living (MG-ADL) assessment, reduction in signs and symptoms of myasthenia gravis and Stabilization, reduction, or discontinuation of dose(s) of baseline immunosuppressive therapy (IST) prior to starting Soliris. NOTE: Add on, dose escalation of IST, or additional rescue therapy from baseline to treat myasthenia gravis or exacerbation of symptoms while on Soliris therapy will be considered as treatment failure.

D. NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD) (SOLIRIS ONLY):
1. Documentation of disease improvement or stabilization by any of the following: decrease in relapse rate

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Soliris (eculizumab) and Ultomiris (ravulizumab) that are not an FDA-approved indication or not included in this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare. Authorization will not be granted if ANY of the following conditions apply: Non-FDA approved indications, hypersensitivity to eculizumab or any component of the product, unresolved serious Neisseria meningitidis infection, current vaccination against Neisseria meningitidis, unless the risks of delaying treatment outweigh the risks of developing a meningococcal infection, or evidence of an active meningococcal infection. Eculizumab is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS). While the few studies available demonstrate possible efficacy of eculizumab in treating Shiga toxin E. coli-related hemolytic uremic syndrome, further studies are warranted to demonstrate that it is both safe and effective for this indication.

OTHER SPECIAL CONSIDERATIONS:
Black Box Warnings: Serious meningococcal infection Life- threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated

BACKGROUND:
PNH is a rare acquired clonal disorder caused by a somatic mutation of the phosphatidylinositol glycan-complementation class A (PIG-A) gene in hematopoietic stem cells. The disorder results in a deficiency of glycosylphosphatidylinositol (GPI), which serves as an anchor for several cell surface proteins including the terminal complement regulator, CD59. The absence of CD59 from the surface

of the affected PNH red blood cells (RBCs) renders them susceptible to terminal complement-mediated lysis. The subsequent chronic hemolysis is the primary clinical manifestation of the disease and leads to disabling morbidities that include anemia, fatigue, thrombosis, pain, and impaired quality of life. Lactate dehydrogenase (LDH) is released during RBC destruction and grossly elevated serum LDH is a common finding in patients with PNH.

Atypical hemolytic uremic syndrome (aHUS) is a genetic, chronic, and progressive inflammatory disease that affects patients of all ages. This syndrome is caused by defects in regulation of the complement system. These defects are inherited, acquired, or both, and they result in chronic, uncontrolled activation of the complement system which leads to platelet, leukocyte, and endothelial-cell activation and systemic thrombotic microangiopathy. Affected patients have a lifelong risk of systemic clinical complications of thrombotic microangiopathy, including damage to multiple organ systems (e.g., the central nervous system, kidneys, heart, and gastrointestinal tract). Eculizumab, which blocks complement C5 activation, has been demonstrated as an effective agent.

Most cases of aHUS are genetic, although some may be acquired due to autoantibodies or idiopathic. The diagnosis of complement-mediated aHUS is made by excluding other forms of TMA. Therefore, aHUS is suspected in patients with TMA without a secondary cause and ADAMTS13 activity >10%, without evidence of STEC-HUS. Plasma exchange or infusion may transiently maintain normal levels of hematologic measures but does not treat the underlying systemic disease aHUS is often misdiagnosed as thrombotic thrombocytopenic purpura (TTP) or STEC-HUS because aHUS shares many of the presenting characteristics of the other thrombotic microangiopathies, and confirmatory genetic results are not available at the time of presentation, the diagnosis relies heavily on the recognition of a clinical syndrome consistent with the diagnosis in the absence of signs of an alternate cause of thrombotic microangiopathy. It is a distinctly different illness from the more common disorder known as typical hemolytic uremic syndrome, which is caused by E.coli-producing Shiga toxins (Stx HUS) and is generally foodborne.

Myasthenia gravis (MG) is relatively rare acquired autoimmune disorder caused by an antibody-mediated blockade of neuromuscular transmission resulting in skeletal muscle weakness. MG is characterized by a pattern of progressively reduced muscle strength with repeated use and recovery of muscle strength after a period of rest. MG is classified into 2 major clinical types: ocular MG and generalized MG (gMG). gMG is a debilitating, chronic and progressive autoimmune neuromuscular disease that can occur at any age.

There is no known cure for MG. The mainstay of therapy for symptomatic treatment of MG involves use of acetylcholinesterase (AChE) inhibitors. If treatment with AChE inhibitors is not effective, or they are not suitable for long-term use, then short-term immunosuppression with oral corticosteroids such as prednisolone is used. Nonsteroidal immunosuppressive agents (azathioprine, cyclosporine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab, and tacrolimus) may be used in addition to steroids, with the aim of reducing the steroid dose over time.

Approximately 10% to 15% of patients with MG have refractory gMG. These patients do not respond to long-term treatment with corticosteroids or multiple immunosuppressive treatments, or they have intolerable side effects to these therapies or require ongoing treatment with either intravenous immunoglobulin (IVIG) or plasma exchange (PE) (Howard et al., 2017). Patients with refractory gMG experience difficulties with speech, swallowing, and mobility, impairment of respiratory function, and extreme fatigue, and may have frequent exacerbations, which can be life-threatening and require hospital admission.

Eculizumab is a recombinant humanized monoclonal antibody that works by binding to complement protein C5, inhibiting its enzymatic cleavage, blocking formation of the terminal complement complex, and thus preventing red cell lysis.
In those patients with paroxysmal nocturnal hemoglobinuria (PNH), eculizumab inhibits terminal complement mediated intravascular hemolysis. In patients with atypical hemolytic uremic syndrome (aHUS), impairment in the regulation of complement activity leads to uncontrolled terminal complement activation, resulting in platelet activation, endothelial cell damage and thrombotic microangiopathy. The precise mechanism by which eculizumab exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.
Ultomiris is a recombinant humanized monoclonal IgG2/4κ antibody. The antibody binds to the complement component C5 and prevents its cleavage to C5a and C5b, which is required for formation of the membrane attack complex (MAC). RBCs are normally protected from MAC formation by the glycosylphosphatidylinositol (GPI)-linked protein CD59 on their surface; PNH red blood cells (RBCs) lacking CD59 are susceptible to MAC formation. Ultomiris interferes with this step and thus reduces intravascular hemolysis. Approval of Ultomiris was based on two open-label, randomized, active-controlled, non-inferiority phase 3 studies: ALXN1210-PNH-301 (NCT02946463) and ALXN1210-PNH-302 (NCT03056040). Study 301 enrolled 246 patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled 195 patients with PNH who were clinically stable after having been treated with Soliris for at least the past 6 months. In both trials, patients were randomized to receive either Ultomiris or Soliris. Patients randomized to Ultomiris received a loading dose followed by maintenance dosing every 8 weeks. Patients randomized to Soliris received a dose on Days 1, 8, 15, and 22, followed by maintenance treatment on Day 29 and every 2 weeks. The results of Study 301 demonstrated that Ultomiris had similar results to Soliris (non-inferior) – patients did not receive a transfusion and had similar incidence of hemolysis measured by the normalization of LDH levels in patients' blood (lactate dehydrogenase, or LDH, is an enzyme required during the process of turning sugar into energy in the body's cells). The results of Study 302 demonstrated similar effects to Soliris (non-inferior) based on several clinical measures including hemolysis and avoiding transfusion. In Study 301, efficacy was established based upon transfusion avoidance and reduction of hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was defined as patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline up to Day 183. Transfusion avoidance was seen in 73.6% and 66.1% of patients who received Ultomiris and Soliris, respectively (rate difference 6.8; 95% CI: -4.66, 18.14) and LDH normalization was seen in 53.6% and 49.4% of patients who received Ultomiris and Soliris, respectively (odds ratio 1.19; 95% CI: 0.80. 1.77). Supportive efficacy data included LDH percent change, breakthrough hemolysis and proportion of patients with stabilized hemoglobin levels. Non-inferiority of Ultomiris to Soliris was demonstrated across the endpoints. In Study 302, efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. LDH percent change was -0.82% and 8.4% for patients who received Ultomiris and Soliris, respectively (rate difference 9.2; 95% CI: -0.42, 18.8). Supportive efficacy data included transfusion avoidance, proportion of patients with stabilized hemoglobin and proportion of patients with breakthrough hemolysis. Non-inferiority of Ultomiris to Soliris was demonstrated across all endpoint.

The efficacy of Soliris for the treatment of NMOSD was established in NMOSD Study 1 (ECU-NMO-301, NCT01892345), a randomized, double-blind, placebo-controlled, multi-center trial that enrolled 143 patients who were anti-AQP4 antibody positive. The primary endpoint 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 patients on placebo (relative risk-reduction 94%; hazard ratio 0.058; P<0.0001).

DISEASE OVERVIEW

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severe, disabling, and potentially life-threatening autoimmune neuroinflammatory disease characterized by acute optic neuritis (ON) and longitudinal transverse myelitis (TM). The disease can strike men and women of all races, backgrounds, and ages without warning, with
a median age of onset of 39 years.

MORBIDITY AND MORTALITY

Up to 92.7% of patients with AQP4 antibody-positive NMOSD have had unpredicatable relapses, often leading to cumulative disability.3,7,8 In a study of anti-AQP4 antibody-positive NMOSD patients, morbidity was significant, with 18% experiencing permanent visual disability, 34% experiencing permanent motor disability, and 23% experiencing wheelchair dependency after a median disease duration of 75 months.3 Attacks that involve the brainstem can result in respiratory failure.4 The overall mortality rates of patients with NMOSD range from 7% to 9% (7% after a mean disease duration of 6.9 years; 9.4% after a median disease duration of 8.25 years).

SIGNS AND SYMPTOMS

In addition to vision loss and blindness, NMOSD patients experience immobility involving limb weakness and sensation loss that can give rise to paralysis. Neuromuscular symptoms, such as cognitive challenges, pain, spasms, loss of bladder or bowel control, hiccups, nausea, vomiting, and seizures, can also arise. Ultimately, respiratory failure and encephalopathy can be among the most injurious consequences of NMOSD.

NMOSD ASSOCIATED WITH AQP4

As 73% of patients with NMOSD are anti-AQP4 antibody positive, complement activation by AQP4 antibodies is a major determinant of disease pathogenesis in patients with NMOSD. AQP4 bound to immunoglobulin G (IgG) passes into the central nervous system through the blood-brain barrier and activates the complement system, causing the infiltration of immune leukocyte cells that cause the death of neural cells known as astrocytes and neurons. Identifying AQP4-IgG in the blood facilitates clinical diagnosis and prognosis, as well as informing
appropriate treatment selection.

DIAGNOSIS

The International Panel for NMO Diagnosis (IPND) established two sets of clinical criteria, both of which involve excluding alternative diagnoses. When patients test positive for blood AQP4-IgG, at least one core clinical characteristic must be identified from among the following: ON, acute myelitis, acute postrema syndrome (APS, characterized by unexplained hiccups or nausea and vomiting), acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions. In the absence of a confirmed AQP4-IgG test, at least two of the aforementioned core clinical characteristics must be identified, one of which must be ON, acute myelitis with longitudinally extensive transverse myelitis (LETM), or APS.

APPENDIX:

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