# Corporate Medical Policy

# Ravulizumab-cwvz (Ultomiris™)

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| **File Name:** | ravulizumab_ultomiris |
| **Origination:** | 4/2019 |
| **Last CAP Review:** | 4/2020 |
| **Next CAP Review:** | 4/2021 |
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## Description of Procedure or Service

Ravulizumab-cwvz (Ultomiris™) is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH), and adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Paroxysmal nocturnal hemoglobinuria

PNH is a rare clonal hematopoietic stem cell disorder clinically characterized by chronic complement-mediated hemolysis, thrombosis, and impaired hematopoiesis. Thrombosis is the major cause of death in PNH and is observed in approximately 40% of patients. The symptoms associated with this disorder, including fatigue, pain, esophageal spasm, and erectile dysfunction, are often severe and disabling.

Hemolytic-uremic syndrome

Hemolytic-uremic syndrome (HUS) is characterized by hemolytic anemia, thrombocytopenia, and renal failure caused by platelet thombi in the microcirculation of the kidney and other organs. Typical (acquired) HUS is triggered by infectious agents such as strains of E. coli (Stx-E. coli) that produce powerful Shiga-like exotoxins, whereas atypical HUS (aHUS) can be genetic, acquired, or idiopathic (of unknown cause). Onset of aHUS ranges from prenatal to adulthood. Individuals with genetic aHUS frequently experience relapse even after complete recovery following the presenting episode. Sixty percent of genetic aHUS progresses to end-stage renal disease (ESRD).

Regulatory status

Ravulizumab-cwvz (Ultomiris) was approved by the U.S. Food and Drug Administration (FDA) in December 2018 for the treatment of PNH. It is a humanized monoclonal antibody that binds to the human C5 complement protein; thus, inhibiting terminal complement-mediated intravascular hemolysis in patients with PNH and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS. In October 2019, the FDA approved ravulizumab-cwvz for the treatment of adult and pediatric patients with aHUS.

Studies conducted on the safety and efficacy of ravulizumab for the treatment of PNH included patients who had never received complement inhibitor therapy and those who had been receiving and were being switched from eculizumab. Eculizumab, a similar complement inhibitor used to treat PNH, has a shorter half-life than ravulizumab.

**Related Policies:**
Eculizumab (Soliris®)

# Ravulizumab-cwvz (Ultomiris™)

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

**BCBSNC will provide coverage for ravulizumab-cwvz (Ultomiris) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Ravulizumab-cwvz (Ultomiris) is covered

**Paroxysmal Nocturnal Hemoglobinuria (PNH)**

**Initial Therapy**

**Complement inhibitor therapy naïve (not switching from eculizumab)**

Ravulizumab-cwvz (Ultomiris) is considered medically necessary for the treatment of adult patients (≥ 18 years old) with paroxysmal nocturnal hemoglobinuria (PNH) who are not switching from eculizumab (Soliris) when the following clinical criteria are met:

1. The patient has a diagnosis of PNH as confirmed by flow cytometry showing reduced levels of GPI-anchored proteins in at least two peripheral blood cell lines and a clone size of at least 5%; **AND**
2. The patient has a lactate dehydrogenase (LDH) level greater than or equal to 1.5 times the upper limit of normal at screening; **AND**
3. The patient has at least one PNH sign or symptom (e.g., fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia (hemoglobin less than 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, erectile dysfunction or history of red blood cell transfusion due to PNH; **AND**
4. The patient has been administered a meningococcal vaccine at least two weeks prior to initiation of ravulizumab therapy; **AND**
5. The patient is re-vaccinated according to current medical guidelines for vaccine use while on ravulizumab therapy; **AND**
6. The patient will not receive ravulizumab concomitantly with other complement inhibitors (e.g., eculizumab).

Initial authorization: 6 months

**Switching from eculizumab**

Ravulizumab-cwvz (Ultomiris) is considered medically necessary for the treatment of adult patients (≥ 18 years old) with PNH who are switching from eculizumab (Soliris) when the following clinical criteria are met:

1. The patient had a diagnosis of PNH confirmed by flow cytometry prior to starting eculizumab therapy which showed reduced levels of GPI-anchored proteins in at least two peripheral blood cell lines and a clone size of at least 5%; **AND**

2. The patient has been receiving eculizumab therapy for at least 6 months and is clinically stable, with an LDH level less than or equal to 1.5 times the upper limit of normal; **AND**
3. The patient has received a meningococcal vaccination within 3 years of initiation of ravulizumab therapy; **AND**
4. The patient is re-vaccinated according to current medical guidelines for vaccine use while on ravulizumab therapy; **AND**
5. The patient will not receive ravulizumab concomitantly with other complement inhibitors (e.g., eculizumab).

Initial authorization: 6 months

**Continuation Therapy**

Continuation of treatment with ravulizumab-cwvz (Ultomiris) beyond 6 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) when the following criteria are met:

- The patient has been receiving ravulizumab treatment previously; **AND**
- The patient has had either stabilization or improvement of symptoms from baseline while on ravulizumab therapy

**Atypical Hemolytic Uremic Syndrome (aHUS)**

**Initial Therapy**

Ravulizumab-cwvz (Ultomiris) is considered medically necessary for the treatment of adult and pediatric patients (≥1 month old) with aHUS to inhibit complement-mediated thrombotic microangiopathy (TMA) when the following criteria are met:

1. The patient has a diagnosis of aHUS with evidence of TMA (see Policy Guidelines); **AND**
2. The patient has been administered a meningococcal vaccine at least two weeks but no more than three years prior to initiation of ravulizumab therapy; **AND**
3. The patient is re-vaccinated according to current medical guidelines for vaccine use while on ravulizumab therapy; **AND**
4. The patient will not receive ravulizumab concomitantly with other complement inhibitors (e.g., eculizumab).

Initial authorization: 6 months

**Continuation Therapy**

Continuation of treatment with ravulizumab-cwvz (Ultomiris) beyond 6 months after initiation of therapy, and every 12 months thereafter, is considered medically necessary for the treatment of atypical hemolytic uremic syndrome (aHUS) when the following criteria are met:

- The patient has been receiving ravulizumab treatment previously; **AND**
- The patient has had a positive clinical response as measured by hematological parameters or thrombotic microangiopathy (TMA) response while on ravulizumab therapy

## When Ravulizumab-cwvz (Ultomiris) is not covered

Ravulizumab-cwvz (Ultomiris) is considered **investigational** and therefore not covered when the above criteria are not met.

Use of ravulizumab-cwvz for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS) is considered **investigational**.

## Policy Guidelines

For the treatment of PNH, the recommended dosing for Ultomiris is administered as a weight-based intravenous infusion consisting of a loading dose followed by maintenance dosing, as shown in Table 1. The maintenance dose (weight-based) is administered once every 8-week interval and should be initiated 2 weeks following administration of the loading dose.

Table 1: Ultomiris Weight-Based Dosing Regimen - PNH

| Body Weight Range (kg) | Loading Dose (mg) | Maintenance Dose (mg) |
|---|---|---|
| greater than or equal to 40 to less than 60 | 2,400 | 3,000 |
| greater than or equal to 60 to less than 100 | 2,700 | 3,300 |
| greater than or equal to 100 | 3,000 | 3,600 |

For atypical hemolytic uremic syndrome (aHUS), evidence of thrombotic microangiopathy (TMA) is demonstrated by parameters such as low platelet count, hemolysis (breaking of red blood cells inside of blood vessels), and decreased kidney function.

For the treatment of aHUS in adult and pediatric patients one month of age and older weighing 5 kg or greater, the recommended dosing for Ultomiris is administered as a weight-based intravenous infusion consisting of a loading dose followed by maintenance dosing, as shown in Table 2. The maintenance dose is administered once every 8 weeks or every 4 weeks (depending on body weight), starting 2 weeks after administration of the loading dose.

Table 2: Ultomiris Weight-Based Dosing Regimen - aHUS

| Body Weight Range (kg) | Loading Dose (mg) | Maintenance Dose (mg) | Maintenance 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 | |
| greater than or equal to 20 to less than 30 | 900 | 2,100 | Every 8 weeks |
| greater than or equal to 30 to less than 40 | 1,200 | 2,700 | |
| greater than or equal to 40 to less than 60 | 2,400 | 3,000 | |
| greater than or equal to 60 to less than 100 | 2,700 | 3,300 | |
| greater than or equal to 100 | 3,000 | 3,600 | |

For patients switching from eculizumab to Ultomiris, the Ultomiris loading dose should be administered 2 weeks following the last eculizumab infusion, and then the maintenance dose administered once every 8 weeks or every 4 weeks (depending on body weight), starting 2 weeks after administration of the loading dose.

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

Patients should be vaccinated for meningococcal disease according to ACIP (Advisory Committee on Immunization Practices) guidelines at least 2 weeks prior to administering the first dose of Ultomiris to reduce risk of serious infection. If Ultomiris therapy must be initiated immediately and vaccines are administered less than 2 weeks before therapy initiation, patients should receive 2 weeks of antibacterial drug prophylaxis.

Due to the risk of meningococcal infections, Ultomiris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), in which providers must enroll in the program and must provide counseling and educational materials to patients about the risk of meningococcal infection/sepsis. Providers must also ensure that patients receive meningococcal vaccinations.

According to the manufacturer's safety information for Ultomiris, the most common adverse reactions in patients with PNH (≥ 10%) include upper respiratory tract infection and headache. The most common adverse reactions in patients with aHUS (≥ 20%) include upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension, and fever.

**Clinical Trial Evidence**

Paroxysmal nocturnal hemoglobinuria

The efficacy and safety of ravulizumab (Ultomiris) in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) was evaluated in two multicenter, open-label, randomized, active-controlled, non-inferiority phase 3 clinical trials: Study 1 (NCT02946463) and Study 2 (NCT03056040). Patients with PNH who were complement inhibitor naïve and with active hemolysis were assessed in Study 1, and Study 2 evaluated patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months. Patients enrolled in both studies received ravulizumab intravenously according to weight-based dosing as described above, given as 4 infusions over 26 weeks. Eculizumab was given on days 1, 8, 15, and 22, followed by a maintenance eculizumab dose of 900 mg on day 29 and every 2 weeks thereafter for a total of 26 weeks, which was the approved dosing regimen and standard of care for PNH at the time of the studies. Prior to or at initiation of ravulizumab or eculizumab treatment, patients were vaccinated against meningococcal infection, or received prophylactic treatment with appropriate antibiotics until two weeks post vaccination. Prophylactic treatment with antibiotics beyond two weeks after vaccination was then based on provider discretion.

Study 1 enrolled 246 patients with PNH who were naïve to complement inhibitor therapy prior to study entry. Patients in the study had a diagnosis of PNH with flow cytometric confirmation of at least 5% PNH cells and lactate dehydrogenase (LDH) level ≥ 1.5 x ULN at screening. Enrolled patients must also have had one or more of the following PNH-related signs or symptoms present within 3 months of screening: fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia (i.e., hemoglobin level <10 g/dL), or history of major adverse vascular events (including thrombosis), dysphagia, erectile dysfunction, or history of packed red blood cell transfusion due to PNH. Patients were randomized 1:1 to receive either ravulizumab or eculizumab. The primary endpoints were the proportion of patients remaining transfusion-free (ravulizumab, 73.6% vs eculizumab, 66.1%; difference of 6.8% [95% CI, -4.66, 18.14]) and hemolysis as measured by LDH normalization (ravulizumab, 53.6% vs eculizumab, 49.4%; odds ratio, 1.19 [95% CI, 0.80, 1.77]). Study results indicated that ravulizumab administered every 8 weeks was noninferior to eculizumab administered every 2 weeks for both primary endpoints ($P_{inf}$< 0.0001). Ravulizumab and eculizumab also shared similar safety and tolerability, and no meningococcal infections occurred during the study.

Study 2 enrolled 195 patients with clinically stable PNH after being treated with eculizumab (900 mg every 2 weeks) for at least the prior 6 months. Patients in the study had a diagnosis of PNH with flow cytometric confirmation of at least 5% PNH cells and LDH level ≤ 1.5 x ULN at

screening. Patients were randomized 1:1 to either continue eculizumab or to switch to ravulizumab. The primary efficacy endpoint was hemolysis measured by percentage change in LDH from baseline to 26 weeks (difference, 9.21% [95% CI, -0.42 to 18.84], p=0.058 for superiority). The most frequently reported adverse event was headache (26.8%, ravulizumab; 17.3%, eculizumab). No meningococcal infections or discontinuation due to adverse events occurred. The study concluded that patients may be safely and effectively switched from eculizumab given every 2 weeks to ravulizumab given every 8 weeks.

Hemolytic uremic syndrome

The efficacy of ravulizumab-cwvz (Ultomiris) in patients with atypical hemolytic uremic syndrome (aHUS) was evaluated in two open-label, single-arm clinical trials. Study 1 (NCT02949128) enrolled adult patients with evidence of thrombotic microangiopathy (TMA) and who were naïve to complement inhibitor treatment. Study participants were required to have a platelet count $\leq 150 \times 10^9$/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis. Study 2 (NCT03131219) enrolled pediatric patients with evidence of TMA who were naïve to eculizumab. Patients enrolled in Study 2 were required to have a platelet count $\leq 150 \times 10^9$/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level $\geq$ 97.5% percentile at screening or required dialysis. Patients were excluded from both Study 1 and Study 2 who presented with TMA due to disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism.

Study 1 assessed 56 patients with aHUS who were naïve to complement inhibitor treatment prior to study entry over a 26-week initial evaluation period, after which patients could enter an extension period for up to 4.5 years. A complete TMA response was achieved in 54% of patients after 26 weeks of ravulizumab-cwvz treatment. Complete TMA response was defined as normalization of platelet count and LDH and at least a 25% improvement in serum creatinine, which had to be met at two separate assessments obtained at least 28 days apart. Median time to complete TMA response was 86 days (range: 7 to 169 days), and 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.

Study 2 is a 26-week ongoing, multicenter, single-arm clinical trial assessing 16 pediatric patients with aHUS. In a 26-week interim analysis including 14 pediatric patients with aHUS who were naïve to eculizumab, a complete TMA response was achieved with ravulizumab-cwvz treatment in 71% of patients. Median time to complete TMA response was 30 days (range: 15 to 88 days), and 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.

**Administration of ravulizumab (Ultomiris) - Site of Care Eligibility**

1. Administration of ravulizumab (Ultomiris) may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of ravulizumab (Ultomiris) infusion is not medically necessary, OR
2. Administration of ravulizumab (Ultomiris) in a hospital outpatient setting is considered medically necessary if the following criteria are met:
    a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.), OR
    b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
    c. First infusion, OR
    d. Less than 3 months since first ravulizumab (Ultomiris) infusion, OR
    e. First infusion after six months of no ravulizumab (Ultomiris) infusions, OR
    f. Requirement of a change in ravulizumab (Ultomiris) product.

3. Members who do not meet the criteria above are appropriate for ravulizumab (Ultomiris) administration in a home-based infusion or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

## Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J1303*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

Alexion Pharmaceuticals, Inc. Ultomiris (ravulizumab-cwvz) injection for intravenous use. Highlights of prescribing information. December 2018. Available at: https://alexion.com/Documents/Ultomiris_USPI.aspx. Accessed April 2019.

U.S. Food and Drug Administration. FDA approves new treatment for adult patients with rare, life-threatening blood disease. December 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm629022.htm. Accessed April 2019.

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Borowitz MJ, Craig FE, DiGiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry Part B (Clinical Cytometry) 2010; 78B:211-230.

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Alexion Pharmaceuticals, Inc. Ultomiris (ravulizumab-cwvz) injection for intravenous use. Highlights of prescribing information. October 2019. Available at: https://alexion.com/Documents/Ultomiris_USPI.aspx. Last accessed February 2020.

Medical Director review 2/2020

Specialty Matched Consultant Advisory Panel review 4/2020

## Policy Implementation/Update Information

4/30/19 New policy developed. Ravulizumab-cwvz (Ultomiris) is considered medically necessary for the treatment of adult patients (≥ 18 years old) with paroxysmal nocturnal hemoglobinuria (PNH). Added HCPCS codes C9399, J3490, and J3590 to Billing/Coding section. References added. Medical Director review 4/2019. (krc)

7/1/19 Added HCPCS code C9052 to Billing/Coding section and deleted codes C9399. (krc)

10/1/19 Added HCPCS code J1303 to Billing/Coding section and deleted codes C9052, J3490, and J3590 effective 10/1/19. (krc)

2/11/20 New indication added to "When Covered" section for atypical hemolytic uremic syndrome (aHUS). Updated "Description" and "Policy Guidelines" sections to include aHUS indication. References added. Medical Director review 2/2020. (krc)

6/9/20 Added dosing and clinical trial information for aHUS indication in Policy Guidelines section. Specialty Matched Consultant Advisory Panel review 4/15/2020. (krc)