PRIOR AUTHORIZATION POLICY

POLICY: Complement Inhibitors – Ultomiris Subcutaneous Prior Authorization Policy
- Ultomiris® (ravulizumab-cwvz subcutaneous injection – Alexion)

REVIEW DATE: 08/03/2022

OVERVIEW

Ultomiris subcutaneous, a complement inhibitor, is indicated for the following uses:[1]
- **Atypical hemolytic uremic syndrome** (aHUS), for maintenance in adults.
- **Paroxysmal nocturnal hemoglobinuria** (PNH), for maintenance in adults.

Ultomiris is also available in an intravenous formulation that is indicated for aHUS, generalized myasthenia gravis, and PNH.[1] Prior to initiation of Ultomiris subcutaneous, a loading dose of Ultomiris intravenous must be administered. Ultomiris subcutaneous is available as a 245 mg single-dose, prefilled cartridge for use with an on-body injector and is not approved for use in pediatric patients.

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.[3] aHUS is a subtype 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.[4] 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.

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 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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ultomiris subcutaneous. 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 subcutaneous as well as the monitoring required for adverse events and long-term efficacy, approval requires Ultomiris subcutaneous 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 subcutaneous 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, B, C, and D):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient does not have Shiga toxin *E. coli* related hemolytic uremic syndrome; AND
   - **C)** Patient has received or will receive Ultomiris intravenous infusion loading dose prior to initiation of Ultomiris subcutaneous; AND
   - **D)** The medication is prescribed by or in consultation with a nephrologist.

2. **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, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** 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
     - **iii.** Patient has received or will receive Ultomiris intravenous infusion loading dose prior to initiation of Ultomiris subcutaneous; AND
     - **iv.** 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, ii, iii, and iv):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
     - **iii.** 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.
     - **iv.** The medication is prescribed by or in consultation with a hematologist.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

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

1. **Concurrent Use with another Complement Inhibitor.** Concurrent use with other complement inhibitors (e.g., Empaveli [pegcetacoplan subcutaneous infusion], Soliris [eculizumab intravenous infusion], or Ultomiris intravenous) is not recommended with Ultomiris subcutaneous. 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 or subcutaneous injection [prescribing information]. New Haven, CT: Alexion; July 2022.
2. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804–2811.
3. Campistol JM, Arias M, Ariceta G, et al. An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia*. 2015;35:421–447.
4. 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 July 29, 2022.