PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris Intravenous Prior Authorization Policy
- Ultomiris® (ravulizumab-cwvz intravenous infusion – Alexion)

REVIEW DATE: 11/09/2022

OVERVIEW

Ultomiris intravenous, a complement inhibitor, is indicated for the following uses:[1]

- **Atypical hemolytic uremic syndrome** (aHUS), in patients ≥ one month of age.
- **Generalized myasthenia gravis** (gMG), in adults who are anti-acetylcholine receptor (AChR) antibody positive.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), in patients ≥ one month of age.

Ultomiris is also available in a subcutaneous formulation that is indicated for maintenance therapy of aHUS and PNH in adults.[1]

Disease Overview

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.[4] The thrombotic microangiopathy process that characterizes HUS can be caused by a variety of things. aHUS is a sub-type of HUS in which thrombotic microangiopathy is the consequence of endothelial damage in the microvasculature of the kidneys and other organs due to a 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.[5] 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, and 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/year in the US; aHUS is approximately 10 times less common than typical HUS.

MG is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles, which are responsible for breathing and moving parts of the body, including the arms and legs.[6] The hallmark of myasthenia gravis 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 MG results from the binding of autoantibodies to components of the neuromuscular junction, most commonly the acetylcholine receptor.[7]

PNH is a rare disorder involving bone marrow failure that manifests with hemolytic anemia, thrombosis, and peripheral blood cytopenias.[2] Due to the absence of two glycosylphosphatidylinositol (GPI)-anchored proteins, CD55 and CD59, uncontrolled complement activation leads to hemolysis and other PNH manifestations. GPI anchor protein deficiency is often due to mutations in phosphatidylinositol glycan class A (PIGA), a gene involved in the first step of GPI anchor biosynthesis. PNH clinical diagnosis should be confirmed with peripheral blood flow cytometry to detect the absence or severe deficiency of GPI-anchored proteins on at least two lineages. Prior to the availability of Soliris® (eculizumab intravenous

infusion) [a complement inhibitor],[3] there was no specific therapy for PNH with only supportive management in terms of the cytopenias and control of thrombotic risk. Supportive measures used include platelet transfusion, immune suppressive therapy for patients with bone marrow failure, use of erythropoietin for anemias, and aggressive anticoagulation. A complement inhibitor is the treatment of choice for patients with severe manifestations of PNH. Bone marrow transplantation is the only cure for PNH but should be reserved for patients with a suboptimal response to medication.

Guidelines

An international consensus guidance for the management of MG was published in 2016.[7] The guidelines recommend pyridostigmine for the initial treatment in most patients with MG. The ability to discontinue pyridostigmine can indicate that the patient has met treatment goals and may guide the tapering of other therapies. Corticosteroids or immunosuppressant therapy should be used in all patients with MG who have not met treatment goals after an adequate trial of pyridostigmine. Nonsteroidal immunosuppressant agents used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. It is usually necessary to maintain some immunosuppression for many years, sometimes for life. Plasma exchange and intravenous immunoglobulin can be used as short-term treatments in certain patients. A 2020 update to these guidelines provides new recommendations for methotrexate, rituximab, and Soliris.[8] All recommendations should be considered extensions or additions to recommendations made in the initial international consensus guidance. Oral methotrexate may be considered as a steroid-sparing agent in patients with generalized MG who have not tolerated or responded to steroid-sparing agents. Rituximab should be considered as an early therapeutic option in patients with muscle specific kinase antibody positive MG who have an unsatisfactory response to initial immunotherapy. Soliris should be considered in the treatment of severe, refractory, anti-acetylcholine receptor antibody positive generalized MG.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ultomiris intravenous. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ultomiris intravenous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris intravenous to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ultomiris intravenous is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Atypical Hemolytic Uremic Syndrome.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient does not have Shiga toxin *Escherichia coli* related hemolytic uremic syndrome; AND
   - **B)** The medication is prescribed by or in consultation with a nephrologist.

2. **Generalized Myasthenia Gravis.** Approve if the patient meets ONE of the following criteria (A or B):
   - **A)** Initial therapy. Approve for 6 months if the patient meets the following criteria (i, ii, iii, iv, v, vi, and vii):

i. Patient is ≥ 18 years of age; AND
ii. Patient has confirmed anti-acetylcholine receptor antibody positive generalized myasthenia gravis; AND
iii. Patient meets both of the following (a and b):
a) Myasthenia Gravis Foundation of America classification of II to IV; AND
b) Myasthenia Gravis Activities of Daily Living (MG-ADL) score of ≥ 5; AND
iv. Patient meets one of the following (a or b):
a) Patient received or is currently receiving pyridostigmine; OR
b) Patient has had inadequate efficacy, a contraindication, or significant intolerance to pyridostigmine; AND
v. Patient meets one of the following (a or b):
a) Patient received or is currently receiving two different immunosuppressant therapies for ≥ 1 year; OR
b) Patient had inadequate efficacy, a contraindication, or significant intolerance to two different immunosuppressant therapies; AND
Note: Examples of immunosuppressant therapies tried include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide.
vi. 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
vii. The medication is being prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Ultomiris intravenous. Approve for 1 year if the patient meets the following (i, ii, and iii):
i. Patient is ≥ 18 years of age; AND
ii. Patient is continuing to derive benefit from Ultomiris intravenous, according to the prescriber; AND
Note: Examples of derived benefit include reductions in exacerbations of myasthenia gravis; improvements in speech, swallowing, mobility, and respiratory function.
iii. The medication is being prescribed by or in consultation with a neurologist.

3. Paroxysmal Nocturnal Hemoglobinuria. Approve for the duration noted if the patient meets ONE of the following (A or B):
A) Initial therapy. Approve for 6 months if the patient meets the following criteria (i and ii):
i. Diagnosis was confirmed by peripheral blood flow cytometry results showing the absence or deficiency of glycosylphosphatidylinositol (GPI)-anchored proteins on at least two cell lineages; AND
ii. The medication is prescribed by or in consultation with a hematologist.
B) Patient is Currently Receiving Ultomiris (intravenous or subcutaneous). Approve for 1 year if the patient meets the following criteria (i and ii):
i. Patient is continuing to derive benefit from Ultomiris (intravenous or subcutaneous), according to the prescriber.
Note: Examples of benefit from Ultomiris (intravenous or subcutaneous) include stabilization of hemoglobin levels, decreased transfusion requirements or transfusion independence, reductions in hemolysis.
ii. The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ultomiris intravenous is not recommended in the following situations:

1. **Concurrent Use with Another Complement Inhibitor or Vyvgart® (efgartigimod alfa-fcab intravenous infusion).** Concurrent use with other complement inhibitors (e.g., Empaveli® [pegcetacoplan subcutaneous infusion], Soliris, or Ultomiris subcutaneous) or Vyvgart is not recommended with Ultomiris intravenous. However, to reduce the risk of hemolysis from abrupt treatment discontinuation, patients currently receiving Soliris or Ultomiris (intravenous or subcutaneous) and switching to Empaveli for paroxysmal nocturnal hemoglobinuria may receive these agents for no more than 4 weeks after starting Empaveli.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Ultomiris® intravenous infusion and subcutaneous injection [prescribing information]. New Haven, CT: Alexion; July 2022.
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804–2811.
3. Soliris® intravenous infusion [prescribing information]. New Haven, CT: Alexion; July 2022.
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5. Genetics Home Reference. Atypical hemolytic-uremic syndrome. National Institutes of Health (NIH). Available at: https://ghr.nlm.nih.gov/condition/atypical-hemolytic-uremic-syndrome#sourcesforpage. Accessed on November 7, 2022.
6. National Institute of Neurological Disorders and Stroke (NINDS). Myasthenia Gravis Fact Sheet. National Institutes of Health (NIH) Publication No. 17-768. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Myasthenia-Gravis-Fact-Sheet. Accessed on November 7, 2022.
7. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. *Neurology*. 2016;87:419–425.
8. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.