# ULTOMIRIS Weight-Based Dosing Regimen[1]
## for PNH or atypical-HUS

ULTOMIRIS® (ravulizumab-cwvz)
injection for intravenous use
300 mg/3 mL vial

### For Patients With Atypical Hemolytic Uremic Syndrome or Paroxysmal Nocturnal Hemoglobinuria[1]

| Body weight range (kg) | Loading dose (mg) | Maintenance dose (mg) and dosing interval | |
|---|---|---|---|
| 5 to <10 | 600 | 300 | Every 4 weeks |
| 10 to <20 | 600 | 600 | |
| 20 to <30 | 900 | 2,100 | Every 8 weeks |
| 30 to <40 | 1,200 | 2,700 | |
| 40 to <60 | 2,400 | 3,000 | |
| 60 to <100 | 2,700 | 3,300 | |
| 100 or greater | 3,000 | 3,600 | |

- Maintenance doses are administered starting 2 weeks after the loading dose
- When transitioning from eculizumab to ULTOMIRIS, the loading dose of ULTOMIRIS should be administered at the time of the next scheduled eculizumab dose

### ULTOMIRIS 100 mg/mL

#### ULTOMIRIS Loading Dose Reference Table: 100 mg/mL Formulation[1]

| Body weight range[a] (kg) | ULTOMIRIS volume | | Volume of 0.9% NaCl[b] | | Total volume (dose) | Minimum infusion time (hr) | Maximum infusion rate (mL/hr) |
|---|---|---|---|---|---|---|---|
| 5 to <10 | 6 mL | + | 6 mL | = | 12 mL (600 mg) | 1.4 | 9 |
| 10 to <20 | 6 mL | + | 6 mL | = | 12 mL (600 mg) | 0.8 | 15 |
| 20 to <30 | 9 mL | + | 9 mL | = | 18 mL (900 mg) | 0.6 | 30 |
| 30 to <40 | 12 mL | + | 12 mL | = | 24 mL (1,200 mg) | 0.5 | 48 |
| 40 to <60 | 24 mL | + | 24 mL | = | 48 mL (2,400 mg) | 0.8 | 60 |
| 60 to <100 | 27 mL | + | 27 mL | = | 54 mL (2,700 mg) | 0.6 | 90 |
| 100 or greater | 30 mL | + | 30 mL | = | 60 mL (3,000 mg) | 0.4 | 150 |

#### ULTOMIRIS Maintenance Dose Reference Table: 100 mg/mL Formulation[1]

| Body weight range[a] (kg) | ULTOMIRIS volume | | Volume of 0.9% NaCl[b] | | Total volume (dose) | Minimum infusion time (hr) | Maximum infusion rate (mL/hr) |
|---|---|---|---|---|---|---|---|
| 5 to <10 | 3 mL | + | 3 mL | = | 6 mL (300 mg) | 0.8 | 8 |
| 10 to <20 | 6 mL | + | 6 mL | = | 12 mL (600 mg) | 0.8 | 15 |
| 20 to <30 | 21 mL | + | 21 mL | = | 42 mL (2,100 mg) | 1.3 | 33 |
| 30 to <40 | 27 mL | + | 27 mL | = | 54 mL (2,700 mg) | 1.1 | 50 |
| 40 to <60 | 30 mL | + | 30 mL | = | 60 mL (3,000 mg) | 0.9 | 67 |
| 60 to <100 | 33 mL | + | 33 mL | = | 66 mL (3,300 mg) | 0.7 | 95 |
| 100 or greater | 36 mL | + | 36 mL | = | 72 mL (3,600 mg) | 0.5 | 144 |

**If an adverse reaction occurs during the intravenous administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician.**

[a]Body weight at time of treatment. [b]Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

## Supplemental Dose of ULTOMIRIS

**Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) treatment have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP, or IVIg.**

### Supplemental Dose of ULTOMIRIS After PE, PP, or IVIg[1]

| Body weight range (kg) | Most recent ULTOMIRIS dose (mg) | Supplemental dose (mg) following each PE or PP intervention | Supplemental dose (mg) following completion of an IVIg cycle |
|---|---|---|---|
| 40 to <60 | 2,400 | 1,200 | 600 |
| | 3,000 | 1,500 | |
| 60 to <100 | 2,700 | 1,500 | 600 |
| | 3,300 | 1,800 | |
| 100 or greater | 3,000 | 1,500 | 600 |
| | 3,600 | 1,800 | |
| Timing of ULTOMIRIS supplemental dose | | Within 4 hours following each PE or PP intervention | Within 4 hours following completion of an IVIg cycle |

### ULTOMIRIS Supplemental Dose Reference Table: 100 mg/mL Formulation[1]

| Body weight range[a] (kg) | Supplemental dose (mg) | ULTOMIRIS volume | | Volume of 0.9% NaCl[b] | | Total volume (dose) | Minimum infusion time (hr) | Maximum infusion rate (mL/hr) |
|---|---|---|---|---|---|---|---|---|
| 40 to <60 | 600 | 6 mL | + | 6 mL | = | 12 mL | 0.25 | 48 |
| | 1,200 | 12 mL | + | 12 mL | = | 24 mL | 0.42 | 57 |
| | 1,500 | 15 mL | + | 15 mL | = | 30 mL | 0.50 | 60 |
| 60 to <100 | 600 | 6 mL | + | 6 mL | = | 12 mL | 0.20 | 60 |
| | 1,500 | 15 mL | + | 15 mL | = | 30 mL | 0.36 | 83 |
| | 1,800 | 18 mL | + | 18 mL | = | 36 mL | 0.42 | 86 |
| 100 or greater | 600 | 6 mL | + | 6 mL | = | 12 mL | 0.17 | 71 |
| | 1,500 | 15 mL | + | 15 mL | = | 30 mL | 0.25 | 120 |
| | 1,800 | 18 mL | + | 18 mL | = | 36 mL | 0.28 | 129 |

[a]Body weight at time of treatment. [b]Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

**Reference: 1.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc.

**With ULTOMIRIS 100 mg/mL, there is an optimal vial mix (3 mL and 11 mL) for each patient weight cohort, ensuring there is no product wastage.**

**Please see reverse for Indications and Important Safety Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.**

## INDICATIONS & IMPORTANT SAFETY INFORMATION

### INDICATIONS

**Paroxysmal Nocturnal Hemoglobinuria (PNH)**
ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).

**Atypical Hemolytic Uremic Syndrome (aHUS)**
ULTOMIRIS is indicated for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitation of Use:
ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

**Subcutaneous Use in Adult Patients with PNH or aHUS**
Subcutaneous administration of ULTOMIRIS is not approved for use in pediatric patients.

### IMPORTANT SAFETY INFORMATION

**WARNING: SERIOUS MENINGOCOCCAL INFECTIONS**

**Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS. Meningococcal infection 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 patients with complement deficiencies.**
- **Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a meningococcal infection. See *Warnings and Precautions* for additional guidance on the management of the risk of meningococcal infection.**
- **Vaccination reduces, but does not eliminate, the risk of meningococcal infections. Monitor patients for early signs of meningococcal infections and evaluate immediately if infection is suspected.**

**Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS REMS.**

### CONTRAINDICATIONS

- Patients with unresolved *Neisseria meningitidis* infection.
- Patients who are not currently vaccinated against *Neisseria meningitidis,* unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection.

### WARNINGS AND PRECAUTIONS

**Serious Meningococcal Infections**
Life-threatening meningococcal infections have occurred in patients treated with ULTOMIRIS. The use of ULTOMIRIS increases a patient's susceptibility to serious meningococcal infections (septicemia and/or meningitis). Meningococcal disease due to any serogroup may occur.

Vaccinate or revaccinate for meningococcal disease according to the most current ACIP recommendations for patients with complement deficiencies. Immunize patients without history of meningococcal vaccination at least 2 weeks prior to the first dose of ULTOMIRIS. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

In clinical studies, 59 adult patients with PNH were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of these patients received antibiotics for prophylaxis of meningococcal infection until at least 2 weeks after meningococcal vaccination. The benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving ULTOMIRIS have not been established. In clinical studies with ULTOMIRIS, <1% of patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

**ULTOMIRIS REMS**
Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a REMS called ULTOMIRIS REMS.

Under the ULTOMIRIS REMS, prescribers must enroll in the program. Prescribers must counsel patients about the risk of meningococcal infection/sepsis, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccines.

Additional information on the REMS requirements is available at www.ultomirisrems.com or 1-888-765-4747.

**Other Infections**
Patients may have increased susceptibility to infections, especially with encapsulated bacteria, such as infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae,* and to a lesser extent, *Neisseria gonorrhoeae*. Children treated with ULTOMIRIS may be at increased risk of developing serious infections due to *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib). Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) infections according to ACIP guidelines. If ULTOMIRIS is administered to patients with active systemic infections, monitor closely for worsening infection.

**Monitoring Disease Manifestations after ULTOMIRIS Discontinuation**
Treatment Discontinuation for PNH
After discontinuing treatment with ULTOMIRIS, closely monitor for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in PNH clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who discontinues ULTOMIRIS for at least 16 weeks to detect hemolysis and other reactions. If signs and symptoms of hemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ULTOMIRIS.

Treatment Discontinuation for aHUS
ULTOMIRIS treatment of aHUS should be a minimum duration of 6 months. Due to heterogeneous nature of aHUS events and patient-specific risk factors, treatment duration beyond the initial 6 months should be individualized. There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, patients should be monitored for clinical symptoms and laboratory signs of TMA complications for at least 12 months.

TMA complications post-discontinuation can be identified if any of the following is observed: Clinical symptoms of TMA include changes in mental status, seizures, angina, dyspnea, thrombosis or increasing blood pressure. In addition, at least two of the following laboratory signs observed concurrently and results should be confirmed by a second measurement 28 days apart with no interruption: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment. If TMA complications occur after discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

**Thromboembolic Event Management**
The effect of withdrawal of anticoagulant therapy during treatment with ULTOMIRIS has not been established. Treatment should not alter anticoagulant management.

**Infusion-Related Reactions**
Intravenous or subcutaneous administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

**Injection Site Reactions-Subcutaneous administration**
27% (23/84) of patients treated with subcutaneous administration of ULTOMIRIS experienced injection site reactions which included application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction.

**Allergies to Acrylic Adhesives**
The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. Premedication can be considered, and supportive measures should be instituted if signs of allergy appear.

### ADVERSE REACTIONS

Adverse Reactions for PNH
Adverse reactions reported in 5% or more of patients treated with ULTOMIRIS vs. Eculizumab was Upper respiratory tract infection (39% vs. 39%), Headache (32% vs. 26%), Diarrhea (9% vs. 5%), Nausea (9% vs. 9%), Pyrexia (7% vs. 8%), Pain in extremity (6% vs. 5%), Abdominal pain (6% vs. 7%), Dizziness (5% vs. 6%), Arthralgia (5% vs. 5%). Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS. One fatal case of sepsis was identified in a patient treated with ULTOMIRIS. In clinical studies, clinically relevant adverse reactions in 1% of adult patients include infusion-related reactions.

Adverse reactions reported in 10% or more of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced was Anemia (20% vs. 25%), Abdominal pain (0% vs. 38%), Constipation (0% vs. 25%), Pyrexia (20% vs. 13%), Upper respiratory tract infection (20% vs. 75%), Pain in extremity (0% vs. 25%), Headache (20% vs. 25%).

Adverse Reactions for aHUS
Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 42 (57%) patients with aHUS receiving ULTOMIRIS. The most frequent serious adverse reactions reported in more than 2 patients (2.7%) treated with ULTOMIRIS were hypertension, pneumonia and abdominal pain. In clinical studies, clinically relevant adverse reactions in <10% of patients include viral tonsillitis in adults and viral infection in pediatric patients and in 3% of adult patients include infusion-related reactions.

Adverse Reactions for Subcutaneous Administration of ULTOMIRIS
Most common adverse reactions (≥10%) with ULTOMIRIS subcutaneous administration via On Body Injector in adult patients with PNH were local injection site reactions, diarrhea, and headache.

### DRUG INTERACTIONS

Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins
Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS.

Neonatal Fc Receptor Blockers
Concomitant use of ULTOMIRIS with neonatal Fc receptor (FcRn) blockers (e.g.,efgartigimod) may lower systemic exposures and reduce effectiveness of ULTOMIRIS. Closely monitor for reduced effectiveness of ULTOMIRIS.

**Please see accompanying full Prescribing Information (bit.ly/UltomirisPI) for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening meningococcal infections/sepsis.**



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