ravulizumab (Ultomiris™)

Policy # 00671
Original Effective Date: 04/24/2019
Current Effective Date: 12/14/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), 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 Company may consider ravulizumab (Ultomiris™)‡ for the treatment of paroxysmal nocturnal hemoglobinuria to be **eligible for coverage.****

Patient Selection Criteria

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

- Initial therapy:
    - Patient has received vaccination against meningococcal infections within 3 years prior to, or at the time of initiating the requested drug; AND
    - If the drug is initiated <2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics until 2 weeks after vaccination; AND
    - Patient is 18 years of age or older; AND
    - Documentation 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
  *(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

  - Dose does not exceed 3,600 mg every 8 weeks following loading dose that does not exceed 3,000 mg.

- Continuation therapy:
  - Patient has received an initial authorization for Ultomiris; 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
      *(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose does not exceed 3,600 mg every 8 weeks.

Atypical Hemolytic Uremic Syndrome (aHUS)

Based on review of available data, the Company may consider ravulizumab (Ultomiris) for the treatment of atypical hemolytic uremic syndrome to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ravulizumab (Ultomiris) for the treatment of atypical hemolytic uremic syndrome will be considered when the following criteria are met for the requested drug:

- Initial therapy:
  - Patient has received vaccination against meningococcal infections within 3 years prior to, or at the time of initiating the requested drug; AND

- If the drug is initiated <2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics until 2 weeks after vaccination; 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
- Dose does not exceed 3,600 mg every 8 weeks after an initial loading dose of 3,000 mg

- Continuation therapy:
  - Patient has received an initial authorization for the requested drug; 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

    *(Note: These specific patient criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Dose does not exceed 3600 mg every 8 weeks

When Services Are Considered Not Medically Necessary

Based on review of available data, the use of ravulizumab (Ultomiris) 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) when the patient has not demonstrated improvement in PNH or aHUS disease manifestations while on therapy is considered to be **not medically necessary.****

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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 Company considers the use of ravulizumab (Ultomiris) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Ultomiris is a monoclonal antibody that inhibits the conversion of the complement protein C5a to C5b and prevent the generation of the terminal complement complex C5b-9. As a result, it inhibits terminal complement-mediated intravascular hemolysis in patients with paroxysmal nocturnal hemoglobinuria (PNH). It is also approved in atypical hemolytic uremic syndrome (aHUS). Ultomiris is structurally similar to another available terminal complement inhibitor, eculizumab (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 2 weeks of 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 the treatment of PNH, Ultomiris requires one loading dose between 2400-3000 mg depending on the patient's weight followed by a weight-based maintenance dose every 8 weeks beginning 2 weeks after the loading dose. Ultomiris should be dosed based on weight for aHUS up to a maximum loading dose of 3,000 mg and a maximum maintenance dose of 3,600 every 8 weeks.

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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ultomiris is approved for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria and adult and pediatric patients with atypical hemolytic uremic syndrome.

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, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Paroxysmal Nocturnal Hemoglobinuria

The safety and efficacy of Ultomiris 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.

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).

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 ≥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-up.

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 ≥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-up.

References

1. Ultomiris [package insert]. Alexion Pharmaceuticals Inc. Boston, MA. October 2019.
2. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and Control of Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendations and Reports. March 2013;62(RR02):1-22.
3. Ultomiris Drug Evaluation. Express Scripts. January 2019.
4. Parker CJ. Update on the diagnosis and management of paroxysmal nocturnal hemoglobinuria. Hematology Am Soc Hematol Educ Program. 2016;2016(1):208-216.

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04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. New policy.
05/29/2019	Coding update
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Updated the diagnostic criteria for PNH and added coverage for Ultomiris for new indication of aHUS.
09/16/2020	Coding update
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 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 Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana 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 Blue Cross Blue Shield of Louisiana 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 Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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, J3490
ICD-10 Diagnosis	D59.3, D59.5, G70.00-G70.01 Added codes eff 10/1/2020: D59.10-D59.19

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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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 BCBSLA 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 Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.