HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ULTOMIRIS™ safely and effectively. See full prescribing information for ULTOMIRIS.

ULTOMIRIS™ (ravulizumab-cwvz) injection, for intravenous use
Initial U.S. Approval: 2018

WARNING: SERIOUS MENINGOCOCCAL INFECTIONS
See full prescribing information for complete boxed warning

Life-threatening meningococcal infections/sepsis have occurred in patients treated with ULTOMIRIS and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).

- **Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).**
- **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 risks of developing a meningococcal infection. (See *Warnings and Precautions* (5.1) for additional guidance on the management of the risk of meningococcal infection.)Vaccination reduces, but does not eliminate, the risk of meningococcal infection.**
- **Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program (5.1).

INDICATIONS AND USAGE
ULTOMIRIS is a complement inhibitor indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1)

DOSAGE AND ADMINISTRATION
Only administer as an intravenous infusion.
Weight-Based Dosage Regimen: (2.1)

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
greater 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

See Full Prescribing Information for important preparation and administration instructions (2.2, 2.3).

DOSAGE FORMS AND STRENGTHS
Injection: 300 mg/30 mL (10 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS
ULTOMIRIS is contraindicated in patients with unresolved *Neisseria Meningitidis* infection (4).

WARNINGS AND PRECAUTIONS
Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).

ADVERSE REACTIONS
The most frequent adverse drug reactions (>10%) were upper respiratory infection and headache (6.1).

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.

See 17 PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS MENINGOCOCCAL INFECTIONS

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING 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 *[see Warnings and Precautions (5.1)]*.

- **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 (5.1)* 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.**

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS REMS, prescribers must enroll in the program *[see Warnings and Precautions (5.1)]*. Enrollment in the ULTOMIRIS REMS program and additional information are available by telephone: 1-844-259-6783 or at www.ultomirisrems.com.

1 INDICATIONS AND USAGE

ULTOMIRIS is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Vaccination and Prophylaxis

Vaccinate patients for meningococcal disease according to current ACIP guidelines to reduce the risk of serious infection *[see Warnings and Precautions (5.1, 5.2)]*.

Provide 2 weeks of antibacterial drug prophylaxis to patients if ULTOMIRIS must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS therapy.

Healthcare professionals who prescribe ULTOMIRIS must enroll in the ULTOMIRIS REMS *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Weight-Based Dosage Regimen

The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. Administer the doses based on the patient's body weight, as shown in Table 1. Starting 2 weeks after the loading dose administration, begin maintenance doses at a once every 8-week interval. 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 dose should be administered according to the original schedule.

For patients switching from eculizumab to ULTOMIRIS, administer the loading dose of ULTOMIRIS 2 weeks after the last eculizumab infusion, and then administer maintenance doses once every 8 weeks, starting 2 weeks after loading dose administration, as shown in Table 1.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

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

2.3 Preparation and Administration

Preparation of ULTOMIRIS

Each vial of ULTOMIRIS is intended for single-dose only.

ULTOMIRIS requires dilution to a final concentration of 5 mg/mL.

Use aseptic technique to prepare ULTOMIRIS as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose *[see Dosage and Administration (2.2)]*.
2. Prior to dilution, visually inspect the solution in the vials; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. Withdraw the calculated volume of ULTOMIRIS from the appropriate number of vials and dilute in an infusion bag using 0.9% Sodium Chloride Injection, USP to a final concentration of 5 mg/mL. Refer to the administration reference tables below. The product should be mixed gently. Do not shake. Protect from light. Do not freeze.
4. Administer the prepared solution immediately following preparation. Refer to the administration reference tables below for minimum infusion duration. Infusion must be administered through a 0.22 micron filter.

5. If the diluted ULTOMIRIS infusion solution is not used immediately, storage under refrigeration at 2°C – 8°C (36°F – 46°F) must not exceed 24 hours taking into account the expected infusion time. Once removed from refrigeration, administer the diluted ULTOMIRIS infusion solution within 6 hours.

Administration of ULTOMIRIS

Only administer as an intravenous infusion.

Dilute ULTOMIRIS to a final concentration of 5 mg/mL.

Administer ULTOMIRIS only through a 0.22 micron filter.

Table 2: Loading Dose Administration Reference Table

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
greater than or equal to 40 to less than 60	2,400	240	240	480	252
greater than or equal to 60 to less than 100	2,700	270	270	540	317
greater than or equal to 100	3,000	300	300	600	333

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

Table 3: Maintenance Dose Administration Reference Table

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Maximum Infusion Rate (mL/hr)
greater than or equal to 40 to less than 60	3,000	300	300	600	257
greater than or equal to 60 to less than 100	3,300	330	330	660	330
greater than or equal to 100	3,600	360	360	720	327

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

Prior to administration, allow the admixture to adjust to room temperature (18°-25°C, 64°-77°F). Do not heat the admixture in a microwave or with any heat source other than ambient air temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

If an adverse reaction occurs during the administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician. Monitor the patient for at least one hour following completion of the infusion for signs or symptoms of an infusion reaction.

3 DOSAGE FORMS AND STRENGTHS

Injection: 300 mg/30 mL (10 mg/mL) as a clear to translucent, slight whitish color solution in a single-dose vial.

4 CONTRAINDICATIONS

ULTOMIRIS is contraindicated in patients with unresolved *Neisseria meningitidis* infection *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Meningococcal Infections

Risk and Prevention

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 for meningococcal disease according to the most current Advisory Committee on Immunization Practices (ACIP) recommendations for patients with complement deficiencies. Revaccinate patients in accordance with ACIP recommendations considering the duration of ULTOMIRIS therapy.

Immunize patients without a history of meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS. If urgent ULTOMIRIS therapy is indicated in an unvaccinated patient, administer meningococcal vaccine(s) as soon as possible and provide patients with 2 weeks of antibacterial drug prophylaxis.

In clinical studies, 59 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.

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical studies, 3 out of 261 PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS; all 3 had been vaccinated. These 3 patients recovered while continuing treatment with ULTOMIRIS.

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 steps to be taken to seek immediate medical care. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider discontinuation of ULTOMIRIS in patients who are undergoing treatment for serious meningococcal infection.

REMS

Due to the risk of meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (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.

Enrollment in the ULTOMIRIS REMS and additional information are available by telephone: 1-888-765-4747 or at www.ultomirisrems.com.

5.2 Other Infections

ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to encapsulated bacteria infections, especially infections caused by *Neisseria meningitidis* but also *Streptococcus pneumoniae, Haemophilus influenzae,* and to a lesser extent, *Neisseria gonorrhoeae.* If ULTOMIRIS therapy is administered to patients with active systemic infections, monitor closely for signs and symptoms of worsening infection.

5.3 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.

5.4 Thromboembolic Event Management

The effect of withdrawal of anticoagulant therapy during ULTOMIRIS treatment has not been established. Therefore, treatment with ULTOMIRIS should not alter anticoagulant management.

5.5 Infusion Reactions

Administration of ULTOMIRIS may result in infusion reactions. In clinical trials, 3 out of 222 patients with PNH treated with ULTOMIRIS experienced infusion reactions (lower back pain, drop in blood pressure and infusion-related pain) during ULTOMIRIS administration. These reactions did not require discontinuation of ULTOMIRIS. Interrupt ULTOMIRIS infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious Meningococcal Infections [see *Warnings and Precautions (5.1)*]
- Other Infections [see *Warnings and Precautions (5.2)*]
- Monitoring PNH Disease Manifestations after ULTOMIRIS Discontinuation [see *Warnings and Precautions (5.3)*]
- Infusion Reactions [see *Warnings and Precautions (5.5)*]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure of 441 adult patients with PNH in Phase 3 studies who received ULTOMIRIS (n = 222) or eculizumab (n = 219) at the recommended dosing regimens with median treatment duration of 6 months for ULTOMIRIS and 6 months for eculizumab. The most frequent adverse drug reactions (>10%) with ULTOMIRIS were upper respiratory tract infection and headache. Table 4 describes adverse reactions that occurred at a rate of 5% or more among patients treated with ULTOMIRIS.

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.

Table 4: Adverse Reactions Reported In 5% or More of ULTOMIRIS Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Patients with PNH

	Number of Patients	
Body System **Adverse Reaction**	**ULTOMIRIS** **(n=222)** n (%)	**Eculizumab** **(n=219)** n (%)

Body System Adverse Reaction	Number of Patients ULTOMIRIS (n=222) n (%)	 Eculizumab (n=219) n (%)
Gastrointestinal disorders		
Diarrhea	19 (9)	12 (5)
Nausea	19 (9)	19 (9)
Abdominal pain	13 (6)	16 (7)
General Disorders and Administration Site Conditions		
Pyrexia	15 (7)	18 (8)
Infections and Infestations		
Upper respiratory tract infection[a]	86 (39)	86 (39)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	14 (6)	11 (5)
Arthralgia	11 (5)	12 (5)
Nervous System Disorders		
Headache	71 (32)	57 (26)
Dizziness	12 (5)	14 (6)

[a] Grouped term includes: Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhoea, Pharyngitis, and Upper respiratory tract inflammation

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibodies) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ravulizumab products may be misleading.

The immunogenicity of ravulizumab-cwvz has been evaluated using an enzyme linked immunosorbent assay (ELISA) for the detection of binding anti-ravulizumab-cwvz antibodies. For patients whose sera tested positive in the screening immunoassay, an in vitro biological assay was performed to detect neutralizing antibodies.

In clinical studies of patients with PNH, treatment-emergent antibodies to ravulizumab-cwvz were detected in 1 of 206 (0.5%) patients. No apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on ULTOMIRIS use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated paroxysmal nocturnal hemoglobinuria (PNH) in pregnancy (see *Clinical Considerations*). Animal studies using a mouse analogue of the ravulizumab-cwvz molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring at doses 0.8-2.2 times the human dose *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or fetal/neonatal risk

PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombotic events, infections, bleeding, miscarriages, and increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

Data

Animal Data

Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 1-2.2 times (loading dose) and 0.8-1.8 times (maintenance dose) the recommended human ULTOMIRIS dose, based on a body weight comparison. When animal exposure to the antibody occurred in the time period from before mating until early gestation, no decrease in fertility or reproductive performance was observed. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, the exposure did not increase fetal loss or neonatal death. When maternal exposure to the antibody occurred in the time period from implantation through weaning, a higher number of male offspring became moribund or died (1/25 controls, 2/25 low dose group, 5/25 high dose group). Surviving offspring had normal development and reproductive function. Human IgG are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in the fetal circulation.

8.2 Lactation

Risk summary

There are no data on the presence of ravulizumab-cwvz in human milk, the effect on the breastfed child, or the effect on milk production. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in a nursing child, breastfeeding should be discontinued during treatment and for 8 months after the final dose.

8.4 Pediatric Use

The safety and efficacy of ULTOMIRIS in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ULTOMIRIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

11 DESCRIPTION

Ravulizumab-cwvz, a complement inhibitor, is a humanized monoclonal antibody (mAb) produced in Chinese hamster ovary (CHO) cells. Ravulizumab-cwvz consists of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148 kDa. The constant regions of ravulizumab-cwvz include the human kappa light chain constant region, and the protein engineered "IgG2/4" heavy chain constant region.

The heavy chain CH1 domain, hinge region, and the first 5 amino acids of the CH2 domain match the human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region (common to both human IgG2 and IgG4 amino acid sequences), while the remainder of the CH2 domain and the CH3 domain match the human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

ULTOMIRIS (ravulizumab-cwvz) injection is a sterile, clear to translucent, slight whitish color, preservative-free solution for intravenous use. Each single-dose vial contains 300 mg ravulizumab-cwvz at a concentration of 10 mg/mL with a pH of 7.0. Each mL also contains polysorbate 80 (0.2 mg) (vegetable origin), sodium chloride (8.77 mg), sodium phosphate dibasic (1.78 mg), sodium phosphate monobasic (0.46 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ravulizumab-cwvz is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b9. ULTOMIRIS inhibits terminal complement-mediated intravascular hemolysis in patients with PNH.

12.2 Pharmacodynamics

Immediate and complete inhibition of serum free C5 (concentration of less than 0.5 mcg/mL) was observed by the end of the first ULTOMIRIS infusion and sustained throughout the entire 26-week treatment period in all patients, both complement-inhibitor naïve and previously treated with eculizumab.

The extent and duration of the pharmacodynamic response in patients with PNH were exposure dependent for ULTOMIRIS. Free C5 levels of <0.5 mcg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition.

Complete terminal complement inhibition following initiation of ULTOMIRIS treatment led to normalization of serum LDH by week 4 in complement-inhibitor naïve patients, and maintained LDH normalization in patients previously treated with eculizumab *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Ravulizumab-cwvz pharmacokinetics increase proportionally over a dose range of 200 to 5400 mg. Ravulizumab-cwvz C_{max} and C_{trough} parameters are presented in Table 5.

Table 5: Mean ± SD (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with PNH who are Complement Inhibitor-Naïve and Patients Previously Treated with Eculizumab

		N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab
C_{max} (mcg/mL)	LD	125	771 ± 166 (21.5)	95	843 ± 204 (24.1)
	MD	124	1379 ± 276 (20.0)	95	1386 ± 268 (19.4)
C_{trough} (mcg/mL)	LD	125	391 ± 137 (35.0)	96	405 ± 121 (29.9)
	MD	124	473 ± 158 (33.4)	95	501 ± 143 (28.6)

LD = Loading Dose; MD = Maintenance Dose

Distribution

The mean (SD) volume of distribution at steady state was 5.34 (0.92) L.

Elimination

The mean (SD) terminal elimination half-life and clearance of ravulizumab-cwvz in patients with PNH are 49.7 (8.9) days and 0.08 (0.022) L/day respectively.

Specific Populations

No clinically significant differences in the pharmacokinetics of ravulizumab-cwvz were observed based on sex, age (18 to 83 years), race, hepatic impairment, or mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2, estimated by MDRD). The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by MDRD) on ravulizumab-cwvz pharmacokinetics is unknown.

Body weight was a significant covariate on the pharmacokinetics of ravulizumab-cwvz.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies of ravulizumab-cwvz have not been conducted.

Genotoxicity studies have not been conducted with ravulizumab-cwvz.

Effects of ravulizumab-cwvz upon fertility have not been studied in animals. Intravenous injections of male and female mice with a murine anti-C5 antibody at up to 0.8-2.2 times the equivalent of the clinical dose of ULTOMIRIS had no adverse effects on mating or fertility.

14 CLINICAL STUDIES

The safety and efficacy of ULTOMIRIS in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies: PNH Study 301 and PNH Study 302. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

In both studies, ULTOMIRIS was dosed intravenously in accordance with the weight-based dosing described in Section 2.1 (4 infusions of ULTOMIRIS over 26 weeks) above. Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of studies.

Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with ULTOMIRIS or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination. Prophylactic treatment with appropriate antibiotics beyond 2 weeks after vaccination was at the discretion of the provider.

14.1 Study in Complement-Inhibitor Naïve Patients with PNH

The Complement-Inhibitor Naïve Study [ALXN1210-PNH-301; NCT02946463] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients naïve to complement inhibitor treatment prior to study entry.

Patients with PNH with flow cytometric confirmation of at least 5% PNH cells were randomized 1:1 to either ULTOMIRIS or eculizumab. The mean total PNH granulocyte clone size was 85%, the mean total PNH monocyte clone size was 88%, and the mean total PNH RBC clone size was 39% . Ninety-eight percent of patients had a documented

PNH-associated condition diagnosed prior to enrollment on the trial: anemia (85%), hemoglobinuria (63%), history of aplastic anemia (32%), history of renal failure (12%), myelodysplastic syndrome (5%), pregnancy (3%), and other (16%). Major baseline characteristics were balanced between treatment groups.

Table 6: Baseline Characteristics in the Complement-Inhibitor Naïve Study

Parameter	Statistics	ULTOMIRIS (N = 125)	Eculizumab (N = 121)
Age (years) at first infusion in study	Mean (SD) Min, max	44.8 (15.2) 18, 83	46.2 (16.2) 18, 86
Sex Male	n (%)	65 (52.0)	69 (57.0)
Race Asian White Black or African American American Indian or Alaska Native Other Not reported	n (%)	 72 (57.6) 43 (34.4) 2 (1.6) 1 (0.8) 4 (3.2) 3 (2.4)	 57 (47.1) 51 (42.1) 4 (3.3) 1 (0.8) 4 (3.3) 4 (3.3)
Pre-treatment LDH levels (U/L)	Median Min, max	1513.5 (378.0, 3759.5)	1445.0 (423.5, 3139.5)
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	6.0 (1, 44)	6.0 (1, 32)
Antithrombotic agents used within 28 days prior to first dose	n (%)	22 (17.6)	22 (18.2)
Patients with a history of MAVE[b]	n (%)	17 (13.6)	25 (20.7)
Patients with a history of thrombosis	n (%)	17 (13.6)	20 (16.5)
Patients with concomitant anticoagulant treatment	n (%)	23 (18.4)	28 (23.1)

[a] "Other" as specified on case report form included thrombocytopenia, chronic kidney disease, and pancytopenia, as well as a number of other conditions.

[b] MAVE = major adverse vascular event

Efficacy was established based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was defined as patients who did not receive a transfusion and not meet the protocol specified guidelines for transfusion from baseline up to Day 183. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH $\geq 2 \times$ ULN, after prior LDH reduction to $< 1.5 \times$ ULN on therapy and the proportion of patients with stabilized hemoglobin.

Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the complement inhibitor naïve treatment population described in the table below.

Table 7: Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect (95% CI)
Transfusion avoidance rate	73.6%	66.1%	Difference in rate	6.8 (-4.66, 18.14)
LDH normalization	53.6%	49.4%	Odds ratio	1.19 (0.80, 1.77)
LDH percent change	-76.84%	-76.02%	Difference in % change from baseline	-0.83 (-5.21, 3.56)
Breakthrough hemolysis	4.0%	10.7%	Difference in rate	-6.7 (-14.21, 0.18)
Hemoglobin stabilization	68.0%	64.5%	Difference in rate	2.9 (-8.80, 14.64)

Note: LDH = lactate dehydrogenase; CI = confidence interval
For the transfusion avoidance endpoint, treatment differences (95% CIs) are based on estimated differences in percent with 95% CI. For the lactate dehydrogenase normalization endpoint, the adjusted prevalence within each treatment is displayed.

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

14.2 Study in Eculizumab-Experienced Patients with PNH

The study in eculizumab-experienced patients [ALXN1210-PNH-302; NCT03056040] was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 195 patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Patients who demonstrated clinically stable disease after being treated with eculizumab for at least the prior 6 months were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. The mean total PNH granulocyte clone size was 83%, the mean total PNH monocyte clone size was 86%, and the mean total PNH RBC clone size was 60%. Ninety five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%). Major baseline characteristics were balanced between the two treatment groups.

Table 8: Baseline Characteristics in Eculizumab-Experienced Patients with PNH

Parameter	Statistics	ULTOMIRIS (N = 97)	Eculizumab (N = 98)
Age (years) at first infusion in study	Mean (SD) Min, max	46.6 (14.41) 18, 79	48.8 (13.97) 23, 77
Race White Asian Black or African American Other Not reported Unknown Multiple	n (%)	 50 (51.5) 23 (23.7) 5 (5.2) 2 (2.1) 13 (13.4) 3 (3.1) 1 (1.0)	 61 (62.2) 19 (19.4) 3 (3.1) 1 (1.0) 13 (13.3) 1 (1.0) 0
Sex Male	n (%)	 50 (51.5)	 48 (49.0)
Pre-treatment LDH levels (U/L)	Median Min, max	224.0 135.0, 383.5	234.0 100.0, 365.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Median Min, max	4.0 (1, 32)	2.5 (2, 15)
Antithrombotic agents used within 28 days prior to first dose	n (%)	20 (20.6)	13 (13.3)
Patients with a history of MAVE[a]	n (%)	28 (28.9)	22 (22.4)
Patients with a history of thrombosis	n (%)	27 (27.8)	21 (21.4)
Patients with concomitant anticoagulant treatment	n (%)	22 (22.7)	16 (16.3)

[a] MAVE = major adverse vascular event

Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183 and supportive efficacy data was transfusion avoidance, proportion of patients with stabilized hemoglobin, and the proportion of patients with breakthrough hemolysis through Day 183.

Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in the patients with PNH previously treated with eculizumab described in the table below.

Table 9: Efficacy Results in the Eculizumab-Experienced Patients with PNH Eculizumab-Experienced Study

	ULTOMIRIS n = 97	Eculizumab n = 98	Statistic for Comparison	Treatment Effect (95% CI)
LDH Percent change	-0.82%	8.4%	Difference in % change from baseline	9.2 (-0.42, 18.8)

Breakthrough hemolysis	0%	5.1%	Difference in rate	5.1 (-8.9, 19.0)
Transfusion avoidance	87.6 %	82.7%	Difference in rate	5.5 (-4.3, 15.7)
Hemoglobin Stabilization	76.3%	75.5%	Difference in rate	1.4 (-10.4, 13.3)

Note: CI = confidence interval

There was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTOMIRIS (ravulizumab-cwvz) injection is a clear to translucent, slight whitish color preservative-free, solution supplied as one 300 mg/30 mL (10 mg/mL) single-dose vial per carton. NDC 25682-022-01.

Store ULTOMIRIS vials refrigerated at 2°C – 8°C (36°F – 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

Refer to Dosage and Administration (2.3) for information on the stability and storage of diluted solutions of ULTOMIRIS.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Meningococcal Infection

Advise patients of the risk of meningococcal infection/sepsis. Inform patients that they are required to receive meningococcal vaccination at least 2 weeks prior to receiving the first dose of ULTOMIRIS, if they have not previously been vaccinated. They are required to be revaccinated according to current medical guidelines for meningococcal vaccines use while on ULTOMIRIS therapy. Inform patients that vaccination may not prevent meningococcal infection. Inform patients about the signs and symptoms of meningococcal infection/sepsis, and strongly advise patients to seek immediate medical attention if these signs or symptoms occur. These signs and symptoms are as follows:

- headache with nausea or vomiting
- headache and a fever
- headache with a stiff neck or stiff back
- fever
- fever and a rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Inform patients that they will be given an ULTOMIRIS Patient Safety Card that they should carry with them at all times. This card describes symptoms which, if experienced, should prompt the patient to immediately seek medical evaluation.

Other Infections

Counsel patients of the increased risk of infections, particularly those due to encapsulated bacteria, especially *Neisseria* species. Advise patients of the need for vaccination against meningococcal infections according to current medical guidelines. Counsel patients about gonorrhea prevention and advise regular testing for patients at risk. Advise patients to report any new signs and symptoms of infection.

Discontinuation

Inform patients with PNH that they may develop hemolysis due to PNH when ULTOMIRIS is discontinued and that they will be monitored by their healthcare professional for at least 16 weeks following ULTOMIRIS discontinuation.

Inform patients who discontinue ULTOMIRIS to keep the ULTOMIRIS Patient Safety Card with them for eight months after the last ULTOMIRIS dose, because the increased risk of meningococcal infection persists for several weeks following discontinuation of ULTOMIRIS.

Infusion reactions

Advise patients that administration of ULTOMIRIS may result in infusion reactions.

Manufactured by:

Alexion Pharmaceuticals, Inc.
121 Seaport Boulevard
Boston, MA 02210 USA

US License Number 1743

This product, or its use, may be covered by one or more US patents, including US Patent No. 9,371,377; 9,079,949 and 9,663,574 in addition to others including patents pending.

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MEDICATION GUIDE

ULTOMIRIS™ (ul-toe-meer'-is)
(ravulizumab-cwvz)
injection, for intravenous use

What is the most important information I should know about ULTOMIRIS?

ULTOMIRIS is a medicine that affects your immune system. ULTOMIRIS can lower the ability of your immune system to fight infections.

- **ULTOMIRIS increases your chance of getting serious and life-threatening meningococcal infections. Meningococcal infections may quickly become life-threatening and cause death if not recognized and treated early.**

1. You must receive meningococcal vaccines at least 2 weeks before your first dose of ULTOMIRIS if you have not already had this vaccine.

2. If your doctor decided that urgent treatment with ULTOMIRIS is needed, you should receive meningococcal vaccination as soon as possible.

3. If you have not been vaccinated and ULTOMIRIS therapy must be initiated immediately, you should also receive 2 weeks of antibiotics with your vaccinations.

4. If you had a meningococcal vaccine in the past, you might need additional vaccination before starting ULTOMIRIS. Your doctor will decide if you need additional meningococcal vaccination.

5. Meningococcal vaccines reduce the risk of meningococcal infection but do not prevent all meningococcal infections. Call your doctor or get emergency medical care right away if you get any of these signs and symptoms of a meningococcal infection:

- headache with nausea or vomiting
- headache with a stiff neck or stiff back
- fever and a rash
- muscle aches with flu-like symptoms
- headache and fever
- fever
- confusion
- eyes sensitive to light

Your doctor will give you a Patient Safety Card about the risk of meningococcal infection. Carry it with you at all times during treatment and for 8 months after your last ULTOMIRIS dose. Your risk of meningococcal infection may continue for several months after your last dose of ULTOMIRIS. It is important to show this card to any doctor or nurse who treats you. This will help them diagnose and treat you quickly.

ULTOMIRIS is only available through a program called the ULTOMIRIS REMS. Before you can receive ULTOMIRIS, your doctor must:

- enroll in the ULTOMIRIS REMS program
- counsel you about the risk of meningococcal infection
- give you information about the symptoms of meningococcal infection
- give you a **Patient Safety Card** about your risk of meningococcal infection, as discussed above
- make sure that you are vaccinated with a meningococcal vaccine

Ultomiris may also increase the risk of other types of serious infections.

- People who take ULTOMIRIS may have an increased risk of getting infections caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.
- Certain people may also have an increased risk of gonorrhea infection. Talk to your healthcare provider to find out if you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing.

Call your healthcare provider right away if you have any new signs or symptoms of infection.

What is ULTOMIRIS?

ULTOMIRIS is a prescription medicine called a monoclonal antibody. ULTOMIRIS is used to treat adults with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
It is not known if ULTOMIRIS is safe and effective in children.

Who should not receive ULTOMIRIS?

Do not start ULTOMIRIS if you have a meningococcal infection.

Before you receive ULTOMIRIS, tell your doctor about all of your medical conditions, including if you:

- have an infection or fever
- are pregnant or plan to become pregnant. It is not known if ULTOMIRIS will harm your unborn baby.

- are breastfeeding or plan to breastfeed. It is not known if ULTOMIRIS passes into your breast milk. You should not breast feed during treatment and for 8 months after your final dose of ULTOMIRIS.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ULTOMIRIS and other medicines can affect each other causing side effects.

Know the medications you take and the vaccines you receive. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I receive ULTOMIRIS?

- ULTOMIRIS is given through a vein by intravenous (I.V.) infusion usually over about 2 hours.
- You will usually receive:
  - a starting dose of ULTOMIRIS as an infusion by your doctor, and then
  - 2 weeks later, you will start to receive an infusion of ULTOMIRIS every 8 weeks.

  If you are changing treatment from SOLIRIS to ULTOMIRIS, you should receive your starting dose of ULTOMIRIS 2 weeks after your last dose of SOLIRIS.
- After each infusion, you should be monitored for at least 1 hour for allergic reactions. See **"What are the possible side effects of ULTOMIRIS?"**
- **If you stop receiving ULTOMIRIS, your doctor will need to monitor you closely for at least 16 weeks after you stop ULTOMIRIS. Stopping ULTOMIRIS may cause breakdown of your red blood cells due to PNH.**

  Symptoms or problems that can happen due to red blood cell breakdown include:
  - drop in the number of your red blood cell count
  - tiredness
  - blood in your urine
  - stomach-area (abdomen) pain
  - blood clots
  - shortness of breath
  - trouble swallowing
  - erectile dysfunction (ED) in males
- If you miss an ULTOMIRIS infusion, call your doctor right away.

What are the possible side effects of ULTOMIRIS?

ULTOMIRIS can cause serious side effects including:

- See **"What is the most important information I should know about ULTOMIRIS?"**
- **Infusion reactions.** Infusion reactions may happen during your ULTOMIRIS infusion. Symptoms of an infusion reaction with ULTOMIRIS may include lower back pain, pain with the infusion, or feeling faint. Tell your doctor or nurse right away if you develop these symptoms, or any other symptoms during your ULTOMIRIS infusion that may mean you are having a serious infusion reaction, including:
  - chest pain
  - trouble breathing or shortness of breath
  - swelling of your face, tongue, or throat
  - feel faint or pass out

  Your doctor will treat your symptoms as needed.

The most common side effects of ULTOMIRIS are upper respiratory infection and headache.

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of ULTOMIRIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of ULTOMIRIS.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about ULTOMIRIS that is written for health professionals.

What are the ingredients in ULTOMIRIS?

Active ingredient: ravulizumab-cwvz

Inactive ingredients: polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, and Water for Injection

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For more information, go to www.ULTOMIRIS.com or Call: 1-888-765-4747
This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 12/2018