09-J3000-26

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Subject: Ravulizumab (Ultomiris™) IV

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DESCRIPTION:

Ravulizumab-cwvz (Ultomiris™) is a humanized monoclonal antibody with a high affinity for C5, a protein in the complement cascade that is essential for the formation of the membrane attack complex responsible for cell lysis. Ravulizumab is a complement inhibitor Food and Drug Administration (FDA) approved for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH) and for adults and pediatric patients with atypical uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

PNH is an uncommon, life-threatening hemolytic anemia; the incidence of PNH ranges from 0.1 to 0.2 per 100,000 persons per year. PNH results from an acquired genetic deficiency in the cytolytic complement cascade that renders red blood cells (RBCs) susceptible to lysis. Chronic destruction of PNH RBCs by complement leads to serious morbidities. Increased hemolysis at night, hypothesized to result from decreased blood pH and activation of the complement system, leads to characteristic bloody morning urination. Excessive or persistent intravascular hemolysis in persons with PNH results in anemia, hemoglobinuria, and complications related to the presence of plasma-free hemoglobin (e.g., thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension). In persons with PNH, ravulizumab's inhibition of C5 reduces hemolysis and transfusion requirements.

The safety and efficacy of ravulizumab was compared to eculizumab in the treatment of PNH in two randomized, open-label, non-inferiority studies. Study 1 was a 26-week study that enrolled 246 patients who were naïve to complement inhibitor treatment prior to study entry. Patients were included with PNH with flow cytometric confirmation of red and white blood cells, with granulocyte or monocyte clone size of at least 5%, and a lactate dehydrogenase level greater than or equal to 1.5 times the upper limit of normal at screening. Patients were also required to have the presence of one or more PNH-related signs or symptoms within 3 months of screening: fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia, history of a major adverse vascular event, dysphagia, erectile dysfunction or history of transfusion due to PNH. Patients were excluded with a platelet count of less than 30 x 10^9/L or an absolute neutrophil count of less than 500/microL (0.5 x 10^9/L) at screening, active infection within 14 days of study drug, history of

N. meningitides infection, or unstable medical conditions that would alter the transfusion protocol. Patients were randomized to receive either ravulizumab or eculizumab. The efficacy was determined based on transfusion avoidance (from baseline up to day 183) and hemolysis as measured by normalization of LDH levels. Additional endpoints included percent change from baseline in LDH, proportion of patients with hemolysis, and proportion of patients with stabilized hemoglobin. Transfusion avoidance was achieved in 73.6% and 66.1% (rate difference 6.8, 95% CI -4.66, 18.14) of patients and LDH normalization was seen in 53.6% and 49.4% (OR 1.19; 95% CI 0.80 – 1.77) of patients who received ravulizumab and eculizumab. Ravulizumab was found to be non-inferior to eculizumab across all additional endpoints. There was no difference between groups in patient reported fatigue.

Study 2 was a 26-week study that enrolled 195 patients who were clinically stable after having been treated with eculizumab for at least the past 6 months. Patients were included with PNH with flow cytometric confirmation of red and white blood cells, with granulocyte or monocyte clone size of at least 5%, and a lactate dehydrogenase level less than or equal to 1.5 times the upper limit of normal at screening. Patients were excluded with a platelet count of less than 30 x 10^9/L or an absolute neutrophil count of less than 500/microL (0.5 x 10^9/L) at screening. Patients were also excluded if a major adverse vascular event occurred in the 6 months prior to day 1, if the LDH value was greater than 2 times the upper limit of normal in the 6 months prior to day 1, if there was an active infection within 14 days before study drug, or presence of unstable medical conditions that would alter the transfusion protocol. Patients were randomized to continue eculizumab or switch to ravulizumab. The efficacy was determined based on hemolysis as measured by LDH percent change from baseline to day 183. Additional endpoints included transfusion avoidance, proportion of patients with stabilized hemoglobin, and proportion of patients with breakthrough hemolysis through day 183. The LDH percent change was -0.82% and 8.4% (rate difference 9.2; 95% CI: -0.42, 18.8) for patients who received ravulizumab and eculizumab. Ravulizumab was found to be non-inferior to eculizumab across all secondary endpoints. There was no difference between groups in patient reported fatigue. Common side effects were headache and upper respiratory infection.

Hemolytic uremic syndrome (HUS) describes the clinical condition of persons who present with simultaneous occurrence of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Typical HUS constitutes 90-95% of HUS and is secondary to infection by Shiga toxin-producing Escherichia coli (STEC). Atypical HUS (aHUS) is the result of uncontrolled activation of the complement system. Persons with aHUS present with nonimmune hemolytic anemia, thrombocytopenia, and severe renal impairment. Microvascular lesions (thrombotic microangiopathy) result from uncontrolled complement action on endothelial walls of capillary beds primarily in the kidney. In aHUS, ravulizumab binds to C5, preventing the formation of C5a (inflammatory peptide) and the membrane-attack complex C5b-9 (cytotoxic), inhibiting terminal complement-mediated thrombotic microangiopathy. In a single arm study in adults with aHUS with evidence of TMA, there were 54% of patients that achieved a complete response to treatment which included a normalized platelet count (84%), normalized LDH (77%), and greater than or equal to 25% improvement in serum creatinine from baseline (59%)]. A similar study was conducted in pediatric patients and up to 71% achieved a complete response to treatment. The most common adverse reactions were gastrointestinal disorders, infections, headache, hypertension, pyrexia, peripheral edema and arthralgia.

POSITION STATEMENT:

Initiation of ravulizumab (Ultomiris) **meets the definition of medical necessity** when used to treat the following indications when the specific criteria are met:

1. **Paroxysmal Nocturnal Hemoglobinuria (PNH)**
    a. Flow cytometry to confirm PNH in both red and white blood cells (with at least 5% granulocyte or monocyte clone size) – documentation must be provided

b. Member meets **BOTH** of the following:
    i. Absolute neutrophil count greater than or equal to 500/mm3
    ii. Platelets greater than or equal to 30,000/mm3
c. **ONE** of the following:
    i. Member's lactate dehydrogenase (LDH) is elevated (i.e., 1.5 times greater than the upper limit of normal [ULN] as determined by the laboratory performing the test) and **ONE** of the following:
        1. Member's disease is transfusion-dependent evidenced by 2 or more transfusions in the 12 months prior to ravulizumab initiation – documentation must be provided
        2. Member has a history of a major adverse vascular event (MAVE) from thromboembolism (e.g., myocardial infarction, cerebrovascular accident, deep vein thrombosis) – documentation must be provided
    ii. Member has been receiving eculizumab (Soliris) for the treatment of PNH and has a beneficial response as evidenced by a decreased requirement for transfusions, stabilization of hemoglobin, or reduction of LDH – documentation must be provided
d. **ONE** of the following:
    i. Member has been vaccinated against meningococcal infection at least 2 weeks prior to therapy initiation
    ii. Member has been vaccinated against memingococcal infection less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination
e. There is no evidence of an active meningococcal infection
f. The member will not receive an additional complement inhibitor (eculizumab)
g. The dose does not exceed the following:
    i. 40 to 59 kg: 2400 mg loading dose, followed 2 weeks later by a 3000 mg maintenance dose given every 8 weeks
    ii. 60 to 99 kg: 2700 mg loading dose, followed 2 weeks later by a 3300 mg maintenance dose every 8 weeks
    iii. 100 kg or more: 3000 mg loading dose, followed 2 weeks later by a 3600 mg maintenance dose given every 8 weeks

2. Atypical Hemolytic Uremic Syndrome (aHUS)

a. Diagnosis is supported by **BOTH** of the following (documentation must be provided):
    i. No evidence of Shiga toxin-producing E. coli infection - all initial and subsequent tests have been negative for the toxin
    ii. ADAMTS-13 level is greater than 5%
b. **ONE** of the following:
    i. Member has not previously received eculizumab (Soliris)
    ii. Member has been receiving eculizumab (Soliris) for the treatment of aHUS and has a beneficial response as evidenced by improved platelet count, reduction of LDH, improved renal function – documentation must be provided

c. **ONE** of the following:
    i. Member has been vaccinated against meningococcal infection at least 2 weeks prior to therapy initiation
    ii. Member has been vaccinated against meningococcal infection less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination
d. There is no evidence of an active meningococcal infection
e. The member will not receive an additional complement inhibitor (eculizumab)
f. The dose does not exceed the following:
    i. 5 to 9 kg: 600 mg loading dose, followed 2 weeks later by a 300 mg maintenance dose given every 4 weeks
    ii. 10 to 19 kg: 600 mg loading dose, followed 2 weeks later by a 600 mg maintenance dose given every 4 weeks
    iii. 20 to 29 kg; 900 mg loading dose, followed 2 weeks later by a 2100 mg maintenance dose given every 8 weeks
    iv. 30 to 39 kg: 1200 mg loading dose, followed 2 weeks later by a 2700 mg maintenance dose given every 8 weeks
    v. 40 to 59 kg: 2400 mg loading dose, followed 2 weeks later by a 3000 mg maintenance dose given every 8 weeks
    vi. 60 to 99 kg: 2700 mg loading dose, followed 2 weeks later by a 3300 mg maintenance dose every 8 weeks
    vii. 100 kg or more: 3000 mg loading dose, followed 2 weeks later by a 3600 mg maintenance dose given every 8 weeks

Approval duration: 6 months

Continuation of ravulizumab **meets the definition of medical necessity** when **ALL** of the following are met

1. The member has been previously approved for ravulizumab in the treatment of PNH or aHUS by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
2. Member has a history of beneficial response to ravulizumab therapy for the treatment of ONE of the following indications:
    a. Paroxysmal nocturnal hemoglobinuria (PNH) –examples of beneficial response include decreased requirement for transfusions, stabilization of hemoglobin, reduction of LDH – documentation must be provided
    b. Atypical hemolytic uremic syndrome (aHUS) – examples of beneficial response include improved platelet count, reduction of LDH, improved renal function – documentation must be provided
3. Member has been revaccinated against meningococcal infection according to current medical guidelines for vaccination while on ravulizumab therapy
4. There is no evidence of an active meningococcal infection
5. The member will not receive an additional complement inhibitor (eculizumab)
6. The dose does not exceed the following:

a. PNH
    i. 40 to 59 kg: 3000 mg maintenance dose given every 8 weeks
    ii. 60 to 99 kg: 3300 mg maintenance dose every 8 weeks
    iii. 100 kg or more: 3600 mg maintenance dose given every 8 weeks
b. aHUS
    i. 5 to 9 kg: 300 mg maintenance dose given every 4 weeks
    ii. 10 to 19 kg: 600 mg maintenance dose given every 4 weeks
    iii. 20 to 29 kg; 2100 mg maintenance dose given every 8 weeks
    iv. 30 to 39 kg: 2700 mg maintenance dose given every 8 weeks
    v. 40 to 59 kg: 3000 mg maintenance dose given every 8 weeks
    vi. 60 to 99 kg: 3300 mg maintenance dose every 8 weeks
    vii. 100 kg or more: 3600 mg maintenance dose given every 8 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- **Paroxysmal Nocturnal Hemoglobinuria (PNH) –** Administer by intravenous infusion as a loading dose on day 1 followed by maintenance dosing 2 weeks after. Each maintenance dose is administered once every 8 weeks. If switching from eculizumab, administer the loading dose 2 weeks after the last eculizumab infusion followed by the maintenance schedule.

Paroxysmal Nocturnal Hemoglobinuria (PNH)		
Body weight range (kg)	**Loading dose (mg)**	**Maintenance dose (mg)**
Greater than or equal to 40 to less than 60	2400	3000
Greater than or equal to 60 to less than 100	2700	3300
Greater than or equal to 100	3000	3600

Atypical Hemolytic Uremic Syndrome (aHUS) to inhibit complement mediated thrombotic microangiopathy (TMA) – Administer by intravenous infusion as a loading dose on day 1 followed by maintenance dosing 2 weeks after. Each maintenance dose is administered once every 8 weeks or every 4 weeks (depending on body weight). If switching from eculizumab, administer the loading dose 2 weeks after the last eculizumab infusion followed by the maintenance schedule. Ravulizumab is not indicated for the treatment of patients with Shiga toxin E.coli related hemolytic uremic syndrome (STEC-HUS).

Atypical Hemolytic Uremic Syndrome (aHUS)			
Body weight range (kg)	**Loading dose (mg)**	**Maintenance dose (mg)**	**Dosing interval**
Greater than or equal to 5 to less than 10	600	300	Every 4 weeks
Greater than or equal to 10 to less than 20	600	600	Every 4 weeks
Greater than or equal to 20	900	2100	Every 8 weeks

to less than 30			
Greater than or equal to 30 to less than 40	1200	2700	Every 8 weeks
Greater than or equal to 40 to less than 60	2400	3000	Every 8 weeks
Greater than or equal to 60 to less than 100	2700	3300	Every 8 weeks
Greater than or equal to 100	3000	3600	Every 8 weeks

Vaccinate patients for meningococcal disease according to current ACIP guidelines to reduce the risk of serious infection. Provide 2 weeks of antibacterial drug prophylaxis if ravulizumab must be initiated immediately and vaccines are administered less than 2 weeks before starting therapy. Healthcare professionals must enroll in the REMS program.

Dose Adjustments

- Administration of plasmapheresis or plasma exchange, or fresh frozen plasma infusion may reduce ravulizumab serum levels. There is no experience with administration of supplemental doses.

Drug Availability

- 300 mg/30 mL (10 mg/mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

Life-threatening and fatal meningococcal infections have occurred in persons treated with ravulizumab and may become rapidly life-threatening or fatal if not recognized and treated early.

- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in persons with complement deficiencies.
- Immunize members with a meningococcal vaccine at least 2 weeks prior to administering the first dose of ravulizumab, unless the risks of delaying ravulizumab therapy outweigh the risks of developing a meningococcal infection.
- Monitor members for early signs of meningococcal infections, and evaluate immediately if infection is suspected.
- Ravulizumab is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

Contraindications

- Ravulizumab is contraindicated in persons with unresolved serious Neisseria meningitis infection

Precautions/Warnings

- Use caution when administering ravulizumab to members with any other systemic infection.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J1303	Injection, ravulizumab-cwvz, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

D59.3	Hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Atypical hemolytic uremic syndrome (aHUS): a rare condition characterized by hemolytic anemia, thrombocytopenia and kidney failure that has no obvious cause.

Hemolysis: breakdown of red blood cells.

Microangiopathic hemolytic anemia: a disorder in which narrowing or obstruction of small blood vessels results in distortion and fragmentation of red blood cells, hemolysis, and anemia.

Paroxysmal nocturnal hemoglobinuria (PNH): A chronic acquired blood cell dysplasia with proliferation of a clone of stem cells producing erythrocytes, platelets, and granulocytes that are abnormally susceptible to lysis by complement; it is marked by episodes of intravascular hemolysis, causing hemolytic anemia, particularly following infections, and by venous thromboses, especially of the hepatic veins.

Thrombocytopenia: a reduced level of circulating platelets, which are cell fragments that normally assist with blood clotting.

RELATED GUIDELINES:

09-J1000-17, Eculizumab (Soliris)

OTHER:

none

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 11/13/19.

GUIDELINE UPDATE INFORMATION:

04/01/19	New Medical Coverage Guideline.
07/01/19	Revision: Added HCPCS code C9052.
10/01/19	Added HCPCS J1303 and removed C9052 and J3590.
12/15/19	Review and revision to guideline; consisting of updating the position statement, description, dosing, coding, and references.