09-J3000-26

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Subject: Ravulizumab (Ultomiris™) Injection

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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 paroxysmal nocturnal hemoglobinuria (PNH) and for atypical uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) in adult and pediatric patients one month of age and older. Ravulizumab is also FDA-approved for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive and for neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive.

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.

Generalized myasthenia gravis is an autoimmune neuromuscular disorder characterized by muscle weakness and fatigue. IgG antibodies occur in up to 85% of patients which are most frequently directed at the acetylcholine receptor. Treatment includes the use of cholinesterase inhibitors to prevent the breakdown of acetylcholine at the neuromuscular junction, immunosuppressive therapies, and thymectomy. Myasthenic crisis may occur which is a medical emergency due to respiratory failure and treatment includes plasmapheresis, IVIG, and corticosteroids. The efficacy of ravulizumab for gMG was evaluated in a randomized, double-blind, placebo-controlled trial in adults with a positive test for anti-AChR antibodies who had a Myasthenia Gravis Foundation of America (MGFA) clinical classification of class II – IV and a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of greater than or equal to 6. Over 80% of patients were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants at study entry and were permitted to continue therapy through the study. The change in baseline between treatment groups in the MG-ADL total score at week 26 was the primary endpoint used to evaluate the efficacy of treatment. The MG-ADL quantifies the impact of gMG on 8 signs or symptoms with a score ranging from 0 to 24, with a higher score indicating less ability to perform a function. A statistically significant improvement in the

change in baseline MG-ADL total score was demonstrated with the use of ravulizumab as compared to placebo (-3.1 vs -1.4, difference -1.6, p<0.001). The change from baseline in QMG score was a secondary endpoint used to assess the impact on muscle weakness (range 0-39 with higher score indicating severe weakness). The change from baseline in QMG score was improved significantly in the patients treated with ravulizumab vs the placebo group (-2.8 vs -0.8, difference -2.0, p<0.001). The proportion of MG-ADL responders with a 3-point improvement at week 26 were higher in the ravulizumab group (56.7% vs 34.1%). The proportion of QMG responders with a 5-point improvement at week 26 was greater for ravulizumab compared to placebo (30% vs 11.3%). The most common adverse reactions in patients with treated with ravulizumab included abdominal pain, upper respiratory tract infection, dizziness, diarrhea, urinary tract infection, and back pain.

POSITION STATEMENT:

Comparative Effectiveness (for Ultomiris on-body delivery system for subcutaneous administration)

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Site of Care: If ravulizumab (Ultomiris IV) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

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) – lab documentation must be provided
    b. **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
            3. Member has anemia with a hemoglobin less than the lower limit of normal – lab documentation must be provided
        ii. Member has been previously receiving eculizumab (Soliris, Epysqli, Bkemv), pegcetacoplan (Empaveli), iptacopan (Fabhalta), crovalimab (Piasky) for the treatment of PNH and is switching to ravulizumab
    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 treatment in combination with an additional complement inhibitor[a] (crovalimab, eculizumab and biosimilars, iptacopan, pegcetacoplan, zilucoplan), efgartigimod, efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rituximab, rozanolixizumab, satralizumab, tocilizumab or chronic immune globulin therapy

f. The dose does not exceed the following:

i. Intravenous:

a) 5 to 9 kg: 600 mg IV loading dose, followed 2 weeks later by a 300 mg IV maintenance dose given every 4 weeks

b) 10 to 19 kg: 600 mg IV loading dose, followed 2 weeks later by a 600 mg IV maintenance dose given every 4 weeks

c) 20 to 29 kg; 900 mg IV loading dose, followed 2 weeks later by a 2100 mg IV maintenance dose given every 8 weeks

d) 30 to 39 kg: 1200 mg IV loading dose, followed 2 weeks later by a 2700 mg IV maintenance dose given every 8 weeks

e) 40 to 59 kg: 2400 mg IV loading dose, followed 2 weeks later by a 3000 mg IV maintenance dose given every 8 weeks

f) 60 to 99 kg: 2700 mg IV loading dose, followed 2 weeks later by a 3300 mg IV maintenance dose every 8 weeks

g) 100 kg or more: 3000 mg IV loading dose, followed 2 weeks later by a 3600 mg IV maintenance dose given every 8 weeks

i. Subcutaneous

a) 40 kg or more: 490 mg subcutaneous once weekly (begin 2 weeks after the initial IV weight based loading dose or 8 weeks after the IV maintenance dose)

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, Bkemv, or Epysqli)

ii. Member has been receiving eculizumab (Soliris, Bkemv, or Epysqli) for the treatment of aHUS and is switching to ravulizumab

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 treatment in combination with an additional complement inhibitor (crovalimab, eculizumab or biosimilars, iptacopan, pegcetacoplan, zilucoplan), efgartigimod, efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rituximab, rozanolixizumab, satralizumab, tocilizumab or chronic immune globulin therapy

f. The dose does not exceed the following:

i. Intravenous:

a) 5 to 9 kg: 600 mg IV loading dose, followed 2 weeks later by a 300 mg IV maintenance dose given every 4 weeks

b) 10 to 19 kg: 600 mg IV loading dose, followed 2 weeks later by a 600 mg IV maintenance dose given every 4 weeks

c) 20 to 29 kg; 900 mg IV loading dose, followed 2 weeks later by a 2100 mg IV maintenance dose given every 8 weeks

d) 30 to 39 kg: 1200 mg IV loading dose, followed 2 weeks later by a 2700 mg IV maintenance dose given every 8 weeks

e) 40 to 59 kg: 2400 mg IV loading dose, followed 2 weeks later by a 3000 mg IV maintenance dose given every 8 weeks

f) 60 to 99 kg: 2700 mg IV loading dose, followed 2 weeks later by a 3300 mg IV maintenance dose every 8 weeks

g) 100 kg or more: 3000 mg IV loading dose, followed 2 weeks later by a 3600 mg IV maintenance dose given every 8 weeks

ii. Subcutaneous

a) 40 kg or more: 490 mg subcutaneous once weekly (begin 2 weeks after the initial IV weight based loading dose or 8 weeks after the IV maintenance dose)

3. Generalized Myasthenia Gravis

a. Member meets **ALL** of the following - documentation must be provided:

i. Anti-acetylcholine receptor (AchR) antibody positive disease - lab documentation must be provided

ii. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II – IV

iii. Myasthenia Gravis Activities of Daily Living (MG-ADL) total score greater than or equal to 6

iv. **ONE** of the following[b]:

1. Member had an inadequate response to at least **ONE** of the following immunosuppressants:

a. azathioprine

b. cyclosporine

c. mycophenolate mofetil

d. tacrolimus

e. methotrexate

f. cyclophosphamide

g. rituximab

2. Member required chronic immune globulin therapy or chronic plasmapheresis/plasma exchange

b. Treatment is prescribed by or in consultation with a neurologist

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. The member will not receive treatment in combination with an additional complement inhibitor (crovalimab, eculizumab and biosimilars, inebilizumab, iptacopan, pegcetacoplan, zilucoplan), efgartigimod, efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rituximab, rozanolixizumab, satralizumab, tocilizumab or chronic immune globulin therapy

e. There is no evidence of an active meningococcal infection

f. The dose does not exceed the following:

i. 40 to 59 kg: 2400 mg IV loading dose, followed 2 weeks later by a 3000 mg IV maintenance dose given every 8 weeks

ii. 60 to 99 kg: 2700 mg IV loading dose, followed 2 weeks later by a 3300 mg IV maintenance dose every 8 weeks

iii. 100 kg or more: 3000 mg IV loading dose, followed 2 weeks later by a 3600 mg IV maintenance dose given every 8 weeks

4. Neuromyelitis Optica Spectrum Disorder (NMOSD)

a. Member meets **ALL** of the following - documentation must be provided:

i. Anti-aquaporin-4 (AQP4) antibody positive disease (lab documentation must be provided)

ii. Member has **ONE** core clinical characteristic of NMOSD and alternative diagnoses have been excluded:

1. Optic neuritis

2. Acute myelitis

3. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting)

4. Acute brainstem syndrome

5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions

6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

iii. Member has a history of at least 1 relapse in the previous year[c]

b. The member will not receive treatment in combination with an additional complement inhibitor (crovalimab, eculizumab and biosimilars, iptacopan, pegcetacoplan, zilucoplan), efgartigimod, efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rituximab, rozanolixizumab, satralizumab, tocilizumab or chronic immune globulin therapy

c. Treatment is prescribed by or in consultation with a neurologist

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 dose does not exceed the following:

i. 40 to 59 kg: 2400 mg IV loading dose, followed 2 weeks later by a 3000 mg IV maintenance dose given every 8 weeks

ii. 60 to 99 kg: 2700 mg IV loading dose, followed 2 weeks later by a 3300 mg IV maintenance dose every 8 weeks

iii. 100 kg or more: 3000 mg IV loading dose, followed 2 weeks later by a 3600 mg IV maintenance dose given every 8 weeks

Approval duration: 6 months

Continuation of ravulizumab (including transitioning between IV and subcutaneous products) **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, aHUS, gMG, NMOSD 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. For continuation of therapy for gMG, member's diagnosis has been confirmed by the following – lab documentation must be provided:
    a. Anti-acetylcholine receptor (AchR) antibody positive disease
3. For continuation of therapy for NMOSD, the member's diagnosis has been confirmed by the following – lab documentation must be provided:
    a. Anti-aquaporin-4 (AQP4) antibody positive disease
4. 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
    c. Generalized Myasthenia Gravis (gMG) - examples of beneficial response include improved MG-ADL total score, Quantitative myasthenia gravis total score – documentation must be provided
    d. Neuromyelitis Optica Spectrum Disorder (NMOSD) - examples of beneficial response include absence or reduction in relapses– documentation must be provided
5. Member has been revaccinated against meningococcal infection according to current medical guidelines for vaccination while on ravulizumab therapy
6. There is no evidence of an active meningococcal infection
7. The member will not receive treatment in combination with an additional complement inhibitor[a] (crovalimab, eculizumab and biosimilars, iptacopan, pegcetacoplan, zilucoplan), efgartigimod,

efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rituximab, rozanolixizumab, satralizumab, tocilizumab or chronic immune globulin therapy

8. The dose does not exceed the following:
    a. PNH
        i. Intravenous:
            a) 5 to 9 kg: 300 mg IV maintenance dose given every 4 weeks
            b) 10 to 19 kg: 600 mg IV maintenance dose given every 4 weeks
            c) 20 to 29 kg; 2100 mg IV maintenance dose given every 8 weeks
            d) 30 to 39 kg: 2700 mg IV maintenance dose given every 8 weeks
            e) 40 to 59 kg: 3000 mg IV maintenance dose given every 8 weeks
            f) 60 to 99 kg: 3300 mg IV maintenance dose every 8 weeks
            g) 100 kg or more: 3600 mg IV maintenance dose given every 8 weeks
        ii. Subcutaneous
            a) 40 kg or more: 490 mg subcutaneous once weekly (begin 8 weeks after the IV maintenance dose)
    b. aHUS
        i. Intravenous:
            a) 5 to 9 kg: 300 mg IV maintenance dose given every 4 weeks
            b) 10 to 19 kg: 600 mg IV maintenance dose given every 4 weeks
            c) 20 to 29 kg; 2100 mg IV maintenance dose given every 8 weeks
            d) 30 to 39 kg: 2700 mg IV maintenance dose given every 8 weeks
            e) 40 to 59 kg: 3000 mg IV maintenance dose given every 8 weeks
            f) 60 to 99 kg: 3300 mg IV maintenance dose every 8 weeks
            g) 100 kg or more: 3600 mg IV maintenance dose given every 8 weeks
        ii. Subcutaneous
            a) 40 kg or more: 490 mg subcutaneous once weekly (begin 8 weeks after the IV maintenance dose)
    c. gMG
        i. 40 to 59 kg: 3000 mg IV maintenance dose given every 8 weeks
        ii. 60 to 99 kg: 3300 mg IV maintenance dose every 8 weeks
        iii. 100 kg or more: 3600 mg IV maintenance dose given every 8 weeks
    d. NMOSD
        i. 40 to 59 kg: 3000 mg IV maintenance dose given every 8 weeks
        ii. 60 to 99 kg: 3300 mg IV maintenance dose every 8 weeks
        iii. 100 kg or more: 3600 mg IV maintenance dose given every 8 weeks

Approval duration: 1 year

[a] Danicopan (Voydeya) is permitted in combination with Ultomiris for the treatment of extravascular hemolysis in adults with PNH if the Florida Blue Medical Coverage Guideline criteria for Voydeya are met

[b] Step not required if the member previously received treatment with eculizumab or biosimilars, efgartigimod, efgartigimod-hyaluronidase, inebilizumab, nipocalimab, rozanolixizumab, or zilucoplan

[c] Step not required if the member previously received treatment with eculizumab or biosimilars, inebilizumab, or satralizumab

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 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. See below for dosing of ravulizumab on-body delivery system for subcutaneous administration. See prescribing information if switching between IV and subcutaneous ravulizumab or if switching from eculizumab after the induction infusion.
- **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). See below for dosing of ravulizumab on-body delivery system for subcutaneous administration. See prescribing information if switching between IV and subcutaneous ravulizumab or if switching from eculizumab after the induction infusion.
- **Generalized Myasthenia Gravis for adults who are anti-acetylcholine receptor (AChR) antibody-positive** - 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. See prescribing information if switching from eculizumab after the induction infusion.

- **Neuromyelitis optica spectrum disorder for adults who are anti-aquaporin-4 (AQP4) receptor antibody-positive** - 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. See prescribing information if switching from eculizumab after the induction infusion.

Ravulizumab for Intravenous infusion - Weight-Based Dosing for PNH, aHUS, and gMG				
PNH and 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 to less than 30	900	2100	Every 8 weeks
	Greater than or equal to 30 to less than 40	1200	2700	Every 8 weeks
PNH, aHUS, gMG, and NMOSD	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

Ravulizumab on-body delivery system for subcutaneous administration - Weight-Based Dosing for PNH, aHUS, and gMG			
PNH and aHUS	**Body weight range (kg)**	**Maintenance dose (mg)**	**Dosing interval**
	Greater than 40 kg	490 mg once weekly in adults	weekly
• For the first subcutaneous dose of ravulizumab, administer two weeks after the IV loading dose of ravulizumab • For transition from ravulizumab IV, administer 8 weeks after the last administered IV maintenance dose • See prescribing information for dosing schedule when transitioning between products and for administration instructions			

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 intravenous immunoglobulin may reduce ravulizumab serum levels. See prescribing information for supplemental doses after plasmapheresis, plasma exchange, or IVIG.

Drug Availability

- 300 mg/3 mL (100 mg/mL) in a single-dose vial
- 1100 mg/ 11 mL (100 mg/mL) in a single-dose vial
- 245 mg/3.5 mL single-dose cartridge on-body subcutaneous delivery system
- Do not mix varied concentrations together

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
- Ravulizumab is contraindicated in persons who are not currently vaccinated against Neisseria meningitidis, unless the risk of delaying treatment outweighs the risk of developing a meningococcal infection.

Precautions/Warnings

- Use caution when administering ravulizumab to members with any other systemic infection.
- Monitor patients during the infusion; interrupt treatment and provide supportive measures for reactions.

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

D59.39	Other hemolytic-uremic syndrome (atypical)
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

G36.0	Neuromyelitis optica [Devic]
G70.00 – G70.01	Myasthenia gravis

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: Florida Blue 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. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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:

Eculizumab (Soliris), 09-J1000-17

Efgartigimod (Vyvgart, Vyvgart Hytrulo), 09-J4000-18

Immune Globulin Therapy, 09-J0000-06

Inebilizumab (Uplizna), 09-J3000-73

Pegcetacoplan (Empaveli), 09-J4000-04

Rituximab Products, 09-J0000-59

Iptacopan (Fabhalta), 09-J4000-80

Pegcetacoplan (Empaveli), 09-J4000-04

Rozanolixizumab-noli (Rystiggo), 09-J4000-55

Satralizumab (Enspryng), 09-J3000-79

Zilucoplan (Zilbrysq), 09-J4000-78

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/11/26.

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.
05/15/20	Review of guideline; consisting of updating references.
11/15/20	Revision to guideline; consisting of updating the position statement.
07/15/21	Revision to guideline; consisting of updating the position statement, description, dosing, and references.
10/15/21	Review and revision to guideline; consisting of updating the position statement, warnings, and references.
07/15/22	Review and revision to guideline; consisting of updating the position statement, description, dosing, and references.
08/15/22	Revision to guideline; consisting of updating the position statement.
10/01/22	Update to ICD-10 coding.
09/15/23	Review and revision to guideline; consisting of including the ravulizumab on-body delivery system and updating the list of agents not to be used in combination. Update to dosing and references.

10/15/23	Review and revision to guideline; consisting of updating the the position statement for myasthenia gravis.
05/15/24	Review and revision to guideline; consisting of updating the the position statement to include neuromyelitis optica spectrum disorder. The position statement also includes updating lab documentation requirements and agents not to be used in combination. Updates to coding and references.
08/15/24	Review and revision; consisting of updating the position statement for NMOSD.
12/15/24	Revision to guidelines; consisting of updating the position statement for agents used in combination for PNH.
06/15/25	Review and revision to guidelines; consisting of updating the position statement for agents used in combination for covered indications.
04/15/26	Revision to guidelines; consisting of updating the position statement for agents used in combination for generalized Myasthenia Gravis.