ULTOMIRIS, the standard of care* for PNH, is the only FDA-approved medication for pediatric patients[1,2,†]

*Based on US market share data.
†For patients 1 month of age and older.

INDICATION

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

SELECT 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*.

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

ULTOMIRIS is the only FDA-approved medication for pediatric patients with PNH[2]

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

ULTOMIRIS was studied in a clinically diverse population of children and adolescents with PNH[1,2,*]

Study design[2]

- **The phase 3, open-label, multicenter, 26-week, pediatric study (N=13 in the interim analysis) included both:**
  - Eculizumab-experienced patients (n=8)
  - Complement inhibitor–naïve patients (n=5)
- Most patients were between 12 and 17 years of age (n=11); the youngest patient was 9 years old

Endpoints[1]

- **Primary:**
  Change in pharmacokinetic (serum concentrations)/pharmacodynamic (free C5 concentrations) parameters
- **Select secondary:**
  - Percent change from baseline in LDH levels
  - Transfusion avoidance[†]
  - Change in fatigue (Pediatric FACIT-Fatigue)
  - Proportion of patients with stabilized hemoglobin[‡]
  - Proportion of patients with breakthrough hemolysis[§]

The study adhered to the recommended weight-based dosing regimen, consisting of a loading dose followed 2 weeks later by maintenance doses every 4 or 8 weeks (depending on body weight)[2]

Weight-based dosing regimen[2,¶]

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	

[¶]The dosing schedule is allowed to occasionally vary within 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS), but the subsequent doses should be administered according to the original schedule.[2]

» ULTOMIRIS is administered every **4 or 8 weeks**[‖] (depending on body weight), offering patients **freedom and flexibility between treatments**[2,3]

*The study patient population included male and female patients. Reported PNH-associated conditions at baseline included anemia, hematuria or hemoglobinuria, aplastic anemia, and renal failure.[1]
[†]Transfusion avoidance was defined as the proportion of patients who remained transfusion-free and did not require a transfusion through Day 183 (Week 26).[1]
[‡]Stabilized hemoglobin was defined as avoidance of a ≥2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26).[1]
[§]Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia, MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH. For patients who entered the study naïve to complement inhibitor treatment, elevated LDH was defined as ≥2 x ULN after prior LDH reduction to <1.5 x ULN on therapy. For patients who entered the study stabilized on eculizumab treatment, elevated LDH was defined as ≥2 x ULN.[1]
[‖]Starting 2 weeks after the initial loading dose, maintenance doses are administered every 8 weeks for adults and every 4 or 8 weeks for pediatric patients (depending on body weight).[2]
[#]Body weight at time of treatment.
FACIT=Functional Assessment of Chronic Illness Therapy; LDH=lactate dehydrogenase; MAVE=major adverse vascular event; ULN=upper limit of normal.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

Serious Meningococcal Infections (continued)

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.

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

The efficacy and safety of ULTOMIRIS in pediatric patients with PNH appeared similar to that observed in pivotal studies of adult patients with PNH[2]

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

Primary endpoint[2]

0% of patients experienced free C5 levels ≥0.5 µg/mL* (n=0/13)

Immediate, complete, and sustained C5 inhibition in pediatric patients[2]

Efficacy across select secondary endpoints[2]

84.6% of patients were transfusion free (n=11/13)[†,‡]

69.2% of patients had stable hemoglobin levels (n=9/13)[‡,§]

0% of patients experienced breakthrough hemolysis (n=0/13)[‖,¶]

- **Control of intravascular hemolysis[#,**]**
  - **Reduction of LDH levels** in complement inhibitor–naïve patients (-47.9% [(-113.4, 17.5] mean [95% CI] change from baseline; n=5)
  - **Maintenance of LDH levels** in eculizumab-experienced patients (4.7% [-36.7, 46.0] mean [95% CI] change from baseline; n=8)
- **Pediatric FACIT-Fatigue scores**
  - All (n=5/5) complement inhibitor-naïve patients had a clinically relevant decrease in fatigue over the 26-week study[††]
  - A slight improvement was also observed in eculizumab-experienced patients (n=8)
  - Patient-reported fatigue may be an underestimation or overestimation because patients were not blinded to treatment assignment

» To learn more, visit www.ULTOMIRIShcp.com

*0.5 µg/mL is the free C5 level threshold correlated with maximal intravascular hemolysis control and complete terminal complement inhibition in clinical studies.[2]
[†]Transfusion avoidance was achieved in 60% of complement inhibitor–naïve patients (n=3/5; 95% CI, 14.7 to 94.7) and 100% of eculizumab-experienced patients (n=8/8; 95% CI, 63.1 to 100.0).[2]
[‡]95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.[2]
[§]Hemoglobin stabilization was achieved in 60% of complement inhibitor–naïve patients (n=3/5; 95% CI, 14.7 to 94.7) and 75% of eculizumab-experienced patients (n=6/8; 95% CI, 34.9 to 96.8).[2]
[‖]Breakthrough hemolysis was defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia, MAVE [including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH. For patients who entered the study naïve to complement inhibitor treatment, elevated LDH was defined as ≥2 x ULN after prior LDH reduction to <1.5 x ULN on therapy. For patients who entered the study stabilized on eculizumab treatment, elevated LDH was defined as ≥2 x ULN.[1]
[¶]No patients experienced breakthrough hemolysis during the primary evaluation period. One patient experienced breakthrough hemolysis at 1.8 years during the extension period.[2]
[#]LDH is an established biomarker of intravascular hemolysis and PNH disease activity.[4-6]
**95% CIs for the mean obtained from t-distribution.[2]
[††]A clinically relevant decrease in fatigue was defined as a mean improvement of >3 units for Pediatric FACIT-Fatigue scores.[2]
CI=confidence interval; FACIT=Functional Assessment of Chronic Illness Therapy; LDH=lactate dehydrogenase; MAVE=major adverse vascular event; ULN=upper limit of normal.

The most common adverse reactions (>20%) in pediatric patients with PNH were upper respiratory tract infection, anemia, abdominal pain, and headache[2]

Adverse events reported in 10% or more of ULTOMIRIS-treated pediatric patients during the 26-week randomized period[2]

Body system Adverse reaction	Number (%) of patients (N=13)
Blood and lymphatic system disorders	
Anemia[‡‡]	3 (23)
Gastrointestinal disorders	
Abdominal pain	3 (23)
Constipation	2 (15)
General disorders and administration site conditions	
Pyrexia	2 (15)
Infections and infestations	
Upper respiratory tract infection[§§]	7 (54)
Musculoskeletal and connective tissue disorders	
Pain in extremity	2 (15)
Nervous system disorders	
Headache	3 (23)

[‡‡]Grouped term includes: anemia and iron deficiency anemia.
[§§]Grouped term includes: nasopharyngitis, upper respiratory tract infection, oropharyngeal pain, and viral upper respiratory tract infection.

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

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.

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


Actor portrayal

Reduce the risk of IVH, the driver of the life-threatening consequences of PNH[7-9]

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

Immediate and complete C5 control[1,2]

ULTOMIRIS provided immediate, complete, and **sustained C5 inhibition in pediatric patients** with PNH

Similar efficacy and safety across age groups[2]

The **efficacy** and **safety** of ULTOMIRIS in pediatric patients with PNH appeared **similar to that observed in pivotal studies of adult patients with PNH**

Freedom and flexibility between treatments[2,3]

ULTOMIRIS is administered **every 4 or 8 weeks** (depending on body weight)*

*Starting 2 weeks after the initial loading dose, maintenance doses are administered every 4 or 8 weeks (depending on body weight).[2]

SELECT IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

ULTOMIRIS and SOLIRIS REMS (continued)

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

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.

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 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%).

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 Important Safety Information throughout and full Prescribing Information for ULTOMIRIS, including Boxed WARNING regarding serious and life-threatening or fatal meningococcal infections.

References: 1. Data on file. Alexion Pharmaceuticals, Inc. **2.** ULTOMIRIS. Prescribing information. Alexion Pharmaceuticals, Inc. **3.** Peipert JD, et al. *PLoS One*. 2020;15(9):e0237497. **4.** Lee JW, et al. *Int J Hematol*. 2013; 97(6):749-757. **5.** Jang JH, et al. *J Korean Med Sci*. 2016;31(2):214-221. **6.** Schrezenmeier H, et al. *Haematologica*. 2014;99(5):922-929. **7.** Hill A, et al. Paroxysmal nocturnal haemoglobinuria. *Nat Rev Dis Primers*. 2017;3:17028. doi:10.1038/nrdp.2017.28 **8.** Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, et al, eds. *Hematology: Basic Principles and Practice*. 6th ed. Churchill Livingstone; 2013:373-382. **9.** Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124(18):2804-2811.

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