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

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

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

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.

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).

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

ULTOMIRIS, a complement inhibitor, increases the risk of serious infections caused by *Neisseria meningitidis* [*see Warnings and Precautions (5.1)*] Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for meningococcal bacteria (for serogroups A, C, W, Y, and B) at least 2 weeks prior to the first dose of ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by meningococcal bacteria.**
- **Patients receiving ULTOMIRIS are at increased risk for invasive disease caused by *Neisseria meningitidis*, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious 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 and SOLIRIS REMS [*see Warnings and Precautions (5.2)*].

CONTRAINDICATIONS

- Initiation in patients with unresolved serious *Neisseria meningitidis* infection.

WARNINGS AND PRECAUTIONS

Serious Meningococcal Infections
ULTOMIRIS, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by meningococcal bacteria (septicemia and/or meningitis) in any serogroup, including non-groupable strains. Life-threatening and fatal meningococcal infections have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors.

Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent ULTOMIRIS therapy is indicated in a patient who is not up to date with meningococcal vaccines according to ACIP recommendations, provide antibacterial drug prophylaxis and administer meningococcal vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including ULTOMIRIS. The benefits and risks of treatment with ULTOMIRIS, as well as those associated with antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by *Neisseria meningitidis*.

Vaccination does not eliminate the risk of serious meningococcal infections, despite development of antibodies following vaccination.

Closely monitor patients for early signs and symptoms of meningococcal infection and evaluate patients immediately if infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection depending on the risks of interrupting treatment in the disease being treated.

ULTOMIRIS and SOLIRIS REMS
Due to the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program called ULTOMIRIS and SOLIRIS REMS.

Prescribers must enroll in the REMS, counsel patients about the risk of serious meningococcal infection, provide patients with the REMS educational materials, assess patient vaccination status for meningococcal vaccines (against serogroups A, C, W, Y, and B) and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of ULTOMIRIS. Antibacterial drug prophylaxis must be prescribed if treatment must be started urgently, and the patient is not up to date with both meningococcal vaccines according to current ACIP recommendations at least two weeks prior to the first dose of ULTOMIRIS. Patients must receive counseling about the need to receive meningococcal vaccines and to take antibiotics as directed, signs and symptoms of meningococcal infection, and be instructed to carry the Patient Safety Card at all times during and for 8 months following ULTOMIRIS treatment.

Further information is available at www.UltSolREMS.com or 1-888-765-4747.

Other Infections
Serious infections with *Neisseria* species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.

ULTOMIRIS blocks terminal complement activation; therefore, 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 recommendations. Patients receiving ULTOMIRIS are at increased risk for infections due to these organisms, even if they develop antibodies following vaccination.

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
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 to 7% of patients, including lower back pain, abdominal pain, muscle spasms, drop or elevation in blood pressure, rigors, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste). These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS and institute appropriate supportive measures.

ADVERSE REACTIONS

Adverse Reactions for PNH
Adverse reactions reported in ≥10% or more of patients with PNH were upper respiratory tract infection and headache. 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% of pediatric patients treated with ULTOMIRIS who were treatment-naïve vs. Eculizumab-experienced were 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%), and 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.

Adverse reactions reported in ≥20% of pediatric patients treated with ULTOMIRIS were diarrhea, constipation, vomiting, pyrexia, upper respiratory tract infection, decreased vitamin D, headache, cough, rash, and hypertension.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ULTOMIRIS during pregnancy. Healthcare providers and patients may call 1-833-793-0563 or go to www.UltomirisPregnancyStudy.com to enroll in or to obtain information about the registry.

To report SUSPECTED ADVERSE REACTIONS, contact Alexion Pharmaceuticals, Inc. at 1-844-259-6783 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information (UltomirisHCP.com/PI) for ULTOMIRIS, or scan QR code for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

ALEXION®
AstraZeneca Rare Disease