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 or subcutaneous 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 called the ULTOMIRIS REMS (5.2).

RECENT MAJOR CHANGES

Indications and Usage (1.3)	04/2022
Dosing and Administration (2.3, 2.4, 2.5)	04/2022
Dosage and Administration (2.1, 2.3, 2.4, 2.6)	07/2022
Warnings and Precautions (5.1, 5.3, 5.6)	04/2022
Warnings and Precautions (5.2, 5.7)	07/2022

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) (1.1).
- the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) (1.2).
  Limitations of Use:
  ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
- the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive (1.3).

DOSAGE AND ADMINISTRATION

- See Full Prescribing Information for instructions on dosage, preparation, and administration (2.1, 2.2, 2.3, 2.4, 2.5, 2.6).
- Dilute ULTOMIRIS before use (2.6).
- Only administer as an intravenous infusion through a 0.2 or 0.22 micron filter (2.6).

DOSAGE FORMS AND STRENGTHS

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

Subcutaneous
Injection: 245 mg/3.5 mL (70 mg/mL) solution in a single-dose prefilled cartridge for use only with supplied single-use on-body injector (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 (5.3).
- Infusion-Related Reactions: Monitor during infusion, interrupt for reactions, and institute appropriate supportive measures (5.6).
- Allergies to Acrylic Adhesives: The on-body injector of ULTOMIRIS uses acrylic adhesive. For patients with a known allergy to acrylic adhesive, use of this product may result in an allergic reaction. (5.7)

ADVERSE REACTIONS

Most common adverse reactions in patients with PNH (incidence ≥ 10%) were upper respiratory tract infection and headache. Injection site reactions and diarrhea occurred in patients (incidence ≥ 10%) receiving ULTOMIRIS subcutaneously (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).

Most common adverse reactions in adult patients with gMG (incidence ≥ 10%) were diarrhea and upper respiratory tract infection (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.

DRUG INTERACTIONS

- Plasma Exchange, Plasmapheresis, or Intravenous Immunoglobulins: concomitant use requires supplemental dose of ULTOMIRIS (7.1).
- Neonatal Fc Receptor Blockers: Closely monitor for reduced effectiveness of ULTOMIRIS (7.2).

USE IN SPECIFIC POPULATIONS

Pediatric Use: Subcutaneous dosing of ULTOMIRIS is not approved for use in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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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.**

Because of the risk of serious meningococcal infections, ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called ULTOMIRIS REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria

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

1.2 Atypical Hemolytic Uremic Syndrome

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

Limitations of Use:

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

1.3 Generalized Myasthenia Gravis

ULTOMIRIS is indicated for the treatment of adult patients with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive.

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2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

ULTOMIRIS may be administered as an intravenous infusion (ULTOMIRIS vial for intravenous administration) in adult or pediatric patients one month of age and older or as a subcutaneous injection for maintenance (ULTOMIRIS on-body delivery system for subcutaneous administration) in adult patients.

Vials are intended for intravenous use only, and on-body delivery systems (prefilled cartridge and on-body injector) are intended for subcutaneous maintenance use only.

2.2 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, 5.3)]*.

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)]*.

2.3 Intravenous Administration in Adult and Pediatric Patients with PNH, aHUS, or gMG

The recommended intravenous ULTOMIRIS loading and maintenance dosing in adult and pediatric patients, one month of age or older weighing 5 kg or greater, with PNH or aHUS, or in adult patients with gMG weighing 40 kg or greater, is based on the patient's body weight, as shown in Table 1, with maintenance doses administered every 4 or 8 weeks, starting 2 weeks after loading dose.

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

Following a missed intravenous ULTOMIRIS dose, the patient should contact their health care provider immediately.

Table 1: ULTOMIRIS Vial for Intravenous (IV) Administration Weight-Based Dosing Regimen – PNH, aHUS, or gMG*

Indications	Body Weight Range (kg)	Loading Dose (mg)**	Maintenance Dose (mg) and Dosing Interval	
PNH and aHUS	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	

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Indications	Body Weight Range (kg)	Loading Dose (mg)**	Maintenance Dose (mg) and Dosing Interval	
PNH, aHUS, and gMG	40 to less than 60	2,400	3,000	Every 8 weeks
	60 to less than 100	2,700	3,300	
	100 or greater	3,000	3,600	

*See Tables 5, 6, 8, and 9 for selection of the proper total volume and maximum infusion rate *[see Dosage and Administration (2.6)]*
**See Table 2 for intravenous ULTOMIRIS treatment initiation instruction and timing of loading dose and maintenance dose

Refer to Table 2 for treatment initiation instructions in patients who are complement inhibitor treatment-naïve, or switching treatment from subcutaneous (SUBQ) administration of ULTOMIRIS or eculizumab.

Table 2: ULTOMIRIS Vial for Intravenous (IV) Administration Treatment Initiation Instructions – PNH, aHUS, or gMG

Population	Weight-based ULTOMIRIS IV Loading Dose	Time of First ULTOMIRIS IV Weight-based Maintenance Dose
Not currently on ULTOMIRIS or eculizumab treatment	At treatment start	2 weeks after ULTOMIRIS IV loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after ULTOMIRIS IV loading dose
Currently treated with ULTOMIRIS on-body delivery system for subcutaneous administration (SUBQ)*	Not applicable	1 week after last ULTOMIRIS SUBQ maintenance dose

*Adult patients with PNH and aHUS only

2.4 Subcutaneous Administration in Adult Patients with PNH or aHUS

Subcutaneous (SUBQ) dosing of ULTOMIRIS is not approved for use in pediatric patients.

The recommended subcutaneous ULTOMIRIS maintenance dose is 490 mg once weekly in adult patients greater than or equal to 40 kg body weight with PNH or aHUS. The 490 mg dose of ULTOMIRIS is delivered using 2 on-body delivery systems. Each on-body delivery system consists of 1 on-body injector and 1 prefilled cartridge containing 245 mg of ravulizumab.

The subcutaneous dosing schedule is allowed to occasionally vary by ± 1 day of the scheduled dose day, but the subsequent dose should be administered according to the original schedule.

Following a missed or partial subcutaneous ULTOMIRIS dose, the patient should contact their health care provider immediately.

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Refer to Table 3 for treatment initiation instructions in patients who are complement inhibitor treatment-naïve, or switching treatment from intravenous administration of ULTOMIRIS or eculizumab.

Table 3: ULTOMIRIS On-Body Delivery System for Subcutaneous (SUBQ) Administration Treatment Initiation Instructions – Adults with PNH or aHUS

Population	Weight-based ULTOMIRIS IV Loading Dose*	Time of First ULTOMIRIS 490 mg SUBQ Maintenance Dose
Not currently on ULTOMIRIS or eculizumab treatment	At treatment start	2 weeks after ULTOMIRIS IV loading dose
Currently treated with eculizumab	At time of next scheduled eculizumab dose	2 weeks after ULTOMIRIS IV loading dose
Currently treated with ULTOMIRIS intravenous (IV) administration	Not applicable	8 weeks after last ULTOMIRIS IV maintenance dose

*See Table 1 for weight-based ULTOMIRIS IV loading dose in patients with body weight ≥ 40 kg

2.5 Dosing Considerations

Supplemental Dose of ULTOMIRIS

Plasma exchange (PE), plasmapheresis (PP), and intravenous immunoglobulin (IVIg) have been shown to reduce ULTOMIRIS serum levels. A supplemental dose of ULTOMIRIS is required in the setting of PE, PP, or IVIg (Table 4).

Table 4: Supplemental Dose of ULTOMIRIS after PE, PP, or IVIg*

Body Weight Range (kg)	Most Recent ULTOMIRIS Dose (mg)	Supplemental Dose (mg) following each PE or PP Intervention	Supplemental Dose (mg) following Completion of an IVIg Cycle
40 to less than 60	2,400	1,200	600
	3,000	1,500	
60 to less than 100	2,700	1,500	600
	3,300	1,800	
100 or greater	3,000	1,500	600
	3,600	1,800	
Timing of ULTOMIRIS Supplemental Dose		Within 4 hours following each PE or PP intervention	Within 4 hours following completion of an IVIg cycle

Abbreviations: IVIg = intravenous immunoglobulin; PE = plasma exchange; PP = plasmapheresis
*See Table 7 and Table 10 for selection of the proper total volume and maximum infusion rate *[see Dosage and Administration (2.6)]*

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2.6 Preparation and Administration

Preparation of ULTOMIRIS Vials for Intravenous Administration

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

ULTOMIRIS vials are for intravenous administration by a healthcare provider and are intended for intravenous administration only.

Dilute before use.

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 IV preparation and minimum infusion duration:

- ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials): see Table 5 (loading doses), Table 6 (maintenance doses), and Table 7 (supplemental doses)
- ULTOMIRIS 10 mg/mL (30 mL vial): see Table 8 (loading doses), Table 9 (maintenance doses), and Table 10 (supplemental doses)

4. Administer the prepared solution immediately following preparation.
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.

Intravenous Administration of ULTOMIRIS (Healthcare Providers)

Only administer as an intravenous infusion through a 0.2 or 0.22 micron filter.

Dilute ULTOMIRIS to a final concentration of:

- 50 mg/mL for the 3 mL and 11 mL vial sizes or

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- 5 mg/mL for the 30 mL vial size.

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.

Table 5: IV 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[c]	600	6	6	12	1.4	9
10 to less than 20[c]	600	6	6	12	0.8	15
20 to less than 30[c]	900	9	9	18	0.6	30
30 to less than 40[c]	1,200	12	12	24	0.5	48
40 to less than 60	2,400	24	24	48	0.8	60
60 to less than 100	2,700	27	27	54	0.6	90
100 or greater	3,000	30	30	60	0.4	150

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

Table 6: IV 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[c]	300	3	3	6	0.8	8
10 to less than 20[c]	600	6	6	12	0.8	15
20 to less than 30[c]	2,100	21	21	42	1.3	33
30 to less than 40[c]	2,700	27	27	54	1.1	50
40 to less than 60	3,000	30	30	60	0.9	67
60 to less than 100	3,300	33	33	66	0.7	95
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.
[c] For PNH and aHUS indications only.

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Table 7: IV Supplemental Dose Reference Table for ULTOMIRIS 100 mg/mL (3 mL and 11 mL vials)

Body Weight Range (kg)[a]	Supplemental Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
40 to less than 60	600	6	6	12	0.25	48
	1,200	12	12	24	0.42	57
	1,500	15	15	30	0.5	60
60 to less than 100	600	6	6	12	0.20	60
	1,500	15	15	30	0.36	83
	1,800	18	18	36	0.42	86
100 or greater	600	6	6	12	0.17	71
	1,500	15	15	30	0.25	120
	1,800	18	18	36	0.28	129

Note: Refer to Table 4 for selection of ravulizumab supplemental dose
[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

Table 8: IV 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[c]	600	60	60	120	3.8	32
10 to less than 20[c]	600	60	60	120	1.9	64
20 to less than 30[c]	900	90	90	180	1.5	120
30 to less than 40[c]	1,200	120	120	240	1.3	185
40 to less than 60	2,400	240	240	480	1.9	253
60 to less than 100	2,700	270	270	540	1.7	318
100 or greater	3,000	300	300	600	1.8	334

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

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Table 9: IV 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[c]	300	30	30	60	1.9	32
10 to less than 20[c]	600	60	60	120	1.9	64
20 to less than 30[c]	2,100	210	210	420	3.3	128
30 to less than 40[c]	2,700	270	270	540	2.8	193
40 to less than 60	3,000	300	300	600	2.3	261
60 to less than 100	3,300	330	330	660	2	330
100 or greater	3,600	360	360	720	2.2	328

[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.
[c] For PNH and aHUS indications only.

Table 10: IV Supplemental Dose Reference Table for ULTOMIRIS 10 mg/mL (30 mL vial)

Body Weight Range (kg)[a]	Supplemental Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Time (hr)	Maximum Infusion Rate (mL/hr)
40 to less than 60	600	60	60	120	0.5	240
	1,200	120	120	240	1.0	240
	1,500	150	150	300	1.2	250
60 to less than 100	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	327
100 or greater	600	60	60	120	0.4	300
	1,500	150	150	300	1.0	300
	1,800	180	180	360	1.1	327

Note: Refer to Table 4 for selection of ravulizumab supplemental dose
[a] Body weight at time of treatment.
[b] Dilute ULTOMIRIS only using 0.9% Sodium Chloride Injection, USP.

If an adverse reaction occurs during the intravenous administration of ULTOMIRIS, the infusion may be slowed or stopped at the discretion of the physician. Monitor the patient for at least 1 hour following completion of the infusion for signs or symptoms of an infusion-related reaction.

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Preparation of ULTOMIRIS On-Body Delivery System for Subcutaneous Administration

ULTOMIRIS on-body delivery system is intended for administration by patients/caregivers. Patients/caregivers may administer after training from a healthcare provider. Refer to the Instructions for Use for detailed instructions on how to use and administer subcutaneous ULTOMIRIS.

1. Remove 2 cartons of ULTOMIRIS on-body delivery system for subcutaneous administration from the refrigerator. Two on-body injectors and 2 prefilled cartridges are required for a full dose (490 mg).
2. Inspect the packaging. The on-body injectors or cartridges should not be used if they have been dropped or appear to be broken or damaged.
3. Wait at least 45 minutes for the on-body injectors and prefilled cartridges in the cartons to naturally reach room temperature prior to administration. Do not return to the refrigerator. Discard after 3 days if unused.
4. Before administration, visually inspect the solution. The solution should not be injected if it contains flakes or particles, or is cloudy or discolored.

Subcutaneous Administration of ULTOMIRIS On-Body Delivery System

ULTOMIRIS on-body delivery system is for subcutaneous administration into the abdomen, thigh, or upper arm region. A patient may self-administer, or the patient caregiver may administer ULTOMIRIS on-body delivery system after the healthcare provider determines it is appropriate. Injection sites should be rotated, and injections should not be given into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks. The 2 on-body delivery systems can be administered concurrently or sequentially. Each injection is delivered over approximately 10 minutes.

1. Load the first clean cartridge into the first on-body injector and secure in place before closing the cartridge door on the injector. Do not insert the cartridge more than 5 minutes before the injection to avoid drying out the solution.
2. Peel away the adhesive backing of the first on-body injector and apply onto the clean, dry, chosen injection site (thigh, abdomen, or upper arm).
3. Start the injection by firmly pressing and releasing the blue start button.
4. Do not remove until the injection is complete (signaled by the solid green status light, 3 beeping sounds, and the white plunger filling the medicine window).
5. Repeat steps 1-4 for the second on-body injector.

If an allergic reaction occurs during the subcutaneous administration of ULTOMIRIS, treatment should be stopped, the on-body injector(s) should be removed, and the patient should seek medical attention prior to further administration.

The patient should monitor for signs or symptoms of infusion-related reaction for at least 1 hour following completion of the injection.

Any unused medicinal product and waste material should be disposed of in accordance with local requirements.

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3 DOSAGE FORMS AND STRENGTHS

Intravenous:

- Injection: 300 mg/3 mL (100 mg/mL) as a translucent, clear to yellowish color solution in a single-dose vial
- Injection: 1,100 mg/11 mL (100 mg/mL) as a translucent, clear to yellowish color solution in a single-dose vial
- Injection: 300 mg/30 mL (10 mg/mL) as a clear to translucent, slight whitish color solution in a single-dose vial

Subcutaneous:

- Injection: 245 mg/3.5 mL (70 mg/mL) as a translucent, clear to yellowish color solution in a single-dose prefilled cartridge for use only with supplied single-use on-body injector

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

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. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving meningococcal vaccine(s) must receive appropriate prophylactic antibiotics until 2 weeks after vaccination.

In clinical studies, 59 adult patients with PNH and 2 adult patients with gMG were treated with ULTOMIRIS less than 2 weeks after meningococcal vaccination. All of

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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 with ULTOMIRIS, < 1% of patients developed serious meningococcal infections/sepsis while receiving treatment with ULTOMIRIS. All were adult patients with PNH who had been vaccinated. These patients recovered while continuing treatment with ULTOMIRIS.

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.

ULTOMIRIS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) *[see Warnings and Precautions (5.2)]*.

5.2 ULTOMIRIS REMS

ULTOMIRIS is available only through a restricted program under a REMS called ULTOMIRIS REMS, due to the risk of meningococcal infections *[see Warnings and Precautions (5.2)]*.

Notable requirements of the ULTOMIRIS REMS include the following:

- Prescribers must enroll in the program
- Prescribers must counsel patients about the risk of meningococcal infection/sepsis
- Prescribers must provide the patients with the REMS educational materials
- Prescribers must ensure patients are vaccinated with meningococcal vaccines or receive 2 weeks of antibacterial drug prophylaxis if treatment must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS
- Patients must receive counseling from the prescriber, take antibiotics as directed by the prescriber after vaccination (if they have to start ULTOMIRIS right away), receive meningococcal vaccines as directed by the prescriber, and carry the Patient Safety Card with them at all times during and for 8 months following treatment with ULTOMIRIS.

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

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5.3 Other Infections

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

5.4 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 lactate dehydrogenase (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;

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- 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.

5.5 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.

5.6 Infusion-Related Reactions

Intravenous or subcutaneous administration of ULTOMIRIS may result in systemic infusion-related reactions, including anaphylaxis *[see Adverse Reactions (6.3)]* and hypersensitivity reactions. In clinical trials, infusion-related reactions occurred in approximately 1% of patients treated with ULTOMIRIS. These events included lower back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), dysgeusia (bad taste), and drowsiness. These reactions did not require discontinuation of ULTOMIRIS. If signs of cardiovascular instability or respiratory compromise occur, interrupt ULTOMIRIS infusion and institute appropriate supportive measures.

5.7 Allergies to Acrylic Adhesives

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

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 (5.3)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.6)]*
- Allergies to Acrylic Adhesives *[see Warnings and Precautions (5.7)]*

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.

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Paroxysmal Nocturnal Hemoglobinuria (PNH)

Adult Population with PNH Treated with Intravenous ULTOMIRIS

The data described below reflect exposure of 441 adult patients with PNH in Phase 3 studies who received intravenously administered 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 11 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 11: Adverse Reactions Reported in 5% or More of Intravenous ULTOMIRIS-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Adult Patients with PNH

Body System **Adverse Reaction**	**Number of Patients**	
	ULTOMIRIS (IV) **(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

Clinically relevant adverse reactions in 1% of patients include infusion-related reactions.

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Pediatric Population with PNH Treated with Intravenous ULTOMIRIS

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 12 describes the adverse reactions that occurred at a rate of 10% or more among pediatric patients treated with ULTOMIRIS administered intravenously in Study ALXN1210-PNH-304.

Table 12: Adverse Reactions Reported in 10% or More of Intravenous 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

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Subcutaneous Administration of ULTOMIRIS

In the Phase 3 study ALXN1210-PNH-303 with subcutaneous administration of ULTOMIRIS via the on-body injector for adult patients with PNH, during the 10-week randomization period the most common adverse reactions (≥ 10%) with ULTOMIRIS subcutaneous administration were local injection site reactions, diarrhea, and headache. Table 13 describes adverse reactions that occurred at a rate of 10% or more among adult patients treated with ULTOMIRIS in Study ALXN1210-PNH-303 during the 10-week randomized period.

Table 13: Adverse Reactions Reported in 10% or More of ULTOMIRIS On-Body Delivery System for Subcutaneous Administration (SUBQ)-Treated and Intravenous ULTOMIRIS-Treated Adult Patients with PNH in Study ALXN1210-PNH-303

	Number of Patients	
Body System **Adverse Reaction**	**ULTOMIRIS (SUBQ)** **(N = 84)** **n (%)**	**ULTOMIRIS (IV)** **(N = 45)** **n (%)**
Gastrointestinal disorders		
Diarrhea	11 (13)	2 (4)
General disorders and administration site conditions		
Injection site reaction[a]	23 (27)	0 (0)
Infections and infestations		
Upper respiratory tract infection[b]	7 (8)	6 (13)
Nervous system disorders		
Headache	11 (13)	4 (9)

[a] Grouped term includes: application site rash, device allergy, infusion site pain, infusion site reaction, injection site bruising, injection site erythema, injection site hematoma, injection site induration, injection site inflammation, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria, medical device site bruise, medical device site erythema, medical device site hematoma, medical device site induration, medical device site pruritus, medical device site rash, and medical device site reaction

[b] Grouped term includes: nasopharyngitis, oropharyngeal pain, pharyngitis, and 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 administered intravenously 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. Table 14, Table 15 and Table 16 describe 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 2 patients and intracranial hemorrhage in

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1 patient. The fourth patient, who was excluded from the trial after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis.

Table 14: Adverse Reactions Reported in ≥ 10% of Intravenous ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-311

Body System Adverse Reaction	ALXN1210-aHUS-311 (N=58)	
	All Grades[c] (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[a]	15 (26)	0 (0)
Urinary tract infection	10 (17)	5 (9)
Gastrointestinal infection[b]	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)

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

Clinically relevant adverse reactions include viral tonsilitis (in < 10% of patients) and infusion-related reactions (in 3% of patients).

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Table 15: Adverse Reactions Reported in ≥ 10% of Intravenous ULTOMIRIS-Treated Patients with aHUS in Study ALXN1210-aHUS-312

Body System Adverse Reaction	ALXN1210-aHUS-312 (N=16)	
	All Grades[b] (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[a]	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)

[a] Grouped term includes nasopharyngitis, pharyngitis, upper respiratory tract infection, rhinitis, viral upper respiratory tract infection, rhinovirus infection, viral pharyngitis, rhinorrhea, and oropharyngeal pain.
[b] Graded per CTCAE v5.0.

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

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Table 16: Adverse Reactions Reported in ≥ 10% of Intravenous 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[a]	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)

[a] 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.

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Generalized Myasthenia Gravis (gMG)

Adult Population with gMG Treated with Intravenous ULTOMIRIS

The safety of ULTOMIRIS has been evaluated in 175 adult patients with gMG, including 169 patients who received at least one dose of intravenously administered ULTOMIRIS, 142 patients who were exposed for at least 6 months, and 95 who were exposed for at least 12 months *[see Clinical Studies (14.3)]*. In a randomized, double-blind, placebo-controlled trial (ALXN1210-MG-306), the most frequent adverse reactions (≥ 10%) with ULTOMIRIS were diarrhea and upper respiratory tract infection. Table 17 describes adverse reactions that occurred at a rate of 5% or more and at greater frequency than placebo. Serious adverse reactions were reported in 20 (23%) patients with gMG receiving ULTOMIRIS and in 14 (16%) patients receiving placebo. The most frequent serious adverse reactions were infections reported in at least 8 (9%) patients treated with ULTOMIRIS and in 4 (4%) patients treated with placebo *[see Warnings and Precautions (5.3)]*. Of these infections, one fatal case of COVID-19 pneumonia was identified in a patient treated with ULTOMIRIS and one case of infection led to discontinuation of ULTOMIRIS.

Table 17: Adverse Reactions Reported in ≥ 5% and at Greater Frequency than Placebo in Intravenous ULTOMIRIS-Treated Adult Patients with gMG in Study ALXN1210-MG-306

Body System **Adverse Reaction**	**Number of Patients**	
	ULTOMIRIS (IV) **(N=86)** n (%)	**Placebo** **(N=89)** n (%)
Gastrointestinal Disorders		
Diarrhea	13 (15)	11 (12)
Abdominal pain	5 (6)	0
Infections and Infestations		
Upper respiratory tract infection	12 (14)	7 (8)
Urinary tract infection	5 (6)	4 (4)
Musculoskeletal and Connective Tissue Disorders		
Back Pain	7 (8)	5 (6)
Nervous System Disorders		
Dizziness	8 (9)	3 (3)

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.

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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 with intravenous administration of ULTOMIRIS, 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 patient populations, no apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed. No treatment-emergent antibodies to ravulizumab-cwvz were detected in patients with gMG treated with ULTOMIRIS.

In patients receiving subcutaneous administration of ULTOMIRIS (N = 128), no treatment-emergent anti-drug antibodies were 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.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ULTOMIRIS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ULTOMIRIS exposure.

Serious Adverse Reaction: Anaphylaxis *[see Warnings and Precautions (5.6)]*

7 DRUG INTERACTIONS

7.1 Plasma Exchange, Plasmapheresis, and Intravenous Immunoglobulins

Concomitant use of ULTOMIRIS with plasma exchange (PE), plasmapheresis (PP), or intravenous immunoglobulin (IVIg) treatment can reduce serum ravulizumab concentrations and requires a supplemental dose of ULTOMIRIS *[see Dosage and Administration (2.5)]*.

7.2 Neonatal Fc Receptor Blockers

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

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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-mouse complement component 5 [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 populations 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, 2 cases of retinal dysplasia and 1 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.

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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 administered intravenously 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 administered intravenously 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 administered intravenously 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 administered intravenously for the treatment of aHUS appear similar in pediatric and adult patients *[see Adverse Reactions (6.1), and Clinical Studies (14.2)]*.

The safety and effectiveness of ULTOMIRIS for the treatment of gMG in pediatric patients have not been established.

Subcutaneous administration of ULTOMIRIS has not been evaluated and is not approved for use in pediatric patients.

8.5 Geriatric Use

Clinical studies of ULTOMIRIS did not include sufficient numbers of subjects aged 65 and over (58 patients with PNH, 9 with aHUS, and 54 with gMG) to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between elderly and younger patients.

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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.

Intravenous:

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.

Subcutaneous:

ULTOMIRIS 70 mg/mL (3.5 mL prefilled cartridge and on-body injector)

ULTOMIRIS (ravulizumab-cwvz) injection 70 mg/mL is a sterile, translucent, clear to yellowish color, preservative-free solution for subcutaneous use. Each on-body delivery system (single-dose prefilled cartridge only for use with single-use on-body injector) delivers a 3.5 mL solution containing 245 mg of ravulizumab-cwvz, L-arginine (15.2 mg), polysorbate 80 (1.75 mg) (vegetable origin), sodium phosphate dibasic (15.4 mg), sodium phosphate monobasic (16.1 mg), sucrose (175 mg), and Water for Injection, USP with a pH of 7.4.

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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 membrane attack complex [MAC or C5b-9]) thus preventing MAC formation. ULTOMIRIS inhibits terminal complement-mediated intravascular hemolysis in patients with PNH and complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS.

The precise mechanism by which ravulizumab-cwvz exerts its therapeutic effect in gMG patients is unknown, but is presumed to involve reduction of terminal complement complex C5b-9 deposition at the neuromuscular junction.

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 intravenous infusion and sustained throughout the entire 26-week treatment period in both adult and pediatric patients with PNH, in the majority (93%) of adult and pediatric patients with aHUS, and all adult patients with gMG.

Complete inhibition of serum free C5 (concentration of less than 0.5 mcg/mL) was observed by the end of the first ULTOMIRIS subcutaneous administration and was sustained throughout the entire treatment period.

The extent and duration of the pharmacodynamic response in patients with PNH, aHUS, and gMG 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 intravenous 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)]*.

The PD results following ULTOMIRIS subcutaneous treatment are consistent with results in adult patients with PNH and aHUS treated with intravenous ULTOMIRIS.

12.3 Pharmacokinetics

Following ULTOMIRIS intravenous (IV) treatment, 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 18, Table 19, and Table 20.

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Table 18: Mean (%CV) Pharmacokinetic Parameters Following Intravenous ULTOMIRIS Treatment 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
C_{max} (mcg/mL)	LD	4	733 (14.5)	8	885 (19.3)	125	771 (21.5)	95	843 (24.1)
	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)

Abbreviations: LD = Loading Dose; MD = Maintenance Dose

Table 19: Mean (%CV) Pharmacokinetic Parameters Following Intravenous ULTOMIRIS Treatment 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)

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

Table 20: Mean (%CV) Pharmacokinetic Parameters Following Intravenous ULTOMIRIS Treatment in Adult Patients with gMG

		N	Adult Patients (ALXN1210-MG-306)
C_{max} (mcg/mL)	LD	86	874 (21.1)
	MD	76	1548 (23.2)
C_{trough} (mcg/mL)	LD	85	418 (27.6)
	MD	70	587 (29.6)

Abbreviations: LD = Loading Dose; MD=Maintenance Dose

Following ULTOMIRIS subcutaneous (SUBQ) treatment, the mean (%CV) ravulizumab-cwvz trough concentration at steady state is 737.7 (28.3%) mcg/mL.

The estimated bioavailability of ULTOMIRIS subcutaneous treatment is approximately 79%.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state in patients with PNH, aHUS, and gMG are shown in Table 21.

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Elimination

The mean (standard deviation [SD]) terminal elimination half-life and clearance of ravulizumab-cwvz are shown in Table 21.

Table 21: Distribution, Biotransformation, and Elimination Parameters Following Intravenous ULTOMIRIS or ULTOMIRIS On-Body Delivery System for Subcutaneous Administration (SUBQ) Treatment

	Adult and Pediatric Patients with PNH (IV)	**Adult and Pediatric Patients with aHUS (IV)**	**Adult Patients with gMG (IV)**	**Adult Patients with PNH (SUBQ)**
Distribution				
Volume of distribution at steady state (liters) Mean (SD)	5.30 (0.95)	5.22 (1.85)	5.74 (1.16)	5.30 (0.95)*
Biotransformation and Elimination				
Terminal elimination half-life (days) Mean (SD)	49.6 (9.08)	51.8 (16.2)	56.6 (8.36)	52.4 (9.72)
Clearance (liters/day) Mean (SD)	0.08 (0.02)	0.08 (0.04)	0.08 (0.02)	0.07 (0.02)*

*Apparent volume of distribution and clearance, respectively, at steady state

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.

Drug Interactions

No drug-drug interaction studies have been performed.

Intravenous immunoglobulin (IVIg) and FcRn blocker treatment may interfere with the endosomal neonatal FcRn recycling mechanism of monoclonal antibodies such as ravulizumab and thereby decrease serum ravulizumab concentrations *[see Drug Interactions (7.1, 7.2)]*.

Concomitant PE, PP, or IVIg treatment requires a supplemental dose of ULTOMIRIS *[see Dosage and Administration (2.5)]*.

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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 administered intravenously in adult patients with PNH was assessed in 2 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 administered intravenously in pediatric patients with PNH was assessed in PNH Study 304, an open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor treatment naïve pediatric patients with PNH.

In Study 301 and Study 302, adults with PNH were dosed with ULTOMIRIS administered 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.

The safety and efficacy of ULTOMIRIS administered subcutaneously in adult patients with PNH was assessed in a controlled Phase 3 trial: PNH Study 303. Study 303 was a PK non-inferiority study in adult patients with PNH who were clinically stable and previously treated with eculizumab for at least 3 months prior to study entry. This study was also designed to assess the performance of the ULTOMIRIS on-body delivery system.

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.

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Study in Complement-Inhibitor Naïve Adult Patients with PNH – Intravenous Administration

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 intravenously administered 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 22 provides the baseline characteristics for the patients enrolled in the complement-inhibitor naïve study.

Table 22: Baseline Characteristics in the Complement-Inhibitor Naïve Study

Parameter	Statistics	ULTOMIRIS (IV) (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	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)

Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; MAVE = major adverse vascular event; pRBC = packed red blood cell; SD = standard deviation

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

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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 ≥ 2 × ULN, after prior LDH reduction to < 1.5 × 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 23 below.

Table 23: Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (IV) (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)

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.
Abbreviations: LDH = lactate dehydrogenase; 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 Adult Patients with PNH – Intravenous Administration

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 administered intravenously. 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%),

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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 2 treatment groups. Table 24 provides the baseline characteristics for the patients enrolled in the eculizumab-experienced study.

Table 24: Baseline Characteristics in Eculizumab-Experienced Adult Patients with PNH

Parameter	Statistics	ULTOMIRIS (IV) (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	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)

Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; MAVE = major adverse vascular event; pRBC = packed red blood cell; SD = standard deviation

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 25 below.

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Table 25: Efficacy Results in the Eculizumab-Experienced Adult Patients with PNH Eculizumab-Experienced Study

	ULTOMIRIS (IV) 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)

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase

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 – Intravenous Administration

The pediatric study, ALXN1210-PNH-304 (NCT03406507), 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 intravenously administered 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 26 presents the baseline characteristics of the pediatric patients enrolled in Study ALXN1210-PNH-304.

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Table 26: 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.
Abbreviations: LDH = lactate dehydrogenase; kg = kilogram; max = maximum; min = minimum; pRBC = packed red blood cells; 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 eculizumab.

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 27 presents secondary efficacy outcomes for the primary evaluation period.

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Table 27: Efficacy Outcomes from the 26-Week Primary Evaluation Period of Pediatric Patient Study in PNH (ALXN1210-PNH-304)

Endpoint	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 breakthrough hemolysis event the patient had adequate C5 inhibition (free C5 < 0.5 mcg/mL).
Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; 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 administered intravenously in pediatric patients with PNH is similar to that observed in adult patients with PNH enrolled in pivotal studies.

Subcutaneous Administration in Adult Patients with PNH

Subcutaneous administration of ULTOMIRIS was assessed in a multi-center, randomized, open-label, Phase 3 study (ALXN1210-PNH-303 [NCT03748823]) conducted in adult patients with PNH who were clinically stable after having been treated with eculizumab for at least 3 months prior to study entry. The study enrolled 136 patients, of which 129 patients were included in the efficacy and safety analyses. The main outcome measure of Study ALXN1210-PNH-303 was the non-inferiority of C_{trough} of ULTOMIRIS when administered subcutaneously via an on-body injector compared to ULTOMIRIS administered intravenously. The study was designed to bridge efficacy and safety data from ULTOMIRIS administered intravenously (IV) to ULTOMIRIS administered subcutaneously (SUBQ).

Patients who completed the 10-week Randomized Treatment Period are followed for up to 172 weeks in the long-term Extension Period. During the Randomized Treatment Period, patients were stratified by weight group (≥ 40 kg to < 60 kg and ≥ 60 kg to < 100 kg) and randomized 2:1 to receive ULTOMIRIS subcutaneously or ULTOMIRIS intravenously. On Day 1, all patients received a weight-based ULTOMIRIS intravenous loading dose. Starting on Day 15, patients randomized to the ULTOMIRIS subcutaneous

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group received once weekly subcutaneous maintenance doses (490 mg), while patients randomized to the ULTOMIRIS intravenous group received the approved weight-based intravenous maintenance dose. Following the Randomized Treatment Period (on Day 71), patients who were randomized to the ULTOMIRIS intravenous group switched to receive 490 mg of ULTOMIRIS subcutaneously weekly through the end of the Extension Period.

The mean total PNH RBC clone size was 48.35%, with a mean total PNH granulocyte clone size of 77.22% and a mean total PNH monocyte clone size of 80.18%. Ninety-two percent of the patients had documented PNH-associated conditions that were diagnosed prior to informed consent. Overall, the disease history and the baseline characteristics were well balanced between the 2 treatment groups. Table 28 presents the baseline characteristics of patients with PNH enrolled in Study ALXN1210-PNH-303.

Table 28: Baseline Characteristics (Study ALXN1210-PNH-303)

Variable	**ULTOMIRIS (SUBQ) (N = 84)**	**ULTOMIRIS (IV) (N = 45)**	**Total (N = 129)**
Sex, n (%)			
Male	40 (47.6)	20 (44.4)	60 (46.5)
Female	44 (52.4)	25 (55.6)	69 (53.5)
Race, n (%)			
White	63 (75.0)	29 (64.4)	92 (71.3)
Not reported	13 (15.5)	6 (13.3)	19 (14.7)
Black or African American	3 (3.6)	4 (8.9)	7 (5.4)
Asian	0	2 (4.4)	2 (1.6)
Unknown or other	5 (6.0)	3 (6.7)	8 (6.2)
American Indian or Alaska Native	0	1 (2.2)	1 (0.8)
Age (years) at informed consent			
Mean (SD)	45.3 (14.47)	46.4 (13.22)	45.7 (14.00)
Median	42.5	44.0	44.0
Min, Max	18, 79	24, 77	18, 79
Age (years) at informed consent category, n (%)			
18 to 65 years	75 (89.3)	41 (91.1)	116 (89.9)
> 65 years	9 (10.7)	4 (8.9)	13 (10.1)
Baseline weight (kg)			
Mean (SD)	72.52 (12.61)	73.68 (12.66)	72.92 (12.59)
Median	72.15	73.00	72.30
Min, Max	43.5, 98.0	52.0, 98.4	43.5, 98.4
Baseline weight (kg) category, n (%)			
≥ 40 kg to < 60 kg	13 (15.5)	8 (17.8)	21 (16.3)
≥ 60 kg to < 100 kg	71 (84.5)	37 (82.2)	108 (83.7)

Note: Percentages are based on the total number of patients. Patients can be counted in more than one category for race.
Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; SD = standard deviation

In Study ALXN1210-PNH-303, treatment with ULTOMIRIS on-body delivery system for subcutaneous administration achieved PK non-inferiority with a margin 0.80,

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compared with intravenously administered ULTOMIRIS treatment for the serum ravulizumab-cwvz C_{trough} at Day 71, with a geometric least squares mean ratio of 1.257 (90% CI: 1.160, 1.361). Serum free C5 concentrations were maintained below the target threshold (< 0.5 mcg/mL) in all patients throughout the one year of subcutaneous treatment.

In patients with PNH randomized to subcutaneous or intravenous ULTOMIRIS, change in LDH, breakthrough hemolysis, transfusion avoidance, hemoglobin stabilization, and FACIT-Fatigue score were evaluated. No noticeable difference between the routes of administration was observed in these endpoints at Day 71.

14.2 Atypical Hemolytic Uremic Syndrome (aHUS)

The efficacy of ULTOMIRIS administered intravenously 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 $\leq 150 \times 10^9$/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 $\leq 150 \times 10^9$/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level $\geq$ 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.

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Study in Adult Patients with aHUS – Intravenous Administration

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 (i.e., postpartum).

Table 29 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set.

Table 29: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-311

Parameter	Statistics	ULTOMIRIS (IV) (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.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum; SD = standard deviation

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.

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

Table 30: 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.
Abbreviations: 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 intravenous treatment, 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 intravenous 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.

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Study in Pediatric Patients with aHUS – Intravenous Administration

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

Table 31: Demographics and Baseline Characteristics in Study ALXN1210-aHUS-312

Parameter	**Statistics**	**ULTOMIRIS (IV) (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.
Abbreviations: 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.

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Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week Initial Evaluation Period as shown in Table 32.

Table 32: 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: One 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.
Abbreviations: 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 intravenous treatment, 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.

14.3 Generalized Myasthenia Gravis (gMG)

The efficacy of ULTOMIRIS for the treatment of gMG was demonstrated in a randomized, double-blind, placebo-controlled, multicenter study (ALXN1210-MG-306; NCT03920293). Patients were randomized 1:1 to either receive ULTOMIRIS (n=86) or placebo (n=89) for 26 weeks. ULTOMIRIS was administered intravenously according to the weight-based recommended dosage *[see Dosage and Administration (2.3)]*.

Patients with gMG with a positive serologic test for anti-AChR antibodies, Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV, and Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score ≥ 6 were enrolled. Baseline and disease characteristics were similar between treatment groups (including age at first dose [mean of 58 years for ULTOMIRIS versus 53 years for placebo], gender [51% female for ULTOMIRIS versus 51% female for placebo], race as White, Asian, and Black or African American [78%, 17%, and 2% for ULTOMIRIS versus 69%, 18%, and

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5% for placebo, respectively], and duration of MG since diagnosis [mean of 10 years, ranging from 0.5 to 39.5 years, for ULTOMIRIS versus mean of 10.0 years, ranging from 0.5 to 36.1 years, for placebo].

Over 80% of patients were receiving acetylcholinesterase inhibitors, 70% were receiving corticosteroids, and 68% were receiving non-steroidal immunosuppressants (ISTs) at study entry. Patients on concomitant medications to treat gMG were permitted to continue on therapy throughout the course of the study.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 26. The MG-ADL is a categorical scale that assesses the impact on daily function of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. The total score ranges from 0 to 24, with the higher scores indicating more impairment.

The secondary endpoints, also assessed from baseline to Week 26, included the change in the Quantitative MG total score (QMG). The QMG is a 13-item categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total score ranges from 0 to 39, where higher scores indicate more severe impairment.

Other secondary endpoints included the proportion of patients with improvements of at least 5 and 3 points in the QMG and MG-ADL total scores, respectively.

Treatment with ULTOMIRIS demonstrated a statistically significant change in the MG-ADL and QMG total scores from baseline at Week 26 as compared to placebo (Table 33).

Table 33: Efficacy Results in Patients with gMG

Efficacy Endpoints: Change from Baseline at Week 26	**Placebo (n = 89) LS Mean**	**ULTOMIRIS (IV) (n = 86) LS Mean**	**Treatment Effect (95% CI)**	**p-value***
Primary Endpoint				
MG-ADL	-1.4	-3.1	-1.6 (-2.6, -0.7)	< 0.001
Secondary Endpoint				
QMG	-0.8	-2.8	-2.0 (-3.2, -0.8)	< 0.001

*p-value calculated using mixed effect model for repeated measures
Abbreviations: CI = confidence interval, LS = least squares; MG-ADL = Myasthenia Gravis Activities of Daily Living profile; QMG = Quantitative Myasthenia Gravis score for disease severity

The proportion of QMG responders with at least a 5-point improvement at week 26 was greater for ULTOMIRIS (30.0%) compared to placebo (11.3%) p = 0.005. The proportion of MG-ADL responders with at least a 3-point improvement at week 26 was also greater for ULTOMIRIS (56.7%) compared to placebo (34.1%). The proportion of clinical responders at higher response thresholds (≥ 4-, 5-, 6-, 7-, or 8-point improvement on MG-ADL, and ≥ 6-, 7-, 8-, 9-, or 10-point improvement on QMG) was consistently greater for ULTOMIRIS compared to placebo.

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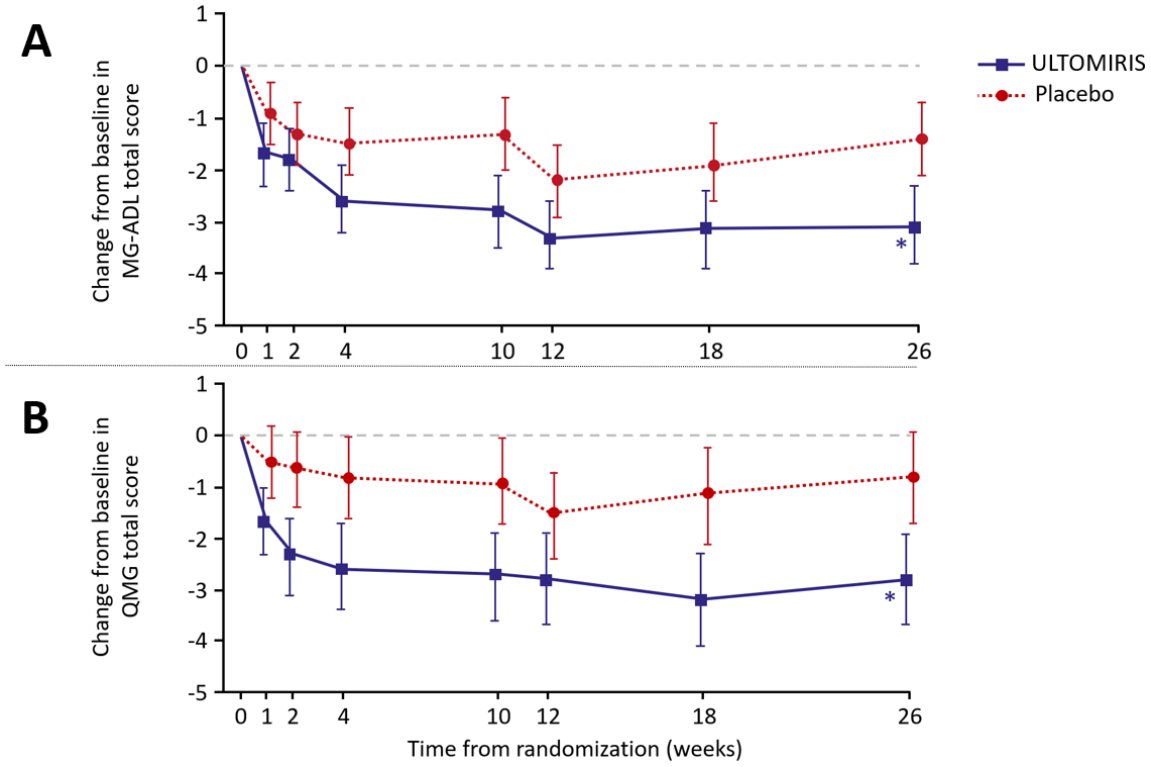
Figure 1: Change from Baseline in MG-ADL Total Score (A) and QMG Total Score (B) Through Week 26 of the Randomized Controlled Period of ALXN1210-MG-306 (Mean and 95% CI)



Note: *p<0.001 versus placebo

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

<u>Intravenous:</u>

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

- 300 mg/3 mL (100 mg/mL) (NDC 25682-025-01)
- 1,100 mg/11 mL (100 mg/mL) (NDC 25682-028-01)

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

- 300 mg/30 mL (10 mg/mL) (NDC 25682-022-01)

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Subcutaneous:

ULTOMIRIS (ravulizumab-cwvz) injection 70 mg/mL is translucent, clear to yellowish color solution supplied in one single-dose cartridge as part of a single-use on-body delivery system:

- 245 mg/3.5 mL (70 mg/mL) carton containing one prefilled cartridge co-packaged with one on-body injector: NDC 25682-031-01

16.2 Storage and Handling

Intravenous:

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.

Subcutaneous:

Store ULTOMIRIS prefilled cartridges and on-body injectors refrigerated at 2°C - 8°C (36°F - 46°F) in the original carton to protect from light and physical damage. Do not freeze. Do not shake or drop. Do not allow the on-body injector to get wet from water or other liquids.

If removed from the refrigerator, store ULTOMIRIS on-body injector and prefilled cartridge in the original carton box at room temperature between 68°F - 77°F (20°C - 25°C) for up to 3 days. If stored at room temperature, discard after 3 days. Do not return to the refrigerator.

The single-use on-body injector with prefilled cartridge is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read FDA-approved patient labeling (Medication Guide and Instructions for Use).

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

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- 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.

ULTOMIRIS REMS

ULTOMIRIS is available only through a restricted program called ULTOMIRIS REMS *[see Warnings and Precautions (5.2)]*.

Inform the patient of the following notable requirements:

- Patients must receive counseling about the risk of serious meningococcal infections.
- Patients must receive written educational materials about this risk.
- Patients must carry the Patient Safety Card with them at all times during and for 8 months following treatment with ULTOMIRIS.
- Patients must be vaccinated against meningococcal disease prior to treatment with ULTOMIRIS or receive 2 weeks of antibacterial drug prophylaxis if treatment must be initiated immediately and vaccines are administered less than 2 weeks before starting ULTOMIRIS.

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 8 months after the last ULTOMIRIS dose, because the increased risk of meningococcal infection persists for several months following discontinuation of ULTOMIRIS.

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Infusion-Related Reactions

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

Allergies to Acrylic Adhesives

Advise patients that the single-use on-body injector used in subcutaneous administration of ULTOMIRIS contains acrylic adhesive that may cause allergic reactions to individuals sensitive to acrylic adhesives.

Administration

Provide training to patients and caregivers on proper subcutaneous administration technique and how to use the single-use on-body injector with prefilled cartridge correctly.

Inform patients that 2 on-body delivery systems (on-body injector with prefilled - cartridge) are required for a full dose.

Additionally, inform patients that it will take about 10 minutes to administer each ULTOMIRIS on-body delivery system for subcutaneous administration.

The single-use on-body injector with prefilled cartridge is not made with natural rubber latex.

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.

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MEDICATION GUIDE

ULTOMIRIS® (ul-toe-meer-is)

(ravulizumab-cwvz)

injection,

for intravenous or subcutaneous 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 healthcare provider decided that urgent treatment with ULTOMIRIS is needed, you should receive meningococcal vaccination as soon as possible.
3. If you have not been vaccinated for meningococcal infections 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 healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider 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 *Haemophilus influenzae* type b (Hib).
- 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 about 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 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).
- adults with a disease called generalized Myasthenia Gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.

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

It is not known if ULTOMIRIS is safe and effective for the treatment of gMG in children.

Subcutaneous administration of ULTOMIRIS has not been evaluated and is not approved for use in children.

Who should not receive ULTOMIRIS?

Do not receive ULTOMIRIS if you:

- have a meningococcal infection.
- have not been vaccinated against meningococcal infection unless your healthcare provider 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 healthcare provider 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 healthcare provider 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 healthcare provider and pharmacist when you get a new medicine.

How should I receive ULTOMIRIS?

- Your healthcare provider will decide how long you need to receive ULTOMIRIS for your PNH, your aHUS, or your gMG.

Adults with PNH, aHUS, or gMG when administered intravenously (by vein)

- You will be given intravenous ULTOMIRIS infusion by a healthcare provider through a needle placed in a vein
- You will usually receive:
  - a starting dose of intravenous ULTOMIRIS infusion by your healthcare provider, **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 when administered intravenously (by vein)

Your child will be given intravenous ULTOMIRIS infusion by a healthcare provider through a needle placed in a vein

- Your child will usually receive:
  - a starting dose of intravenous ULTOMIRIS infusion by your healthcare provider, **and then**
  - your healthcare provider will decide how often your child will receive their intravenous ULTOMIRIS infusion, either every 4 weeks or every 8 weeks, depending on their weight, starting 2 weeks after the starting dose.

Adults with PNH or aHUS when administered subcutaneously (under your skin)

- You or your caregiver will administer subcutaneous ULTOMIRIS under your skin through an on-body injector.
- Use ULTOMIRIS exactly as your healthcare provider tells you to.
- **Read the Instructions for Use that comes with subcutaneous ULTOMIRIS for instructions about the right way to prepare and give your subcutaneous ULTOMIRIS injections through an on-body injector.**
- If your healthcare provider decides that you or a caregiver can give your injections of subcutaneous ULTOMIRIS, you or your caregiver should receive training on the right way to prepare and inject subcutaneous ULTOMIRIS. It is important that you receive training from your healthcare provider on how to inject subcutaneous ULTOMIRIS before giving an injection.
- You will need 2 on-body delivery systems (each containing 1 on-body injector and 1 prefilled cartridge) for a full subcutaneous ULTOMIRIS dose, and each injection will take about 10 minutes.
- You or your caregiver can administer the injections at the same time or 1 after the other into your stomach (abdomen), thigh, or upper arm.
- **If you are not currently being treated with intravenous ULTOMIRIS or SOLIRIS, you will usually receive:**
  - a starting dose of intravenous ULTOMIRIS infusion by your healthcare provider, and then
  - 2 weeks later, you or your caregiver will start to administer maintenance doses of subcutaneous ULTOMIRIS weekly.

If you are changing treatment between ULTOMIRIS administered intravenously, ULTOMIRIS administered subcutaneously, or SOLIRIS:

- **From intravenous ULTOMIRIS to subcutaneous ULTOMIRIS,** you should receive your first dose of subcutaneous ULTOMIRIS 8 weeks after your last dose of intravenous ULTOMIRIS. No intravenous ULTOMIRIS starting dose is needed.

- **From subcutaneous ULTOMIRIS to intravenous ULTOMIRIS,** you should receive your first dose of intravenous ULTOMIRIS 1 week after your last dose of subcutaneous ULTOMIRIS.
- **From SOLIRIS to intravenous ULTOMIRIS,** you should receive your starting dose of intravenous ULTOMIRIS at time of your next scheduled dose of SOLIRIS.
- **From SOLIRIS to subcutaneous ULTOMIRIS,** you should receive your starting dose of intravenous ULTOMIRIS at time of your next scheduled dose of SOLIRIS, and then your first dose of subcutaneous ULTOMIRIS 2 weeks after your starting dose of intravenous ULTOMIRIS.
- After each administration, you should monitor for allergic and infusion reactions for at least 1 hour. See **"What are the possible side effects of ULTOMIRIS?"**
- If you have PNH and you stop receiving ULTOMIRIS, your healthcare provider 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 healthcare provider 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 intravenous or subcutaneous dose, or administer a partial subcutaneous dose of ULTOMIRIS, call your healthcare provider 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 intravenous or subcutaneous treatment. Symptoms of an infusion-related reaction with ULTOMIRIS may include lower back pain, tiredness, feeling faint, discomfort in your arms or legs, bad taste, or drowsiness. Stop treatment of ULTOMIRIS and tell your healthcare provider 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
- **Allergic reactions to acrylic adhesive**. Allergic reactions to the acrylic adhesive may happen with your subcutaneous ULTOMIRIS treatment. If you have an allergic reaction during the delivery of subcutaneous ULTOMIRIS, remove the on-body injector and get medical help right away. Your healthcare provider may treat you with medicines to help prevent or treat allergic reaction symptoms as needed.

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

- upper respiratory tract infection
- local injection site reactions
- headache
- diarrhea

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

The most common side effects of ULTOMIRIS in people with gMG are:

- diarrhea
- upper respiratory tract infections

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ULTOMIRIS.

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 healthcare provider for information about ULTOMIRIS that is written for health professionals.

What are the ingredients in ULTOMIRIS?

Active ingredient: ravulizumab-cwvz.

Inactive ingredients:

Intravenous:

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.

Subcutaneous:

ULTOMIRIS 70 mg/mL: L-arginine, polysorbate 80 (vegetable origin), sodium phosphate dibasic, sodium phosphate monobasic, sucrose, and Water for Injection.

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

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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. Revised: 07/2022

INSTRUCTIONS FOR USE
On-Body Delivery System for
ULTOMIRIS (uhl-toh-mee-ris)
(ravulizumab-cwvz)
injection, for subcutaneous use

Single-Use, On-Body Injector and 245 mg/3.5 mL Prefilled Cartridge

This Instructions for Use contains information on how to inject ULTOMIRIS subcutaneously using an on-body delivery system.

Read this Instructions for Use prior to each use of the ULTOMIRIS on-body injector and prefilled cartridge as there may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. See the Medication Guide that comes with ULTOMIRIS for important information.

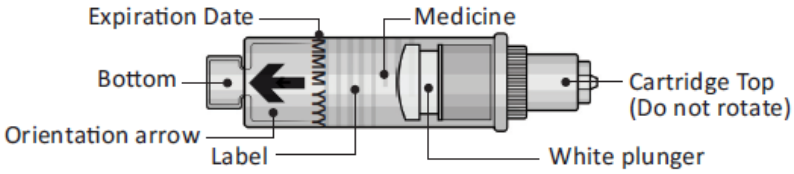
Important Information You Need to Know Before Injecting ULTOMIRIS Subcutaneously

- It is important that you receive training from your healthcare provider on how to inject ULTOMIRIS before giving an injection.
- If you have a serious allergic reaction (such as chest pain, trouble breathing, facial swelling, and/or feeling faint), **remove the on-body injector(s) to stop the injection and get medical help right away.**
- You will need 2 ULTOMIRIS on-body injectors and 2 prefilled cartridges to receive your full dose.

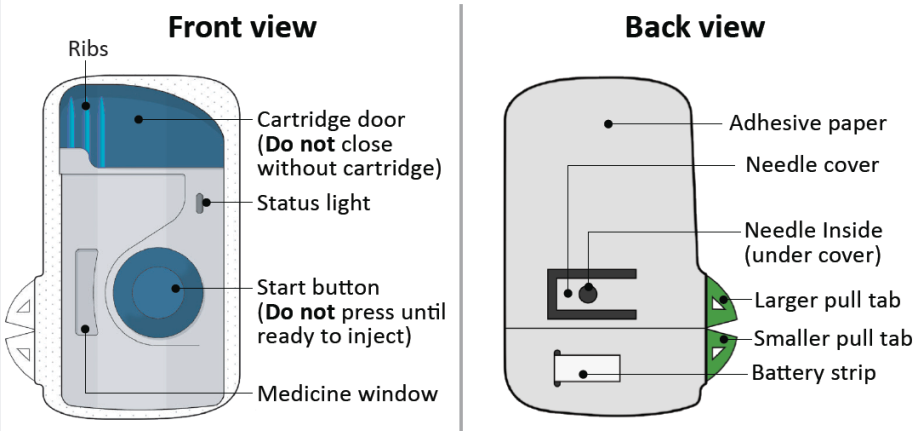
1 Full Dose of ULTOMIRIS =
2 ULTOMIRIS On-Body Injectors and
2 Prefilled Cartridges each week

Guide to Parts

Prefilled cartridge (Also referred to as “Cartridge”)



On-Body Injector (Also referred to as “Injector”)



Important: Needle is inside.

Important
Storing your ULTOMIRIS on-body injector and prefilled cartridge: • Store ULTOMIRIS injector and cartridge in the refrigerator between 36°F to 46°F (2°C to 8°C). • Keep the injector and cartridge in the original carton to protect from light or physical damage • For your injection, take **2** injectors and **2** cartridges out of the refrigerator and let them sit at room temperature for **at least 45 minutes** before you inject. • **Do not** return to the refrigerator. The injector and cartridge may be stored in the original carton box at room temperature between 68°F to 77°F (20°C to 25°C) for up to **3 days.** Discard (throw away) after 3 days if unused. • **Do not** freeze. • **Keep ULTOMIRIS and all medicines out of the reach of children.** **Using your ULTOMIRIS on-body injector and prefilled cartridge:** • **Do not** shake or drop the injector or cartridge. • **Do not** remove the injector or cartridge from the carton or clear tray until you are ready to inject. • **Do not** press the blue start button on the injector until you place the loaded injector onto your skin and are ready to inject. • **After you insert** the cartridge into the injector, **make sure you inject within 5 minutes.** Loading the cartridge more than 5 minutes before your injection can dry out the medicine. • **Do not** use the injector or cartridge if the packaging appears to be opened, or if the injector or cartridge has been dropped or appears to be broken or damaged. Part of the on-body injector or prefilled cartridge may be broken even if you cannot see the damage. • **Do not** reuse the on-body injector and prefilled cartridge. **They are single-use only.** • **Do not** let the injector get wet from water or other liquids. It contains electronic parts that should not get wet. • Keep the on-body injector a minimum of 4 inches (10 cm) away from other electronics such as cellular phones. • **Do not** use the injector or cartridge past the expiration date printed on the carton and cartridge.

Step 1: Prepare	
1A	Remove **2** ULTOMIRIS on-body delivery system cartons from the refrigerator. You will need to use **2** injectors and **2** cartridges for a full dose. (See Figure A)

Figure A

1B	Wait at least **45** minutes.

Important: Wait at least **45** minutes for the injectors and cartridges in the cartons to naturally reach room temperature. (See Figure B)

- **Do not** use a microwave, hot water, hair dryer, or any other heat sources to warm the prefilled cartridge.
- **Do not** return to the refrigerator. The injectors and cartridges may be stored in the original carton box at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 days. Throw away (discard) after 3 days if unused.

See the *Frequently Asked Questions* section for additional information on returning the on-body injector and prefilled cartridge to the refrigerator.

Figure B

1C	Open the cartons and peel away the white paper covers (See Figure C). Remove the plastic covers from the clear trays using the finger hole (See Figure D).

Figure C

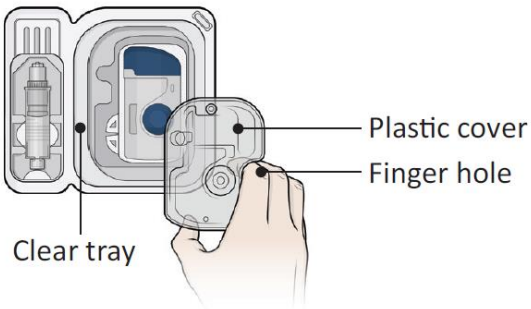


Figure D

Leave the injectors and cartridges in the trays until ready to use.

- **Do not** touch the blue start button until the injectors are on your skin and you are ready to inject.
- **Do not** use if the white paper cover(s) or plastic cover(s) is missing or damaged. If either is missing, call 1-888-765-4747.

1D	Gather all supplies needed for your injection and then wash your hands with soap and water. You can also wear gloves.

On a clean, well-lit work surface, place the:

- **2** clear trays containing the on-body injectors and prefilled cartridges (See Figure E)

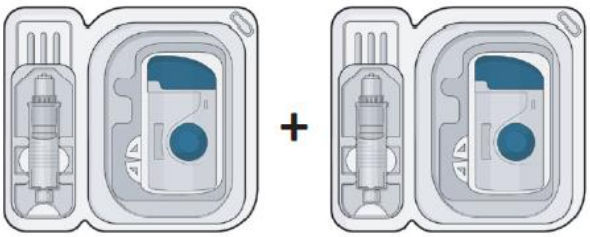


Figure E

Additional supplies (See Figure F):

- Alcohol wipes
- Cotton ball or gauze pad
- Adhesive bandage
- Sharps disposal container

Figure F
(Supplied Separately)

Wash your hands

1E	Prepare and clean **2 different** injection sites. Wipe both injection sites with a new alcohol wipe and let your skin air dry. (See Figure G)

The sites you may choose are:

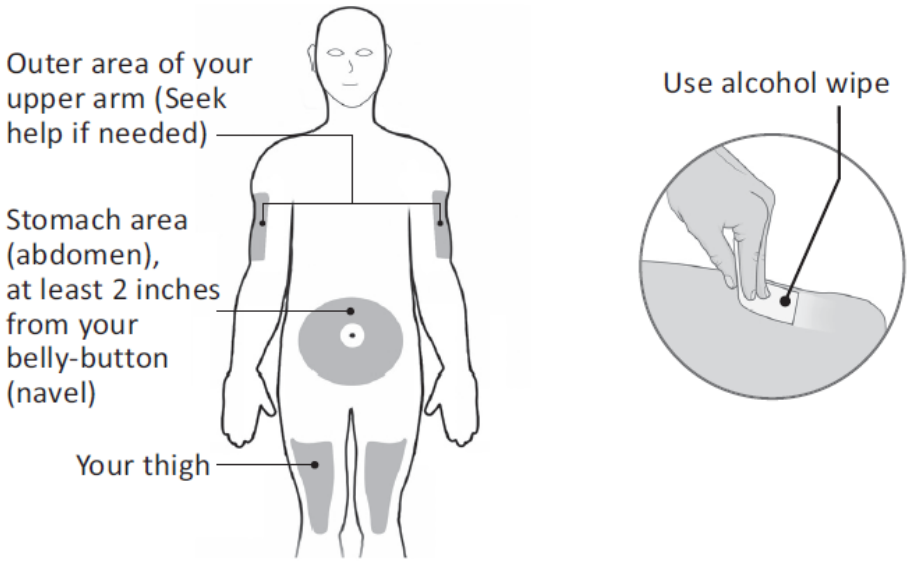


Figure G

- **Do not** inject into areas of the skin that are tender, bruised, red or hard, or areas with wrinkles, skin folds, scars, tattoos, stretch marks, moles, or excessive hair.
- **Do not** use the same sites 2 weeks in a row. Change (rotate) your injection sites every week to reduce irritation.

REPEAT Steps 2A - 3C for each injection

Step 2: Get Ready	
2A	Swing open the blue cartridge door (See Figure H). Leave the door open. **Do not** close the cartridge door before the cartridge is loaded.

The door should not be closed when removed from the package. If the door is closed, **press firmly** on the **ribbed side** of the door and **swing** the door to open. (See Figure I)

Figure H

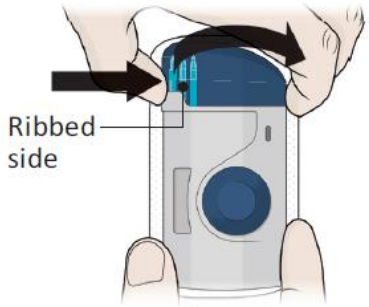


Figure I

2B	Inspect the cartridge. (See Figure J)

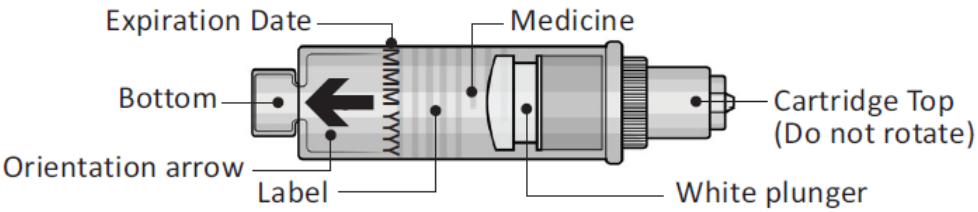


Figure J

Check the expiration date. **Do not** use the cartridge if the expiration date has passed.

Check the medicine in the cartridge. The medicine should be clear and colorless to slightly yellow in color.

- **Do not** use if the medicine is cloudy, discolored, or contains flakes or particles.
- **Do not** use if any part of cartridge looks cracked, broken, or if pieces are missing.

In any of the above cases, use a new on-body injector and prefilled cartridge and contact 1-888-765-4747.

2C	Clean the cartridge bottom with a new alcohol wipe. (See Figure K)

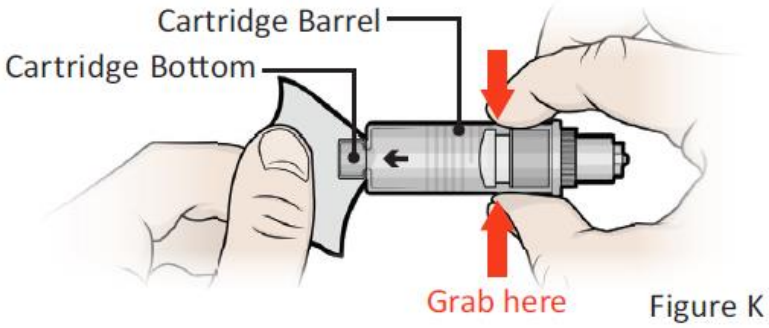


Figure K

With 1 hand, hold the prefilled cartridge barrel in the middle.

- **Do not** hold it by the ends.
- **Do not** turn (rotate) or remove the top or bottom of the cartridge.
- **Do not** touch the cartridge bottom after cleaning.

2D	Load the cleaned cartridge into the injector and **gently** press on the top until it is secured in place. (See Figure L)

Insert the cartridge into the injector with the arrow pointing down (bottom first).

- Note: It is okay to see a few drops of the medicine coming out of the needle.

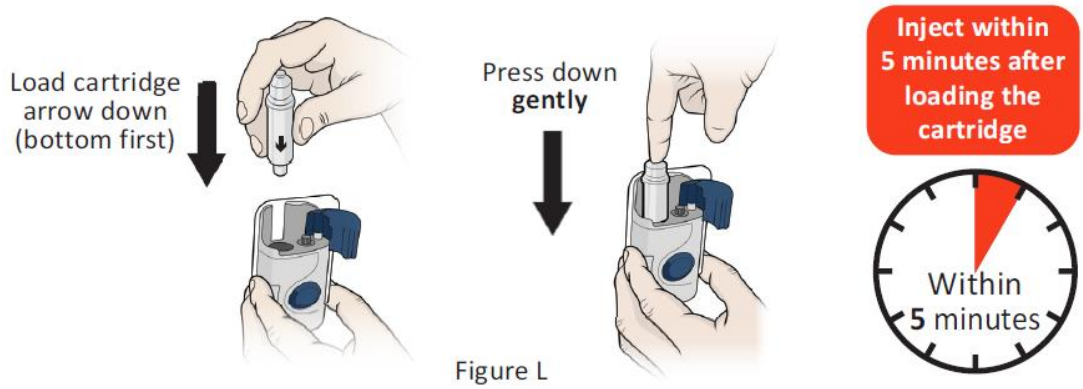


Figure L

Important: Do not insert the cartridge more than 5 minutes before your injection. This can dry out the medicine. See the *Frequently Asked Questions* section for more information.

2E	Close the cartridge door. Squeeze it firmly until it snaps shut and there are no gaps between the injector and the cartridge door. (See Figure M)

Do not re-open door or remove the cartridge.

Do not touch the blue start button until you have placed the injector onto your skin or the injector **will not work.**

Important: Go to the next step right way after loading the cartridge and closing the door.

Step 3: Inject

3A	Peel away both green pull tabs to show adhesive. (See Figure N)

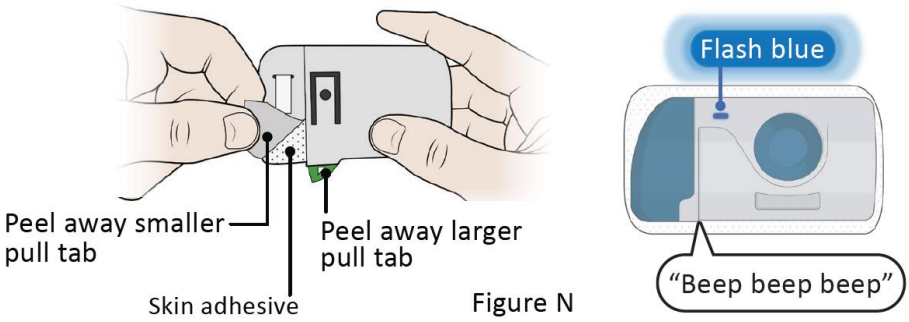


Figure N

The Injector will turn on when the smaller pull tab is removed (along with battery strip).

You will hear 3 “beeps” repeating every 30 seconds until the blue button is pressed.

The status light will begin to flash blue.

- **Do not** pull the skin adhesive backing off of the injector.
- **Do not** touch the skin adhesive.
- **Do not** touch the start button until you have placed the loaded injector onto your skin.
- To prevent injury, **do not** touch the needle cover area.
- **Do not** place the loaded injector on your body if the red status light flashes continuously.
- **Do not** fold the skin adhesive over onto itself.

3B	Stick the injector onto the clean, dry, chosen injection site(s). (See Figure O)

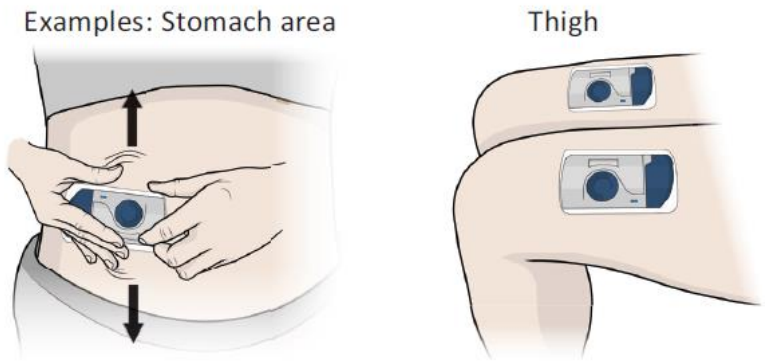


Figure O

Place the injector so that:

- You can see the status light.
- The injectors are at least 1 inch (2.5 cm) apart.
- Clothing is kept away from adhesive.

Firmly press the injector onto the skin.

Run your finger around the adhesive edges to make sure the adhesive is secure.

- **Do not** move the loaded injector after it has been placed onto your skin.

Important: If placing on stomach, stretch any loose skin as shown with 1 hand. Standing up may make this easier.

3C	Firmly press and release the blue start button on the injector to start the injection. (See Figure P)

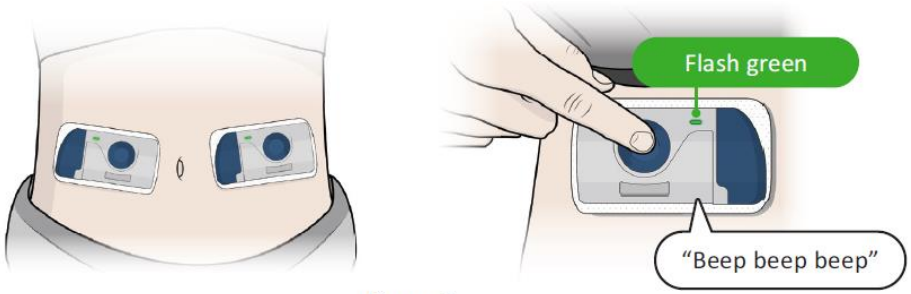


Figure P

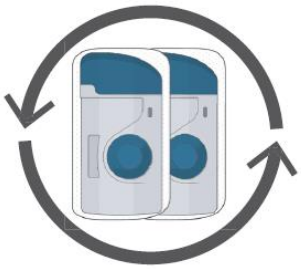
- You will hear 3 “beeps” when the blue button is pressed and injection starts.
- The status light will **flash green** during the injection.
- The sound of the injector motor will be heard for about **10 minutes** during the injection.
- You may feel a pinch.
- Light physical activities can be done during injection, such as walking, reaching, and bending.
- The injector should stay dry. Do not let the injector get wet from water or other liquids. It contains electronic parts that should not get wet.

Important: If you have a serious allergic reaction (such as chest pain, trouble breathing, facial swelling, and/or feeling faint), **remove the injector(s) to stop the injection and get medical help right away.**

3D	**REPEAT** Steps 2A - 3C with the **second injector**.

You must use 2 injectors to receive 1 full dose.

When the second injector is activated, continue to Step 4.



Step 4: Monitor

4A	Monitor both injectors until they are complete. Each injection takes about **10 minutes** to finish. (See Figure Q)

The Injection is complete when each injector:

- Status light turns solid green.
- Begins “beeping” 3 times every 30 seconds.
- White plunger fills the medicine window. (See Figure Q)

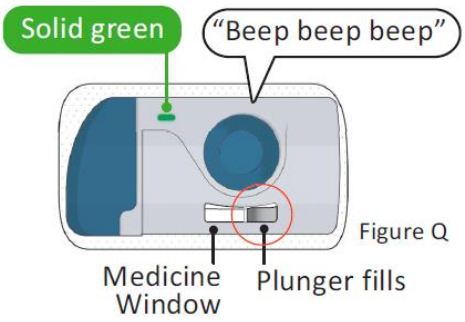


Figure Q

Step 5: Removal and Disposal	
5A	Remove the injectors after both injections are complete. Grip the adhesive and peel the injectors off your skin. (See Figure R)

The green status light will turn off when the injector is removed from your skin.

The injector will “beep” 3 times and then stop making noise.

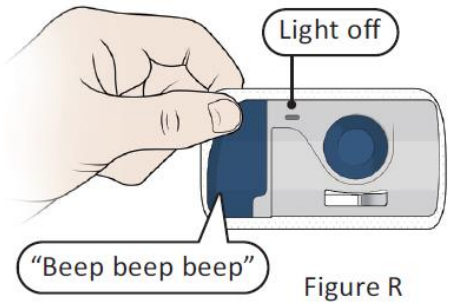


Figure R

5B	Dispose of (throw away) the used ULTOMIRIS on-body injectors and prefilled cartridges. (See Figure S).

- Put the used ULTOMIRIS on-body injectors and prefilled cartridges in an FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) the ULTOMIRIS on-body injectors and prefilled cartridges in your household trash.
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state you live in, go to the FDA’s website at: http://www.fda.gov/safesharpsdisposal
- **Do not** recycle your used sharps disposal container.

Figure S

5C	Check the injection sites.

- If there is blood at the injection sites, press a cotton ball or gauze pad on site.
- Apply an adhesive bandage if necessary.
- **Do not** rub the injection site.

Troubleshooting

What do I do if the loaded on-body injector status light flashes red and I hear “beeps”?

Important: If the status light turns red, injector leaks, or either injector does not complete injection, remove and call 1-888-765-4747 immediately (See Figure T).

A red status light indicates that the injector will not work.

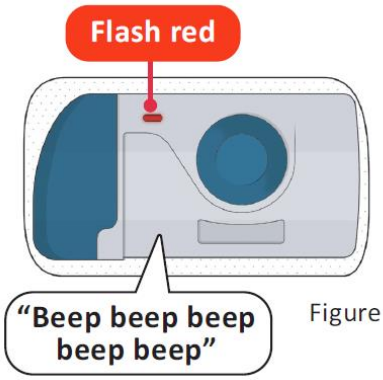


Figure T

Frequently Asked Questions

How many on-body injectors do I need for a full dose?

- You need **2** on-body injectors and **2** prefilled cartridges for a full weekly dose. You may prepare and use **2** on-body injectors and **2** prefilled cartridges at the same time.

What happens if the status light flashes red and I hear beeps?

- If the status light flashes red at any time, this means there is an error and the on-body injector will no longer work. Remove the on-body injector from the body (if it is attached) and place it in the original packaging. **Do not** remove the prefilled cartridge from the on-body injector. Contact 1-888-765-4747 and return the on-body injector and cartridge per the instructions given.

I cannot open the blue cartridge door. How do I open it?

- See Step 2A and Figure I. If you still cannot open it, contact 1-888-765-4747.

What if the on-body injector does not beep and the blue status light does not blink when I remove the pull tabs?

- First check that both pull tabs on the back of the on-body injector have been fully removed, including the battery strip. If the on-body injector still does not turn on, use a new on-body injector and prefilled cartridge. Contact 1-888-765-4747.

What if I push the blue start button before I stick the on-body injector on the skin?

- If you removed the pull tabs and pressed the start button, the on-body injector will make a beeping sound and you will see the status light flash red. The on-body injector will no longer work. Stop using the on-body injector and contact 1-888-765-4747.

What if the on-body injector is already on the skin but does not start after pressing the blue start button?

- Make sure you firmly press the blue start button. If it still does not start, remove the on-body injector and contact 1-888-765-4747. Do not reapply the same on-body injector as it will not work. Use a new on-body injector and prefilled cartridge.

What if a part of the packaging is missing or damaged (for example: carton, paper cover, plastic cover, etc.)?

- **Do not** use the on-body injector or prefilled cartridge and contact 1-888-765-4747.

What happens if I do not inject within 5 minutes after loading the prefilled cartridge?

- It is important to inject within 5 minutes after loading the prefilled cartridge.
- After you load the prefilled cartridge into the on-body injector, it is completely normal to see the medicine drop out of the needle. This is to get rid of the air from the on-body injector needle. However, if you wait more than 5 minutes to start your injection, you may lose some of your medicine. Additionally, this may dry out the medicine and clog the on-body injector needle.

If I am not ready to inject after waiting at least 45 minutes, can I return the on-body injector and prefilled cartridge to the refrigerator?

- **Do not** return to the refrigerator the on-body injectors and prefilled cartridges after they reach room temperature. This may degrade the medicine. If needed, the on-body injectors and prefilled cartridges may be stored in the original carton box at room temperature between 68°F to 77°F (20°Cto 25°C) for up to 3 days. Throw away after 3 days if unused.

For any additional questions or support, contact **1-888-765-4747.**

Additional Environmental Conditions

- Relative humidity range is 15% to 85%.
- Altitude range is -984 feet to 11483 feet (-300 meters to 3500 meters).
- During injection, keep the on-body injector a minimum of 4 inches (10 cm) away from other electronics such as cellular phones.
- Warning: Do not modify the on-body injector or prefilled cartridge.
- Warning: Magnetic Resonance (MR) is unsafe, the on-body injector for ULTOMIRIS should not enter the MR scanning room.
- On-body injector operating temperature range is 59°F to 104°F (15°C to 40°C).