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).

RECENT MAJOR CHANGES

Indications and Usage (1)	06/2021
Dosing and Administration (2.4)	10/2020
Dosing and Administration (2.2)	06/2021

INDICATIONS AND USAGE

ULTOMIRIS is a complement inhibitor indicated for:

- the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH) (1).
- the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) (1).

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

DOSAGE AND ADMINISTRATION

See Full Prescribing Information for instructions on dosage, preparation, and administration (2.1, 2.2, 2.3, 2.4, 2.5).

DOSAGE FORMS AND STRENGTHS

Injection:
300 mg/30 mL (10 mg/mL) in a single-dose vial (3).
300 mg/3 mL (100 mg/mL) in a single-dose vial (3).
1,100 mg/11 mL (100 mg/mL) in a single-dose vial (3).

CONTRAINDICATIONS

ULTOMIRIS is contraindicated in:

- Patients with unresolved *Neisseria Meningitidis* infection (4).
- Patients who are not currently vaccinated against *Neisseria meningitidis*, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection (4, 5.1).

WARNINGS AND PRECAUTIONS

- Other Infections: Use caution when administering ULTOMIRIS to patients with any other systemic infection (5.2).
- Infusion-Related Reactions: Monitor patients during infusion, interrupt for reactions, and institute appropriate supportive measures (5.5).

ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence ≥10%) were upper respiratory tract infection and headache (6.1).

Most common adverse reactions in patients with aHUS (incidence ≥20%) were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia (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: 06/2021

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: 1-888-765-4747 or at www.ultomirisrems.com.

1 INDICATIONS AND USAGE

ULTOMIRIS is indicated for:

- the treatment of adult and pediatric patients one month of age and older with paroxysmal nocturnal hemoglobinuria (PNH).
- the treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Limitations of Use:

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

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 - PNH and aHUS

The recommended dosing regimen in adult and pediatric patients, one month of age or older weighing 5 kg or greater, with PNH and aHUS consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The dosing is based on the patient's body weight, as shown in Table 1. Starting 2 weeks after the loading dose administration, begin maintenance doses once every 4 or 8 weeks, based on body weight.

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.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen - PNH and aHUS

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
5 to less than 10	600	300	Every 4 weeks
10 to less than 20	600	600	
20 to less than 30	900	2,100	Every 8 weeks
30 to less than 40	1,200	2,700	
40 to less than 60	2,400	3,000	
60 to less than 100	2,700	3,300	
100 or greater	3,000	3,600	

2.3 Dosing Considerations

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

Administration of PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) may reduce ULTOMIRIS serum levels. There is no experience with administration of supplemental doses of ULTOMIRIS.

2.4 Preparation and Administration

Preparation of ULTOMIRIS

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

Do not mix ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials) and 10 mg/mL (30 mL vial) concentrations together.

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:
   - 50 mg/mL for the 3 mL and 11 mL vial sizes or
   - 5 mg/mL for the 30 mL vial size.

   The product should be mixed gently. Do not shake. Protect from light. Do not freeze.

   Refer to the following reference tables for preparation:

ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials): see Table 2 (loading doses) and Table 3 (maintenance doses)

ULTOMIRIS 10 mg/mL (30 mL vial): see Table 4 (loading doses) and Table 5 (maintenance doses)

4. Administer the prepared solution immediately following preparation. Refer to Table 2 (loading doses) and Table 3 (maintenance doses) for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials) and Table 4 (loading doses) and Table 5 (maintenance doses) for ULTOMIRIS 10 mg/mL (30 mL vial) for minimum infusion duration. Infusion must be administered through a 0.2 or 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 if prepared with ULTOMIRIS 30 mL vials or within 4 hours if prepared with ULTOMIRIS 3 mL or 11 mL vials.

Administration of ULTOMIRIS

Only administer as an intravenous infusion.

Dilute ULTOMIRIS to a final concentration of:

- 50 mg/mL for the 3 mL and 11 mL vial sizes or
- 5 mg/mL for the 30 mL vial size.

Administer ULTOMIRIS only through a 0.2 or 0.22 micron filter.

Table 2: Loading Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10	600	6	6	12	1.4	8
10 to less than 20	600	6	6	12	0.8	16
20 to less than 30	900	9	9	18	0.6	30
30 to less than 40	1,200	12	12	24	0.5	46
40 to less than 60	2,400	24	24	48	0.8	64
60 to less than 100	2,700	27	27	54	0.6	92
100 or greater	3,000	30	30	60	0.4	144

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

Table 3: Maintenance Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10	300	3	3	6	0.8	8
10 to less than 20	600	6	6	12	0.8	16
20 to less than 30	2,100	21	21	42	1.3	33
30 to less than 40	2,700	27	27	54	1.1	49
40 to less than 60	3,000	30	30	60	0.9	65
60 to less than 100	3,300	33	33	66	0.7	99

100 or greater	3,600	36	36	72	0.5	144

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

Table 4: Loading Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10	600	60	60	120	3.8	31
10 to less than 20	600	60	60	120	1.9	63
20 to less than 30	900	90	90	180	1.5	120
30 to less than 40	1,200	120	120	240	1.3	184
40 to less than 60	2,400	240	240	480	1.9	252
60 to less than 100	2,700	270	270	540	1.7	317
100 or greater	3,000	300	300	600	1.8	333

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

Table 5: Maintenance Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
5 to less than 10	300	30	30	60	1.9	31
10 to less than 20	600	60	60	120	1.9	63
20 to less than 30	2,100	210	210	420	3.3	127
30 to less than 40	2,700	270	270	540	2.8	192
40 to less than 60	3,000	300	300	600	2.3	257
60 to less than 100	3,300	330	330	660	2	330
100 or greater	3,600	360	360	720	2.2	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°C - 25°C, 64°F - 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-related reaction.

3 DOSAGE FORMS AND STRENGTHS

ULTOMIRIS 100 mg/mL

Injection: 300 mg/3 mL (100 mg/mL) and 1,100 mg/11 mL (100 mg/mL) as a translucent, clear to yellowish color solution in a single-dose vial.

ULTOMIRIS 10 mg/mL

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

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In PNH clinical studies in adult patients, 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. In the PNH study in pediatric patients, no meningococcal infections occurred among the 13 patients receiving 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.* 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 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

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 reappearance 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;
    - an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment.

If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiation of ULTOMIRIS treatment or appropriate organ-specific supportive measures.

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-Related Reactions

Administration of ULTOMIRIS may result in infusion-related reactions. In clinical trials, 4 out of 309 patients treated with ULTOMIRIS experienced infusion-related reactions (lower back pain, drop in blood pressure, elevation in blood pressure and limb discomfort) 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)]*
- Infusion-Related 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.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Adult population with PNH

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 reactions (≥10%) with ULTOMIRIS were upper respiratory tract infection and headache. Table 6 describes adverse reactions that occurred at a rate of 5% or more among patients treated with ULTOMIRIS in PNH studies.

Serious adverse reactions were reported in 15 (6.8%) patients with PNH 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 6: Adverse Reactions Reported in 5% or More of ULTOMIRIS-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Adult Patients with PNH

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, rhinorrhea, pharyngitis, and upper respiratory tract inflammation

Pediatric population with PNH

In pediatric patients with PNH (aged 9 to 17 years old) included in the pediatric PNH Phase 3 study, the safety profile appeared similar to that observed in adult patients with PNH and in pediatric and adult patients with aHUS. The most common adverse reactions (>20%) were upper respiratory tract infection, anemia, abdominal pain, and headache. Table 7 describes the adverse reactions that occurred at a rate of 10% or more among pediatric patients treated with ULTOMIRIS in Study ALXN1210-PNH-304.

Table 7: Adverse Reactions Reported in 10% or More of ULTOMIRIS-Treated Pediatric Patients with PNH in Study ALXN1210-PNH-304

Body System Adverse Reaction	Treatment Naïve (N=5)	Eculizumab Experienced (N=8)	Total (N=13)
	n (%)	n (%)	n (%)
Blood and lymphatic system disorders			
Anemia[a]	1 (20)	2 (25)	3 (23)
Gastrointestinal disorders			
Abdominal pain	0 (0)	3 (38)	3 (23)
Constipation	0 (0)	2 (25)	2 (15)
General disorders and administration site conditions			
Pyrexia	1 (20)	1 (13)	2 (15)
Infections and infestations			
Upper Respiratory tract infection[b]	1 (20)	6 (75)	7 (54)
Musculoskeletal and connective tissue disorders			
Pain in extremity	0 (0)	2 (25)	2 (15)
Nervous system disorders			
Headache	1 (20)	2 (25)	3 (23)

[a] Grouped term includes: anemia and iron deficiency anemia
[b] Grouped term includes: nasopharyngitis, upper respiratory tract infection, oropharyngeal pain and viral upper respiratory tract infection

Atypical Hemolytic Uremic Syndrome (aHUS)

The data described below reflect exposure of 58 adult and 16 pediatric patients with aHUS in single-arm trials who received ULTOMIRIS at the recommended dose and schedule. The most frequent adverse reactions reported in ≥20% of patients treated with ULTOMIRIS were upper respiratory tract infection, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Tables 8, 9 and 10 describes adverse reactions that occurred at a rate of 10% or more among patients treated with ULTOMIRIS in aHUS studies. 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. Four patients died during the ALXN1210-aHUS-311 study. The cause of death was sepsis in two patients and intracranial hemorrhage in one patient. The fourth patient, who was excluded from the trial after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis.

Table 8: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-311

Body System Adverse Reaction	ALXN1210-aHUS-311 (N=58)	
	All Grades*** (n=53) n (%)	≥ Grade 3 (n=14) n (%)
Blood and lymphatic system disorders		
Anemia	8 (14)	0 (0)
Gastrointestinal disorders		
Diarrhea	18 (31)	2 (3)
Nausea	15 (26)	2 (3)
Vomiting	15 (26)	2 (3)
Constipation	8 (14)	1 (2)
Abdominal pain	7 (12)	1 (2)
General disorders and administration site conditions		
Pyrexia	11 (19)	1 (2)
Edema peripheral	10 (17)	0 (0)
Fatigue	8 (14)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	15 (26)	0 (0)
Urinary tract infection	10 (17)	5 (9)
Gastrointestinal infection**	8 (14)	2 (3)
Metabolism and nutrition disorders		
Hypokalemia	6 (10)	1 (2)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (22)	0 (0)
Back pain	7 (12)	1 (2)
Muscle spasms	6 (10)	0 (0)
Pain in extremity	6 (10)	0 (0)
Nervous system disorders		
Headache	23 (40)	1 (2)
Psychiatric disorders		
Anxiety	8 (14)	1 (2)
Respiratory, thoracic and mediastinal disorders		
Cough	10 (17)	0 (0)
Dyspnea	10 (17)	1 (2)
Skin and subcutaneous tissue disorders		
Alopecia	6 (10)	0 (0)
Dry skin	6 (10)	0 (0)
Vascular disorders		
Hypertension	14 (24)	7 (12)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.
**: Grouped term includes gastroenteritis, gastrointestinal infection, enterocolitis infectious,infectious colitis, and enterocolitis.
***: Graded per CTCAE v5.0.

Clinically relevant adverse reactions in <10% of patients include viral tonsillitis.

Table 9: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Reaction	ALXN1210-aHUS-312 (N=16)	
	All Grades** (n=16) n (%)	≥ Grade 3 (n=6) n (%)
Blood and lymphatic system disorders		
Anemia	2 (13)	1 (6)
Lymphadenopathy	2 (13)	0 (0)
Gastrointestinal disorders		
Diarrhea	6 (38)	0 (0)
Constipation	4 (25)	0 (0)
Vomiting	4 (25)	1 (6)
Abdominal pain	3 (19)	0 (0)
Nausea	2 (13)	0 (0)
General disorders and administration site conditions		
Pyrexia	8 (50)	0 (0)
Infections and infestations		
Upper respiratory tract infection*	7 (44)	1 (6)
Gastroenteritis viral	2 (13)	2 (13)
Pneumonia	2 (13)	1 (6)
Tonsillitis	2 (13)	0 (0)
Injury, poisoning and procedural complications		
Contusion	3 (19)	0 (0)
Investigations		
Vitamin D decreased	3 (19)	0 (0)
Metabolism and nutrition disorders		
Decreased appetite	2 (13)	0 (0)
Iron deficiency	2 (13)	0 (0)
Musculoskeletal and connective tissue disorders		
Myalgia	3 (19)	0 (0)
Pain in extremity	2 (13)	0 (0)
Nervous system disorders		
Headache	5 (31)	0 (0)
Respiratory, thoracic and mediastinal disorders		
Cough	3 (19)	0 (0)
Dyspnea	2 (13)	0 (0)
Skin and subcutaneous tissue disorders		
Rash	3 (19)	0 (0)
Vascular disorders		
Hypertension	4 (25)	1 (6)
Hypotension	2 (13)	0 (0)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.

**: Graded per CTCAE v5.0.

Clinically relevant adverse reactions in <10% of patients include viral infection.

Table 10: Adverse Reactions Reported in ≥10% of ULTOMIRIS-Treated Patients from Birth to 16 Years of Age with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Reaction	ALXN1210-aHUS-312			
	Age 0 to <2 (N=2)	Age 2 to <12 (N=12)	Age 12 to 16 (N=1)	Total (N=15)
	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders				
Lymphadenopathy	0 (0)	2 (17)	0 (0)	2 (13)
Gastrointestinal disorders				
Diarrhea	1 (50)	3 (25)	1 (100)	5 (33)
Constipation	0 (0)	4 (33)	0 (0)	4 (27)
Vomiting	0 (0)	3 (25)	0 (0)	3 (20)
Abdominal pain	0 (0)	2 (17)	0 (0)	2 (13)
General disorders and administration site conditions				
Pyrexia	1 (50)	5 (42)	1 (100)	7 (47)
Infections and infestations				
Upper respiratory tract infection*	1 (50)	6 (50)	0 (0)	7 (47)
Gastroenteritis viral	0 (0)	2 (17)	0 (0)	2 (13)
Tonsillitis	1 (50)	1 (8)	0 (0)	2 (13)
Injury, poisoning and procedural complications				
Contusion	0 (0)	2 (17)	0 (0)	2 (13)
Investigations				
Vitamin D decreased	0 (0)	2 (17)	1 (100)	3 (20)
Metabolism and nutrition disorders				
Decreased appetite	1 (50)	1 (8)	0 (0)	2 (13)
Iron deficiency	0 (0)	2 (17)	0 (0)	2 (13)
Musculoskeletal and connective tissue disorders				
Myalgia	1 (50)	1 (8)	0 (0)	2 (13)
Pain in extremity	0 (0)	2 (17)	0 (0)	2 (13)
Nervous system disorders				
Headache	0 (0)	4 (33)	0 (0)	4 (27)
Respiratory, thoracic and mediastinal disorders				
Cough	0 (0)	3 (25)	0 (0)	3 (20)
Dyspnea	1 (50)	1 (8)	0 (0)	2 (13)
Skin and subcutaneous tissue disorders				
Rash	1 (50)	2 (17)	0 (0)	3 (20)
Vascular disorders				
Hypertension	1 (50)	3 (25)	0 (0)	4 (27)
Hypotension	0 (0)	2 (17)	0 (0)	2 (13)

*: Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain

Clinically relevant adverse reactions in <10% of patients include viral infection.

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-cwvz 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, treatment-emergent antibodies to ravulizumab-cwvz were detected in 1 of 219 (0.5%) patients with PNH and 1 of 71 (1.4%) patients with aHUS. In these 2 patients, no apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed. However, the assay used to measure anti-drug antibodies (ADA) is subject to interference by serum ravulizumab-cwvz, possibly resulting in an underestimation of the incidence of antibody formation. Due to the limitation of the assay conditions, the potential clinical impact of antibodies to ravulizumab-cwvz is not known.

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 PNH and aHUS 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.

In pregnancy, aHUS is associated with adverse maternal outcomes, including preeclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including intrauterine growth restriction (IUGR), fetal death and low birth weight.

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 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 effectiveness of ULTOMIRIS for the treatment of PNH have been established in pediatric patients aged one month and older. Use of ULTOMIRIS for this indication is supported by evidence from adequate and well-controlled trials in adults with additional pharmacokinetic, efficacy and safety data in pediatric patients aged 9 to 17 years *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1)]*. The safety and efficacy for the treatment of pediatric and adult patients with PNH appear similar. Use of ULTOMIRIS in pediatric patients with PNH aged less than 9 years and body weight <30 kg is based on extrapolation of pharmacokinetic /

pharmacodynamic (PK/PD), and efficacy and safety data from aHUS and PNH clinical studies *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

The safety and effectiveness of ULTOMIRIS for the treatment of aHUS have been established in pediatric patients aged one month and older. Use of ULTOMIRIS for this indication is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic, safety, and efficacy data in pediatric patients aged 10 months to <17 years. The safety and efficacy of ULTOMIRIS for the treatment of aHUS appear similar in pediatric and adult patients *[see Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

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 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 100 mg/mL (3 mL and 11 mL vials)

ULTOMIRIS (ravulizumab-cwvz) injection 100 mg/mL is a sterile, translucent, clear to yellowish color, preservative-free solution for intravenous use. Each single-dose vial contains 300 mg or 1,100 mg ravulizumab-cwvz at a concentration of 100 mg/mL with a pH of 7.4. Each mL also contains L-arginine (4.33 mg), polysorbate 80 (0.5 mg) (vegetable origin), sodium phosphate dibasic (4.42 mg), sodium phosphate monobasic (4.57 mg), sucrose (50 mg) and Water for Injection, USP.

ULTOMIRIS 10 mg/mL (30 mL vial)

ULTOMIRIS (ravulizumab-cwvz) injection 10 mg/mL 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 and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

12.2 Pharmacodynamics

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 both adult and pediatric patients with PNH and in the majority (93%) of adult and pediatric patients with aHUS.

The extent and duration of the pharmacodynamic response in patients with PNH and aHUS 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 in patients with PNH.

Complete terminal complement inhibition following initiation of ULTOMIRIS treatment led to normalization of serum LDH by week 4 in complement-inhibitor naïve patients with PNH, and maintained LDH normalization in patients previously treated with eculizumab with PNH *[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 11 and Table 12.

Table 11: Mean (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with PNH who are Complement Inhibitor-Naïve and Patients Previously Treated with Eculizumab

		Pediatric Patients				Adult Patients			
		ALXN1210-PNH-304				ALXN1210-PNH-301		ALXN1210-PNH-302	
		N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab	N	Complement Inhibitor-Naïve	N	Previously Treated with Eculizumab
	LD	4	733 (14.5)	8	885 (19.3)	125	771 (21.5)	95	843 (24.1)

C_{max} (mcg/mL)	MD	4	1490 (26.7)	8	1705 (9.7)	124	1,379 (20.0)	95	1,386 (19.4)
C_{trough} (mcg/mL)	LD	4	368 (14.7)	8	452 (15.1)	125	391 (35.0)	96	405 (29.9)
	MD	4	495 (21.3)	8	566 (12.2)	124	473 (33.4)	95	501 (28.6)

LD = Loading Dose; MD = Maintenance Dose

Table 12: Mean (%CV) Pharmacokinetic Parameters of ULTOMIRIS in Patients with aHUS

		Pediatric Patients (ALXN1210-aHUS-312)				Adult Patients (ALXN1210-aHUS-311)	
		N	< 20 kg MD Q4W	N	≥ 20 to < 40 kg MD Q8W	N	≥ 40 kg MD Q8W
C_{max} (mcg/mL)	LD	8	656 (38.1)	4	600 (17.3)	52	754 (35.2)
	MD	7	1,467 (37.8)	6	1,863 (15.3)	46	1,458 (17.6)
C_{trough} (mcg/mL)	LD	9	241 (52.1)	5	186 (16.5)	55	313 (33.9)
	MD	7	683 (46.1)	6	549 (34.1)	46	507 (42.5)

LD = Loading Dose; MD = Maintenance Dose; Q4W = Every 4 Weeks; Q8W = Every 8 Weeks

Distribution

The mean (%CV) volume of distribution at steady state was 5.30 (17.9) L and 5.22 (35.4) L in patients with PNH and aHUS, respectively.

Elimination

The mean (%CV) terminal elimination half-life of ravulizumab-cwvz was 49.6 (18.3) days and 51.8 (31.3) days in patients with PNH and aHUS, respectively. The mean (%CV) clearance of ravulizumab-cwvz was 0.08 (28.1) L/day and 0.08 (53.3) L/day in patients with PNH and aHUS, respectively.

Specific Populations

No clinically significant differences in the pharmacokinetics of ravulizumab-cwvz were observed based on sex, age (10 months to 83 years), race, hepatic impairment, or any degree of renal impairment, including patients with proteinuria or receiving dialysis.

Body weight was a clinically 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

14.1 Paroxysmal Nocturnal Hemoglobinuria (PNH)

The safety and efficacy of ULTOMIRIS in adult 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. The safety and efficacy of ULTOMIRIS in pediatric patients with PNH was assessed in PNH Study 304, open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients with PNH.

In both adult studies, ULTOMIRIS was dosed intravenously in accordance with the weight-based dosing described in Section 2.2 (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 the 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.

Study in Complement-Inhibitor Naïve Adult 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 complications (3%), and other (16%). Major baseline characteristics were balanced between treatment groups. Table 13 provides the baseline characteristics for the patients enrolled in the complement-inhibitor naïve study.

Table 13: 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 [a]	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] 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 did 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 Table 14 below.

Table 14: 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.

Study in Eculizumab-Experienced Adult 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 in 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 15 provides the baseline characteristics for the patients enrolled in the eclulizumab-experienced study.

Table 15: Baseline Characteristics in Eculizumab-Experienced Adult 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 Table 16 below.

Table 16: Efficacy Results in the Eculizumab-Experienced Adult 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.

Study in Eculizumab-Experienced and Complement-Inhibitor Naïve Pediatric Patients with PNH

The pediatric study, ALXN1210-PNH-304, was a multi-center, open-label Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment-naïve pediatric patients with PNH. A total of 13 pediatric patients with PNH completed ULTOMIRIS treatment during the Primary Evaluation Period (26 weeks). Five of the 13 patients had never been treated with complement inhibitors and 8 patients were treated with eculizumab. Eleven of the thirteen patients were between 12 and 17 years of age at first infusion, with 2 patients under 12 years old (11 and 9 years old). Table 17 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-PNH-304.

Table 17: Baseline Characteristics for Pediatric Patients with PNH

Variable	Complement Inhibitor Treatment-naïve Patients (N = 5)	Eculizumab-Experienced Patients (N = 8)	All Patients (N = 13)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Age at first infusion (years)			
Mean (SD)	14.4 (2.2)	14.4 (3.1)	14.4 (2.7)
Median (min, max)	15.0 (11, 17)	15.0 (9, 17)	15.0 (9, 17)
Age at first infusion (years) category, n (%)			
< 12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥ 12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline weight (kg)			
Mean (SD)	56.3 (11.6)	56.3 (12.2)	56.3 (11.5)
Median (min, max)	55.6 (39.5, 72.0)	55.5 (36.7, 69.0)	55.6 (36.7, 72.0)
Baseline weight (kg) category, n (%)			
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)	4 (30.8)
Units of pRBC/whole blood transfused within 12 months prior to first dose			-
Median (min, max)	7.0 (3, 11)	2.0 (2, 2)	
Pre-treatment LDH levels (U/L)			-
Median (min, max)	588.5 (444, 2269.7)	251.5 (140.5, 487)	

Note: Percentages were based on the total number of patients in each cohort, or overall.
kg = kilogram; max = maximum; min = minimum; SD = standard deviation.

Based on body weight, patients received a loading dose of ULTOMIRIS on Day 1, followed by maintenance treatment on Day 15 and once every 8 weeks (q8w) thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. For patients who entered the study on eculizumab therapy, Day 1 of study treatment was planned to occur 2 weeks from the patient's last dose of SOLIRIS.

The weight-based dose regimen of ravulizumab-cwvz provided inhibition of terminal complement in all patients throughout the entire 26-week treatment period regardless of prior experience with eculizumab. Following initiation of ravulizumab-cwvz treatment, steady-state therapeutic serum concentrations of ravulizumab-cwvz were achieved after the first dose and maintained throughout the primary evaluation period in both cohorts. Three of 5 complement inhibitor treatment-naïve patients and 6 out of 8 eculizumab-experienced patients achieved hemoglobin stabilization by Week 26, respectively. Transfusion avoidance was reached for 11 out of 13 of patients during the 26-week Primary Evaluation Period. One patient experienced breakthrough hemolysis during the extension period. Table 18 presents secondary efficacy outcomes for the primary evaluation period.

Table 18: Efficacy Outcomes from the 26-Week Primary Evaluation Period of Pediatric Patient Study in PNH (ALXN1210-PNH-304)

End Point	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)
LDH- Percent Change from Baseline (%)[a]	-47.9 (-113.4, 17.5)	4.7 (-36.7, 46.0)
Transfusion Avoidance (%)[b]	60.0 (14.7, 94.7)	100.0 (63.1, 100.0)
Change in FACIT-Fatigue[a]	3.4 (-4.2, 11.0)	1.3 (-3.1, 5.7)
Hemoglobin Stabilization (%)[b]	60.0 (14.7, 94.7)	75.0 (34.9, 96.8)
Breakthrough Hemolysis (%)	0	0[c]

[a] 95% CIs for the mean obtained from t-distribution were presented.
[b] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
[c] No patients experienced breakthrough hemolysis during the primary evaluation period. One patient experienced breakthrough hemolysis at 1.8 years during the extension period; however, at the time of the BTH event the patient had adequate C5 inhibition (free C5 < 0.5 µg/mL).
LDH = lactate dehydrogenase

A clinically relevant improvement from baseline in fatigue as assessed by Pediatric FACIT-Fatigue (i.e., mean improvement of > 3 units for Pediatric FACIT Fatigue scores) was sustained throughout the primary evaluation period in the 5-complement inhibitor treatment naïve patients. A slight improvement was also observed in eculizumab-experienced patients. However, patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.

The efficacy of ULTOMIRIS in pediatric patients with PNH is similar to that observed in adult patients with PNH enrolled in pivotal studies.

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

The efficacy of ULTOMIRIS in patients with aHUS was assessed in 2 open-label, single-arm studies. Study ALXN1210-aHUS-311 enrolled adult patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis.

Study ALXN1210-aHUS-312 enrolled pediatric patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥97.5% percentile at screening or required dialysis. In both studies, enrollment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Patients with confirmed diagnosis of STEC-HUS after enrollment were excluded from the efficacy evaluation.

Study in Adult Patients with aHUS

The adult study [ALXN1210-aHUS-311; NCT02949128] was conducted in patients who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week Initial Evaluation Period and patients were allowed to enter an extension period for up to 4.5 years.

A total of 56 patients with aHUS were evaluated for efficacy. Ninety-three percent of patients had extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 71.4% (n = 40) of patients had Stage 5 chronic kidney disease (CKD). Fourteen percent had a medical history of kidney transplant and 51.8% were on dialysis at study entry. Eight patients entered the study with evidence of TMA for > 3 days after childbirth (ie, postpartum).

Table 19 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 19: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-311

Parameter	Statistics	ULTOMIRIS (N=56)
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Female	 n (%)	 37 (66.1)
Race [a] White Asian Unknown Other	n (%)	 29 (51.8) 15 (26.8) 8 (14.3) 4 (7.1)
Platelets (10^9/L) blood [normal range 130 to 400 × 10^9/L]	n Median (min,max)	56 95.25 (18, 473)
Hemoglobin (g/L) blood [normal range 115 to 160 g/L (female), 130 to 175 g/L (male)]	n Median (min,max)	56 85.00 (60.5, 140)
LDH (U/L) serum [normal range 120 to 246 U/L]	n Median (min,max)	56 508.00 (229.5, 3249)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	n (%) Mean (SD) Median (min,max)	55 15.86 (14.815) 10.00 (4, 80)

Note: Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.
eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The efficacy evaluation was based on Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period as shown in Table 20.

Table 20: Efficacy Results in aHUS during the 26-Week Initial Evaluation Period (ALXN1210-aHUS-311)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	56	30	0.54 (0.40, 0.67)
Components of Complete TMA Response			
Platelet count normalization	56	47	0.84 (0.72, 0.92)
LDH normalization	56	43	0.77 (0.64, 0.87)
≥25% improvement in serum creatinine from baseline	56	33	0.59 (0.45, 0.72)
Hematologic normalization	56	41	0.73 (0.60, 0.84)

[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

One additional patient had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period. Complete TMA Response was achieved at a median time of 86 days (range: 7 to 169 days). The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months). All responses were maintained through all available follow-up.

Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR).

An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks).

Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. In patients with Complete TMA Response, renal function continued to improve after the Complete TMA Response was achieved .

Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up and 6 of 27 (22%) patients were off dialysis at baseline were on dialysis at last available follow-up.

Study in Pediatric Patients with aHUS

The Pediatric Study [ALXN1210-aHUS-312; NCT03131219] is a 26-week ongoing, multicenter, single-arm study conducted in 16 pediatric patients.

A total of 14 eculizumab-naïve patients with documented diagnosis of aHUS were enrolled and included in this interim analysis. The median age at the time of first infusion was 5.2 years (range 0.9, 17.3 years). The overall mean weight at Baseline was 19.8 kg; half of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (71%) had pretreatment extra-renal signs (cardiovascular, pulmonary, central

nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 35.7% (n = 5) of patients had a CKD Stage 5. Seven percent had history of prior kidney transplant and 35.7% were on dialysis at study entry.

Table 21 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 21: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-312

Parameter	Statistics	ULTOMIRIS (N = 14)
Age at time of first infusion (years) category	n (%)	
Birth to < 2 years		2 (14.3)
2 to < 6 years		7 (50.0)
6 to < 12 years		4 (28.6)
12 to < 18 years		1 (7.1)
Sex	n (%)	
Female		9 (64.3)
Race[a]	n (%)	
White		7 (50.0)
Asian		4 (28.6)
Black or African American		2 (14.3)
American Indian or Alaskan Native		1 (7.1)
Unknown		1 (7.1)
Platelets (10^9/L) blood [normal range 229 to 533 × 10^9/L]	Median (min, max)	64.00 (14, 125)
Hemoglobin (g/L) blood [normal range 107 to 131 g/L]	Median (min, max)	74.25 (32, 106)
LDH (U/L) serum [normal range 165 to 395 U/L]	Median (min, max)	2077.00 (772, 4985)
eGFR (mL/min/1.73 m^2) [normal range ≥ 60 mL/min/1.73 m^2]	Mean (SD) Median (min, max)	28.4 (23.11) 22.0 (10, 84)

Note: Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.
eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

Efficacy evaluation was based upon Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week Initial Evaluation Period as shown in Table 22.

Table 22: Efficacy Results in aHUS during the 26-Week Initial Evaluation Period (ALXN1210-aHUS-312)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	14	10	0.71 (0.42, 0.92)
Components of Complete TMA Response			
Platelet count normalization	14	13	0.93 (0.66, 0.99)
LDH normalization	14	12	0.86 (0.57, 0.98)
≥25% improvement in serum creatinine from baseline	14	11	0.79 (0.49, 0.95)
Hematologic normalization	14	12	0.86 (0.57, 0.98)

Note: 1 patient withdrew from study after receiving 2 doses of ravulizumab-cwvz.
[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range:15 to 88 days). The median duration of Complete TMA Response was 5.08 months (range: 3.08 to 5.54 months). All responses were maintained through all available follow-up.

Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR.

An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50 × 10^9/L at baseline to 296.67 × 10^9/L at Day 8 and remained above 296 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) by 26 weeks.

Four of the 5 patients who required dialysis at study entry were able to discontinue dialysis after the first month in study and for the duration of ULTOMIRIS treatment. No patient started dialysis during the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTOMIRIS (ravulizumab-cwvz) injection 100 mg/mL is translucent, clear to yellowish color solution supplied in single-dose vials as:

- 300 mg/3 mL (100 mg/mL) carton containing one vial: NDC 25682-025-01
- 1,100 mg/11 mL (100 mg/mL) carton containing one vial: NDC 25682-028-01

ULTOMIRIS (ravulizumab-cwvz) injection 10 mg/mL is clear to translucent, slight whitish color solution supplied in single-dose vials as:

- 300 mg/30 mL (10 mg/mL) carton containing one vial: 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)* 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 or aHUS that they may develop hemolysis or TMA, respectively, when ULTOMIRIS is discontinued and that they will be monitored by their healthcare professional for at least 16 weeks for PNH or at least 12 months for aHUS 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-Related Reactions

Advise patients that administration of ULTOMIRIS may result in infusion-related 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. 9,079,949; 9,107,861; 9,206,251; 9,371,377; 9,663,574; 9,803,007; and 10,227,400 in addition to others including patents pending.

ULTOMIRIS is a trademark of Alexion Pharmaceuticals, Inc.

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, and if needed, get revaccinated with the meningococcal vaccine. Ask your doctor if you are not sure if you need to be revaccinated.

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*.
- If your child is treated with ULTOMIRIS, make sure that your child receives vaccinations against *Streptococcus pneumoniae* and *Haemophilis influenzae* type b (Hib).
- Certain people may also have an increased risk of gonorrhea infection. Talk to your doctor to find out if you are at risk for gonorrhea infection, about gonorrhea prevention, and regular testing.

Call your doctor 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 and children 1 month of age and older with a disease called Paroxysmal Nocturnal Hemoglobinuria (PNH).
- adults and children 1 month of age and older with a disease called atypical hemolytic uremic syndrome (aHUS).

ULTOMIRIS is not used in treating people with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

It is not known if ULTOMIRIS is safe and effective in children younger than 1 month of age.

Who should not receive ULTOMIRIS?

Do not receive ULTOMIRIS if you:

- have a meningococcal infection
- have not been vaccinated against meningococcal infection unless your doctor decides that urgent treatment with ULTOMIRIS is needed. See **"What is the most important information I should know about ULTOMIRIS."**

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 breastfeed 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 medicines 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

If you are an adult with PNH or aHUS, 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.

Children 1 month of age and older with PNH or aHUS will usually receive:

- a starting dose of ULTOMIRIS as an infusion by your doctor, and then
- your doctor will decide how often your child will receive ULTOMIRIS, either every 4 weeks or every 8 weeks, depending on their weight, starting 2 weeks after the starting dose.

Your doctor will decide how long you need to take ULTOMIRIS for your PNH or your aHUS.

- **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 infusion reactions. See **"What are the possible side effects of ULTOMIRIS?"**
- **If you have PNH and 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 your red blood cell count
  - tiredness
  - blood in your urine
  - stomach-area (abdomen) pain
  - shortness of breath
  - blood clots
  - trouble swallowing
  - erectile dysfunction (ED) in males
- **If you have aHUS, your doctor will need to monitor you closely for at least 12 months after stopping treatment for signs of worsening aHUS or problems related to a type of abnormal clotting and breakdown of your red blood cells called thrombotic microangiopathy (TMA).**
  Symptoms or problems that can happen with TMA may include:
  - confusion or loss of consciousness
  - seizures
  - chest pain (angina)
  - difficulty breathing
  - blood clots or stroke

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-related reactions.** Infusion-related reactions may happen during your ULTOMIRIS infusion. Symptoms of an infusion-related reaction with ULTOMIRIS may include lower back pain, feeling faint, or discomfort in your arms or legs. 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 in people treated for PNH are:

- upper respiratory tract infection
- headache

The most common side effects of ULTOMIRIS in people treated for aHUS are:

- upper respiratory tract infection
- diarrhea
- nausea
- vomiting
- headache
- high blood pressure
- fever

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:

ULTOMIRIS 100 mg/mL: L-arginine, polysorbate 80 (vegetable origin), sodium phosphate dibasic, sodium phosphate monobasic, sucrose and Water for Injection

ULTOMIRIS 10 mg/mL: polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic and Water for Injection

Manufactured by Alexion Pharmaceuticals, Inc., 121 Seaport Boulevard, Boston, MA 02210 USA. U.S. License Number 1743
For more information, go to www.ULTOMIRIS.com or call: 1-888-765-4747
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