Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 6/10/2021

Ultomiris™ (ravulizumab)

FDA approval: 12/21/2018
HCPCS: C9052, J1303
Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Documented diagnosis of paroxysmal nocturnal hemoglobinuria (PNH)
      i. Prescribed by or in consultation with a hematologist
      ii. Flow cytometric confirmation of PNH type III red cells
      iii. Had at least 1 transfusion in 24 months preceding ravulizumab
      OR
      iv. Documented history of major adverse thrombotic vascular events from thromboembolism
      OR
      v. Patient has high disease activity defined as a lactic dehydrogenase (LDH) level ≥ 1.5 times the upper limit of normal with one of the following symptoms
         1. Weakness
         2. Fatigue
         3. Hemoglobinuria
         4. Abdominal pain
         5. Dyspnea
         6. Hemoglobin < 10 g/dL
         7. A major vascular event
         8. Dysphagia
         9. Erectile dysfunction
      vi. Must not be used in combination with Soliris® or other medications to treat PNH
   c. Documentation diagnosis of atypical hemolytic uremic syndrome (aHUS)
      i. Prescribed by or in consultation with a hematologist or nephrologist
      ii. Common causes of typical hemolytic uremic syndrome have been ruled out, including infectious causes of HUS and thrombotic thrombocytopenic purpura (TTP)
      iii. Must present with the following symptoms:
         1. Hemoglobin < 10 g/dL

2. Platelets < 150,000/mm^3
3. Documented evidence of hemolysis, such as, elevated lactate dehydrogenase levels, decreased haptoglobin level, or schistocytosis
4. Increased serum creatinine OR currently undergoing dialysis

iv. Must not be used in combination with Soliris or other medications to treat aHUS

d. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. **FDA approved indication/Diagnosis**

**Please refer to most recent prescribing information.*

B. **Background Information**

a. Ultomiris is a complement inhibitor indicated for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Ultomiris is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

b. Paroxysmal nocturnal hemoglobinuria

i. Paroxysmal nocturnal hemoglobinuria is a rare acquired hematopoietic stem cell disorder in which red blood cells undergo cell lysis prematurely mediated by the alternative pathway of complement (APC). PNH arises due to a somatic mutation of a the PIGA gene whose protein product is a glycosyl transferase. Glycosyl transferase is part of the biosynthetic pathway that generates glycosyl phosphastidylinositol (GPI) that serves as an anchor for membrane bound proteins on hematopoietic lineage cells. The mutation in PIGA results in a lack of glycosyl transferase activity and near-complete or complete absence of expression of all proteins that are GPI-anchored including the complement inhibitory proteins CD55 and CD59. The deficiency of CD55 and CD59 cause the complement-mediated intravascular hemolysis characteristic of PNH.

ii. Phenotypic mosaicism of the peripheral blood is a characteristic feature of PNH and is based on quantitative differences in complement sensitivity. Cell complement sensitivity is divided into 3 types. PNH type I cells are defined by having normal sensitivity to complement-mediated lysis. PNH type II cells are moderately complement sensitive or 2 - 4 times more sensitive than normal. Finally, PNH type III cells are markedly complement sensitive or 15 - 25 times more sensitive than

normal. Complement sensitivity varies greatly from patient to patient depending on their unique phenotypic mosaicism. Erythrocyte phenotype is clinically relevant as patients with primarily type II cells have a relatively benign clinical course. In contrast, those who have more type III cells, which are completely deficient in CD55 and CD59, will have a more severe clinical course due to increased complement-mediated hemolysis. As Ultomiris is a complement inhibitor, it was studied only in patients with greater than 5% PNH type III cells on flow cytometry.

iii. For patients with high disease activity, PNH complications increase significantly. High disease activity is defined as an elevated LDH greater than or equal to 1.5 times the upper limit of normal with constitutional symptoms of weakness, fatigue, hemoglobinuria, abdominal pain, dyspnea, hemoglobin less than 10 g/dL, dysphagia, and erectile dysfunction. Patients with an elevated LDH and at least one additional symptoms should begin treatment with Ultomiris.

iv. Thrombolytic complications are the leading cause of morbidity and mortality in PNH. Acute thrombotic events require anticoagulation with heparin. If there is no contraindication, anticoagulation should continue indefinitely for a patient with PNH who has experienced a thromboembolic complication. For patients being treated with Ultomiris and no history of thromboembolic complications, prophylactic anticoagulation may be unnecessary, although it is recommended that anticoagulation continue for those patients who experienced a thromboembolic event prior to initiating therapy with Ultomiris.

v. Ultomiris has been shown to decrease the number of blood transfusions required by patients and stabilize hemoglobin levels and to be non-inferior to Soliris in regards to these endpoints. Soliris has been studied in patients receiving as few on 1 blood transfusion in 24 months while the Ultomiris studies had patients averaging at least 1 blood transfusion within the 12 months prior to the trial.

vi. Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat PNH, such as, Soliris.

c. Atypical hemolytic uremic syndrome

i. Atypical hemolytic uremic syndrome is an extremely rare disease characterized by hemolytic anemia, thrombocytopenia, and acute kidney failure. Acute presentation may also include neurological findings, including seizures, gastrointestinal symptoms, and cardiovascular involvement, including hypertensive emergency and acute coronory events. Chronic kidney disease (CKD) is the most common long-term complication and may result in the need for dialysis. The signs and symptoms of aHUS result from the formation of microthrombi in various small blood vessels of the body. These clots reduce or prevent proper blood flow to various organs especially the kidneys. Multiple factors, including certain genetic, environmental, and immunologic factors, all play a role in its development.

ii. The nomenclature and terminology surrounding aHUS can be confusing. Atypical hemolytic uremic syndrome is considered a form of thrombotic microangiopathy (TMA). TMA is broken down into two main forms, thrombotic thrombocytopenia purpura (TTP) and hemolytic uremic syndrome (HUS).

1. TTP is group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to

different therapies. TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif 13 or ADAMTS13. Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity less than 10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP and therefore, Ultomiris should not be prescribed.

2. HUS is also broken down into two main forms, aHUS and secondary HUS. Secondary HUS are caused by Shiga toxin E. coli, S. pneumoniae, malignancy, HIV infection, solid organ transplants, hematopoietic stem cell transplants, autoimmune disorders and the use of certain drugs or medications. HUS caused by infectious bacteria typically presents with diarrhea and responds well to antibiotic therapy. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious HUS and Soliris should not be initiated in these patients. Atypical hemolytic uremic syndrome typically results from complement abnormalities, however, it is a diagnosis of exclusion, meaning the diagnosis is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.

iii. Most patients with aHUS present with the complete triad symptoms: hemoglobin less than 10 g/dL, platelets less than 150,000/mm^3, and renal insufficiency with increased serum creatinine or the need for dialysis. The presence of schizocytes, undetectable haptoglobin, and high LDH levels confirm the microangiopathic intravascular origin of hemolysis. Ultomiris should be initiated in patients with these symptoms and a lack of secondary or infectious causes.

iv. Ultomiris has not been studied and there is no data to support use in combination with other medications used to treat aHUS, such as, Soliris.

C. **Efficacy**

**Please refer to most recent prescribing information.*

D. **Medication Safety Considerations**

**Please refer to most recent prescribing information.*

E. **Dosing and administration**

**Please refer to most recent prescribing information.*

F. **How supplied**

**Please refer to most recent prescribing information.*

References:

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<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.7</td><td>Effective Date: 06/10/2021</td><td>Update to remove platelet requirement for PNH and the percentage of PNH type III cells required</td></tr>
<tr><td>1.6</td><td>Effective Date: 12/03/2020</td><td>Updated to remove meningitis vaccine criteria, added prescriber for PNH and aHUS diagnoses, added requirement to rule out typical hemolytic uremic syndrome, added trial and failure of preferred products statement, and changed renewal criteria to general standard statement.</td></tr>
<tr><td>1.5</td><td>Effective Date: 12/05/2019</td><td>Updated to add new indication of aHUS</td></tr>
<tr><td>1.4</td><td>Effective Date: 08/15/2019</td><td>Updated criteria to exclude combination use with Soliris</td></tr>
<tr><td>1.3</td><td>Effective Date: 06/03/2019</td><td>PA added to MAPPO and BCNA
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm*