PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrULTOMIRIS®

Ravulizumab for injection

10 mg/mL concentrate for solution for infusion

Selective immunosuppressant

Alexion Pharma GmbH

Giesshübelstrasse 30

CH-8045 Zürich, Switzerland

Date of Initial Authorization:
AUG 28, 2019

Date of Revision:
SEP 22, 2021

Submission Control Number: 252228

RECENT MAJOR LABEL CHANGES

None

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ULTOMIRIS® (ravulizumab for injection) is indicated for:

- the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

1.1 Pediatrics

The safety and effectiveness of ULTOMIRIS for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

1.2 Geriatrics

ULTOMIRIS may be administered to patients with PNH aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population.

2 CONTRAINDICATIONS

ULTOMIRIS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Section 6, Dosage Forms, Strengths, Composition and Packaging.

Do not initiate ULTOMIRIS therapy in patients with unresolved *Neisseria meningitidis* infection.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 *Section 7, Warnings and Precautions*).

- Comply with the most current National Advisory Committee on Immunization (NACI) recommendations for meningococcal vaccination in patients with complement deficiencies.
- Patients must be vaccinated against meningococcal infections prior to, or at the time of, initiating ULTOMIRIS, unless the risks of delaying ULTOMIRIS therapy outweigh the risks of developing a meningococcal infection (see also *Serious Meningococcal infections* in *Section 7* for additional guidance on the management of the risk of meningococcal infections).
- Monitor patients for early signs of meningococcal infections and treat immediately if infection is suspected.

ULTOMIRIS in Canada is available under a controlled distribution program. Patients are enrolled in a dedicated Patient Support Program (PSP).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Vaccinate patients according to current NACI guidelines to reduce the risk of serious infection (see *Section 3, Serious Warnings and Precautions Box*).

Provide two 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.

The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. Starting 2 weeks after loading dose administration, maintenance doses should be administered at a once every 8-week interval. Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS) but the subsequent dose should be administered according to the original schedule.

For patients switching from Soliris® to ULTOMIRIS, the loading dose of ULTOMIRIS should be administered at the time of the next scheduled Soliris infusion, and then maintenance doses are administered once every 8 weeks, starting 2 weeks after loading dose administration as shown in Table 1.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
≥40 to < 60	2400	3000
≥60 to < 100	2700	3300
≥100	3000	3600

PNH is a chronic disease and treatment with ULTOMIRIS is recommended to continue for the patient's lifetime. (See *Section 7, Warnings & Precautions, Treatment Discontinuation*)

4.3 Reconstitution

Parenteral Products: Each vial of ULTOMIRIS is intended for single use only.

ULTOMIRIS requires dilution to a final concentration of 5 mg/mL.
Aseptic technique must be used.

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 *Section 4.2 Recommended Dose and Dosage Adjustment*.
2. Prior to dilution, the solution in the vials should be visually inspected; the solution should be free of any particulate matter or precipitation. Do not use if there is evidence of particulate matter or precipitation.
3. The calculated volume of medicinal product is withdrawn from the appropriate number of vials

and diluted in an infusion bag using sodium chloride 9 mg/mL (0.9%) solution for injection as diluent. Refer to the administration reference tables below. The product should be mixed gently. It should not be shaken.

4. After dilution, the final concentration of the solution to be infused is 5 mg/mL.
5. The prepared solution should be administered immediately following preparation. Do not administer as an intravenous push or bolus injection. Refer to the administration reference tables below for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after reconstitution, storage times at 2°C - 8°C must not exceed 24 hours taking into account the expected infusion time.

Table 2: Loading Dose Administration Reference Table

Body Weight Range (kg)[a]	Loading Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Duration Minutes (hours)
≥ 40 to < 60	2400	240	240	480	114 (1.9)
≥ 60 to < 100	2700	270	270	540	102 (1.7)
≥ 100	3000	300	300	600	108 (1.8)

[a]Body weight at time of treatment

[b]ULTOMIRIS should only be diluted using sodium chloride 9 mg/mL (0.9%) solution

Table 3: Maintenance Dose Administration Reference Table

Body Weight Range (kg)[a]	Maintenance Dose (mg)	ULTOMIRIS Volume (mL)	Volume of NaCl Diluent[b] (mL)	Total Volume (mL)	Minimum Infusion Duration Minutes (hours)
≥ 40 to < 60	3000	300	300	600	140 (2.4)
≥ 60 to < 100	3300	330	330	660	120 (2.0)
≥ 100	3600	360	360	720	132 (2.2)

[a] Body weight at time of treatment

[b] ULTOMIRIS should only be diluted using sodium chloride 9 mg/mL (0.9%) solution

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

Prior to administration, the admixture should be allowed to adjust to room temperature (18°-25° C, 64°-77° F). The admixture must not be heated 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.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Reconstitution and dilution should only use sodium chloride 9 mg/mL (0.9%) solution for injection as diluent.

4.4 Administration

Only administer as an intravenous infusion.

Do not administer as an Intravenous Push or Bolus Injection.

- ULTOMIRIS must be diluted to a final concentration of 5 mg/mL.
- For intravenous infusion only.
- Must be administered through a 0.2 µm filter.

4.5 Missed Dose

In case of a missed dose, resume the regular schedule as soon as possible. Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ULTOMIRIS) but the subsequent dose should be administered according to the original schedule.

5 OVERDOSAGE

No case of overdose has been reported to date.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Intravenous infusion	300 mg/ 30 mL (10 mg/mL), single dose vial	Polysorbate 80 Sodium chloride Sodium phosphate, dibasic Sodium phosphate, monobasic Water for injections

Description:

ULTOMIRIS is a formulation of ravulizumab which is a long-acting humanized monoclonal IgG2/4K antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

One vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL). Clear to translucent, slight whitish color, pH 7.0 solution.

7 WARNINGS AND PRECAUTIONS

For serious meningococcal infections, please see *Section 3, Serious Warnings and Precautions Box* at the beginning of Part I: Health Professional Information.

Serious Meningococcal Infections

Due to its mechanism of action, the use of ULTOMIRIS increases the patient's susceptibility to meningococcal infection/sepsis (Neisseria meningitidis). Meningococcal disease due to any serogroup may occur. To reduce this risk of infection, all patients must be vaccinated against meningococcal infections prior to, or at the time of, initiating ULTOMIRIS. Patients who initiate ULTOMIRIS treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serogroups A, C, Y, W135, and B, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. Consideration should be given to official guidance on the appropriate use of antibacterial agents. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with ULTOMIRIS and with other terminal complement inhibitors. All patients should be monitored for early signs of meningococcal infection and sepsis, evaluated immediately if infection is suspected and treated with appropriate antibiotics. Patients should be informed of these signs and symptoms and steps should be taken to seek medical care immediately. Patients should be provided with information from the patient information leaflet and a patient safety card.

Immunization
Vaccination may further activate complement. As a result, patients with complement mediated diseases, including PNH, may experience increased signs and symptoms of their underlying disease, such as hemolysis. Therefore, patients should be closely monitored for disease symptoms after recommended vaccination.

General

Excipients

ULTOMIRIS when diluted with 0.9% sodium chloride for IV administration contains 2.65 g sodium per 720 mL at the maximum dose, which is above Health Canada's maximum daily intake recommendation of 2.3 g sodium. This should be taken into consideration by patients on a controlled sodium diet.

Infusion Reactions

Administration of ULTOMIRIS may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In clinical trials, some patients with PNH experienced infusion reactions) which were mild in severity and transient (e.g., lower back pain and drop in blood pressure).

These reactions did not require discontinuation of ULTOMIRIS. In case of infusion reaction, infusion of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

Other Systemic Infections

ULTOMIRIS therapy should be administered with caution to patients with active systemic infections. ULTOMIRIS blocks terminal complement activation; therefore, patients may have increased susceptibility to infections, especially infections caused by *Neisseria* species. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported in patients treated with ULTOMIRIS.

Patients should be provided with information from the Patient Leaflet to increase their awareness of the signs and symptoms of potential serious infections. Physicians should advise patients about gonorrhoea prevention.

Aplastic Anemia
In phase 3 PNH clinical studies, ULTOMIRIS was administered to 75/222 (33.8%) patients with aplastic anemia and PNH, some of which were treated with concomitant medications for aplastic anemia (including immunosuppressive therapies). There is no evidence indicating any special precautions are required for treating patients with aplastic anemia.

Renal and Hepatic Impairment
Studies have not been conducted to examine the effects of renal or hepatic impairment. There is no evidence that dose adjustments are required in patients with renal or hepatic impairment. (See *Section 10.2, Pharmacodynamics*)

Treatment Discontinuation
PNH is a chronic disease and treatment with ULTOMIRIS is recommended to continue for the patient's lifetime.
If patients with PNH must discontinue treatment with ULTOMIRIS, they should be closely monitored for signs and symptoms of hemolysis, identified by elevated LDH along with sudden decrease in – Glycophosphatidylinositol (GPI)-deficient red blood cell (RBC) clone size or hemoglobin, or re-appearance of symptoms such as fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Monitor any patient who must discontinue 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.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed.

Immune

Treatment with any therapeutic protein may induce an immune response. In PNH patient studies (N = 261), only 1 (0.38%) treatment-emergent anti-drug antibody has been reported with ULTOMIRIS. As with all therapeutic proteins, there is the potential for immunogenicity with ULTOMIRIS. Immunogenicity tests are generally product-specific and are highly dependent on the sensitivity and specificity of the assay. Comparison of incidence of antibodies between products by different tests may be misleading.

Reproductive Health: Female and Male Potential

- **Women of childbearing potential**

Women of childbearing potential should use effective contraception methods during treatment and up to 8 months after treatment.

- **Fertility**

No specific non-clinical study on fertility has been conducted with ravulizumab.

Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on fertility of the treated females or males. (see *Section 16, Non-Clinical Toxicology, Reproductive and Developmental Toxicology*)

7.1 Special Populations

7.1.1 Pregnant Women

No clinical data on exposed pregnancies are available.

Nonclinical reproductive and developmental toxicology studies were not conducted with ravulizumab due to lack of pharmacologic activity in non-human species. Reproductive and developmental toxicology studies were conducted in mice using the murine surrogate antibody molecule BB5.1, which assessed effect of C5 blockade on the reproductive system. No clear test-article related reproductive and developmental toxicities were identified in these studies (see *Section 16, Non-Clinical Toxicology, Reproductive and Developmental Toxicology*).

Animal studies are not always predictive of human response; therefore, it is unknown whether ULTOMIRIS can cause fetal harm when administered to a pregnant woman. Human IgG are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the fetal circulation.

ULTOMIRIS should not be used during pregnancy unless the potential benefit justifies the potential risk to the mother and the fetus.

7.1.2 Breast-feeding

It is unknown whether ULTOMIRIS is excreted into human milk. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breastfeeding should be discontinued during treatment and up to 8 months after treatment.

Nonclinical reproductive toxicology studies conducted in mice with the murine surrogate molecule BB5.1 identified no adverse effect to pups resulting from consuming milk from treated dams; however, animal studies are not always predictive of human response (see *Section 16, Non-Clinical Toxicology, Reproductive and Developmental Toxicology*).

7.1.3 Pediatrics

Pediatrics (0 to <18 years of age): The safety and effectiveness of ULTOMIRIS for the treatment of PNH in pediatric patients below the age of 18 years have not been established.

7.1.4 Geriatrics

Geriatrics (>65 years of age): ULTOMIRIS may be administered to patients with PNH aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse drug reaction was headache. The most serious adverse reactions in patients in clinical trials were meningococcal infection and meningococcal sepsis.

Meningococcal infections were reported in the ravulizumab clinical development program. These patients were treated with antibiotics and recovered while remaining on ravulizumab without treatment interruption.

Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek medical care immediately.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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

Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reaction was reported in more than 1 patient treated with ULTOMIRIS.

Table 5: Treatment-Emergent Adverse Events Reported by ≥5% of Patients by Pooled Treatment Groups (Phase 3 PNH Population)

System Organ Class Preferred Term	All ravulizumab (N = 222)		All Eculizumab	
	n (%)	E	n (%)	E
Gastrointestinal disorders				

Diarrhoea				
Nausea	19 (8.6)	23	19 (8.7)	23
Abdominal pain	13 (5.9)	16	16 (7.3)	16
General disorders and administration site conditions				
Pyrexia	15 (6.8)	18	18 (8.2)	23
Chest pain	5 (2.3)	9	14 (6.4)	19
Infections and infestations				
Nasopharyngitis	32 (14.4)	40	38 (17.4)	41
Upper respiratory tract infection	31 (14.0)	37	17 (7.8)	20
Musculoskeletal and connective tissue disorders				
Pain in extremity	14 (6.3)	15	11 (5.0)	14
Arthralgia	11 (5.0)	15	12 (5.5)	13
Myalgia	9 (4.1)	10	13 (5.9)	16
Nervous system disorders				
Headache	71 (32.0)	101	57 (26.0)	98
Dizziness	12 (5.4)	12	14 (6.4)	18
Respiratory, thoracic and mediastinal disorders				
Oropharyngeal pain	12 (5.4)	14	15 (6.8)	15

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse event; E = number of events; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

8.5 Post-Market Adverse Reactions

Infusion reactions

Administration of ULTOMIRIS may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis). In case of infusion reaction, infusion of ULTOMIRIS should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

ULTOMIRIS was administered to 75/222 (33.8%) patients with a history of Aplastic Anemia and PNH some of which were treated with concomitant medications for Aplastic Anemia, including immunosuppressive therapies. No evidence of drug interactions was observed in these patients.

ULTOMIRIS may be administered to patients with PNH treated with concomitant medications for Aplastic Anemia, including immunosuppressive therapies.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5

with high affinity, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b9.

In patients with PNH, ULTOMIRIS inhibits terminal complement-mediated intravascular hemolysis.

10.2 Pharmacodynamics

Following ULTOMIRIS treatment in both complement-inhibitor naïve patients and Soliris-experienced patients with PNH, immediate and complete inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all PNH patients.

The extent and duration of the pharmacodynamic response in patients with PNH were exposure dependent for ULTOMIRIS. Free C5 levels of <0.5 µg/mL were correlated with maximal intravascular hemolysis control and complete terminal complement inhibition. This complete terminal complement inhibition following ULTOMIRIS treatment led to normalization (or near normalization) of serum lactate dehydrogenase (LDH) in complement inhibitor-naïve patients and maintenance of LDH normalization in patients previously treated with Soliris (eculizumab).

10.3 Pharmacokinetics

The ravulizumab PK following intravenous (IV) administration increase proportionally over a dose range of 200 to 5400 mg.

Table 6 presents ravulizumab serum maximum concentration (Cmax) and the concentration at the end of the dosing interval (Ctrough) in complement inhibitor-naïve and prior Soliris-treated patients with PNH following the recommended body-weight dose regimen of ULTOMIRIS.

Table 6: PK Parameters of ULTOMIRIS after the loading dose and the last maintenance dose in complement inhibitor-naïve patients (Study ALXN1210-PNH-301) or prior Soliris –treated patients (Study ALXN1210-PNH-302) with PNH

PK Parameter	Dosing Period	Complement Inhibitor-Naïve		Prior Soliris-treated	
		n	Mean ± SD (%CV)	n	Mean ± SD (%CV)
Cmax (µg/mL)	LD	125	771.4 ± 165.9 (21.5)	95	842.9 ± 203.5 (24.1)
	Last MD	124	1378.5 ± 275.9	95	1386.3 ± 268.4 (19.4)
Ctrough (µg/mL)	LD	125	391.2 ± 136.8 (35.0)	96	405.4 ± 121.2 (29.9)
	Last MD	124	472.7 ± 157.9 (33.4)	95	500.8 ± 143.2 (28.6)

LD = loading dose; MD = maintenance dose

Distribution: The mean (SD) volume of distribution at steady state for patients with PNH on the studied weight-based dose regimen was 5.34 (0.92) L.

Elimination: The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with PNH are 49.7 (8.9) days and 0.00332 (0.000941) L/h respectively.

Special Populations and Conditions

No formal clinical studies of the effect of sex, race, age, hepatic or renal impairment on the pharmacokinetics of ravulizumab were conducted. Based on population PK assessment, body weight was identified as a significant covariate on the pharmacokinetics of ravulizumab. No clinically meaningful differences in pharmacokinetics of ravulizumab was observed based on gender, age (18 to 83 years), race, hepatic impairment or mild to moderate renal impairment.

No patients with severe renal impairment were enrolled in ravulizumab PNH studies.

11 STORAGE, STABILITY AND DISPOSAL

ULTOMIRIS vials must be stored under refrigerated conditions at 2°C – 8°C.

Keep the vial in the outer carton to protect from light.

Do not use beyond the expiration date stamped on the carton.

12 SPECIAL HANDLING INSTRUCTIONS

Vials must not be frozen or shaken.

After dilution, the medicinal product should be used immediately. However, chemical and physical stability of the diluted product have been demonstrated for up to 24 hours at 2°C-8°C and up to 6 hours at room temperature.

Refer to *Section 4.3, Reconstitution* for information on the stability and storage of diluted solutions of ULTOMIRIS.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

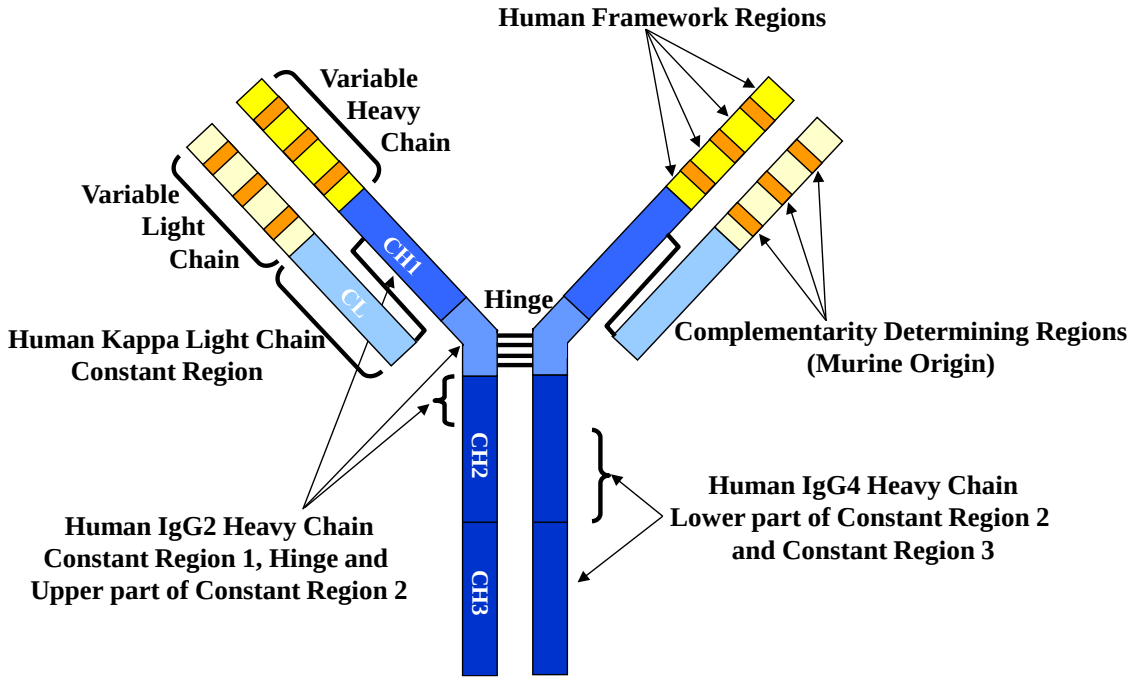
Drug Substance

Proper name: ravulizumab

Chemical name: Immunoglobulin G2/G4, anti-(human complement C5) (human-Mus musculus ALXN1210 heavy chain), disulfide with human-Mus musculus ALXN1210 kappa-chain, dimer

Molecular formula: $C_{6542}H_{10,072}N_{1704}O_{2106}S_{48}$

Structural formula:



Physicochemical properties:

Ravulizumab drug substance is a humanized IgG2/4 kappa antibody. Table 7 lists the general physicochemical properties of ravulizumab drug substance.

Table 7: Ravulizumab Physicochemical Properties

Property	Result
Number of Amino Acids Heavy Chain[a]	448
Number of Amino Acids Light Chain[a]	226
Theoretical Molecular Weight[b]	147,827.62 Da
Isoelectric (pI) range	Multiple bands between pI 5.5 and 6.8

Extinction Coefficient at 290 nm[c]	1.479 AU$(mg/mL)^{-1}(cm)^{-1}$

[a]Antibody is comprised of duplicate identical heavy and light chains
[b]Assumes antibody contains eighteen disulfide bonds, two heavy chain N-terminal pyroglutamations, the clipping of two heavy chain C terminal lysines, and the addition of two G0F glycan residues
[c]Extinction coefficient was theoretically-determined and experimentally-confirmed

Product Characteristics:

Ravulizumab is a humanized monoclonal antibody (mAb) consisting of 2 identical 448 amino acid heavy chains and 2 identical 214 amino acid light chains and has a molecular weight of approximately 148kDa. The constant regions of ravulizumab 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.

Description:

ULTOMIRIS is a formulation of ravulizumab which is a long-acting humanized monoclonal IgG2/4K antibody produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

One vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL). Clear to translucent, slight whitish color, pH 7.0 solution.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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

ULTOMIRIS was dosed in accordance with the recommended dosing described in *Section 4.2, Recommended Dose and Dosage Adjustment* (4 infusions of ULTOMIRIS over 26 weeks) while Soliris was administered according to the approved dosing regimen of Soliris (15 infusions over 26 weeks) which was the standard-of-care for PNH at the time of studies.

To reduce the risk of meningococcal infection (*Neisseria meningitidis*), all patients were required to have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

A summary of key study design features and patient demographics for each study is given

in Table 8 below:

Table 8: Summary of patient demographics for clinical trials in adult patients with PNH

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age[b] (Range)	Sex n (%)
ALXN-PNH-301	Phase III, Multicenter, Open-label, randomized, active controlled in patients naïve to complement inhibitor treatment	ULTOMIRIS Weight based[a]; Loading dose on day 1 followed by maintenance dose on Day 15 and every 8 weeks after; Soliris Induction Dose of 600 mg on Days 1, 8, 15, and 22, followed by maintenance dose of 900 mg on Day 29, and every 2 weeks after; Intravenous Infusion; 26 Weeks	ULTOMIRIS n=125 Soliris n=121 Total n=246	ULTOMIRIS 44.8 (18 – 83) Soliris 45 (18-86)	ULTOMIRIS Male 65 (52) Female 60 (48) Soliris Male 69 (57) Female 52 (43)

ALXN-PNH-302	Phase III, Multicenter, Open-label, randomized, active controlled in clinically stable patients treated with Soliris for at least 6 months	<u>ULTOMIRIS</u> Weight based[a]; Loading dose on day 1 followed by maintenance dose on Day 15 and every 8 weeks after; <u>Soliris</u> 900 mg every 2 weeks Intravenous Infusion; Duration: 26 Weeks followed by an extension period in which all patients receive ULTOMIRIS maintenance dose q8w (patients switching from eculizumab received a weight-based loading dose followed 2 weeks later by a weight-based maintenance dose q8w)	<u>ULTOMIRIS</u> n=97 <u>Soliris</u> n=98 Total n=195	<u>ULTOMIRIS</u> Mean- 46.6 (18-79) <u>Soliris</u> Mean- 48.8 (23-77)	<u>ULTOMIRIS</u> Male 50 (51.5) Female 47 (48.5) <u>Soliris</u> Male 48 (49) Female 50 (51)

[a]See *Section 4.2 Recommended Dose and Dosage Adjustment*
[b]Age (years) at first infusion in study

<u>ALXN1210-PNH-301 Study in complement-inhibitor naïve patients with PNH</u>

Study PNH-301 was a 26-week, multicenter, open-label, randomized, active-controlled, non-inferiority Phase 3 study conducted in 246 patients who were naïve to complement inhibitor treatment prior to study entry. Eligible patients to enter this trial had to have a documented diagnosis of PNH with granulocyte or monocyte clone size of ≥ 5%. 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 complication (3%), and other (16%).

In addition, eligible patients had to demonstrate high disease activity, defined as LDH level ≥ 1.5 × ULN at screening along with the presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin <10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.

Patients were stratified into 6 groups based on their transfusion history in the 1 year prior to the first dose of study drug, and screening LDH levels. The patients within each of the 6 groups were then

randomly assigned in a 1:1 ratio to receive either ULTOMIRIS or Soliris. Enrollment of patients without a history of transfusion in the previous year was capped at 20%.

Table 9 presents the baseline characteristics of the PNH patients enrolled in the Complement-Inhibitor Naïve Study.

Table 9: Baseline characteristics in the Complement-Inhibitor Naïve Study

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

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

[b] MAVE = major adverse vascular event

ALXN1210-PNH-302 Study in PNH patients previously treated with Soliris

Study PNH-302 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 Soliris for at least the past 6 months.

Patients with PNH who were clinically stable (LDH level ≤1.5X ULN at screening) after having been treated with Soliris for at least 6 months were eligible for enrollment in the study. Ninety five percent of patients had a documented PNH-associated condition diagnosed prior to enrollment on the trial: anemia (67%), hematuria or hemoglobinuria (49%), history of aplastic anemia (37%), history of renal failure (9%), myelodysplastic syndrome (5%), pregnancy complication (7%), and other (14%).

Patients were stratified into 1 of 2 groups based on their transfusion history within the previous 12 months. Patients within each of the 2 groups were then randomly assigned in a 1:1 ratio to either continue treatment with Soliris or switch to ULTOMIRIS.

Table 10 presents the baseline characteristics of the PNH patients enrolled in the Soliris-Experienced Study.

Table 10: Baseline characteristics in the Soliris-Experienced Study

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

[a] MAVE = major adverse vascular event

14.2 Study Results

ALXN1210-PNH-301 Study in complement-inhibitor naïve patients with PNH

The coprimary endpoints were transfusion avoidance, and reduction of hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance was considered as achieved only by the patients who did not receive a transfusion and did not meet the protocol specified guidelines for transfusion from baseline to Day 183. Key secondary endpoints included the percent change from baseline in LDH levels; change in quality of life (FACIT-Fatigue); 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 proportion of patients with stabilized hemoglobin.

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

Table 11: Efficacy Results in the Complement-Inhibitor Naïve Study

	ULTOMIRIS (N=125)	Eculizumab (N=121)	Statistic for Comparison	Treatment Effect

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

Note: LDH = lactate dehydrogenase; CI = confidence interval

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

A type I error of 1-sided 2.5% was used for the coprimary endpoints. Once noninferiority was declared for the coprimary endpoints, the key secondary endpoints were tested in a prespecified hierarchical testing procedure to control the Type-I error rate.

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.

ALXN1210-PNH-302 Study in PNH patients previously treated with Soliris

The primary endpoint was hemolysis as measured by LDH percent change from baseline. Secondary endpoints included the proportion of patients that experienced breakthrough hemolysis, quality-of-life (FACIT-Fatigue), transfusion avoidance (TA), and proportion of patients with stabilized hemoglobin.

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

Table 12: Efficacy Results in the Eculizumab-Experienced Patients with PNH Eculizumab- Experienced Study

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

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

Note: CI = confidence interval

A type I error of 1-sided 2.5% was used for the primary endpoint. Once noninferiority was declared for the primary endpoint, the key secondary endpoints were tested in a prespecified sequential testing procedure to control the Type-I error rate.

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

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

The tissue cross-reactivity of ULTOMIRIS was evaluated by assessing binding to a panel of human tissues. C5 expression in the human tissue panel examined in this study is consistent with published reports of C5 expression. No unexpected tissue cross-reactivity was observed.

A 26-week, repeat-dose, toxicity study in mice with a surrogate antibody BB5.1, directed against murine C5, was performed. The treatment did not affect any of the toxicity parameters examined. C5-induced hemolytic activity in an ex vivo assay was effectively blocked throughout the course of the study in both female and male mice.

Carcinogenicity:

No studies have been performed to evaluate the carcinogenic potential of ravulizumab.

Genotoxicity:

No studies have been performed to evaluate the genotoxic potential of ravulizumab.

Reproductive and Developmental Toxicology:

Animal reproductive and developmental toxicology studies have not been conducted with ravulizumab, due to a lack of pharmacologic activity in non-human species, but were conducted in mice with a murine surrogate complement inhibitory antibody, BB5.1. No clear treatment-related effects or adverse effects were observed in the murine surrogate reproductive and developmental toxicology studies in mice. When maternal exposure to the antibody occurred during organogenesis, two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose; however, these findings were not clearly test-article related.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ULTOMIRIS™
Ravulizumab for injection

Read this carefully before you start taking **ULTOMIRIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ULTOMIRIS**.

Serious Warnings and Precautions

- 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.
- You must be vaccinated against meningococcal infections prior to, or at the time of, initiating ULTOMIRIS.
- You must be monitored for early signs of meningococcal infections, evaluated immediately if infection is suspected, and treated with antibiotics.

Consult your doctor before you take ULTOMIRIS to be sure that you receive vaccination against *Neisseria meningitidis* prior to, or at the time of, beginning therapy. If you start therapy less than 2 weeks after being vaccinated, you must take antibiotics to reduce the risk of infection for 2 weeks. Ensure that your current meningococcal vaccinations are up to date. You should also be aware that vaccination may not prevent this type of infection. In accordance with national recommendations, your doctor might consider that you need supplementary measures to prevent infection.

Meningococcal infection symptoms
Because of the importance of rapidly identifying and treating meningococcal infection in patients who receive ULTOMIRIS, you will be provided a card to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis. This card is named: “Patient Safety Card”.

If you experience any of the following symptoms, you should immediately inform your doctor:

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

What is ULTOMIRIS used for?
ULTOMIRIS is used to treat adult patients with a certain type of disease affecting the blood system called Paroxysmal Nocturnal Haemoglobinuria (PNH). In patients with PNH, their red blood cells can be destroyed which can lead to low blood counts (anemia), tiredness, difficulty in functioning, pain, dark urine, shortness of breath, and blood clots.

How does ULTOMIRIS work?
ULTOMIRIS contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies. Ravulizumab binds to and inhibits a specific protein in the body that causes inflammation and so prevents your body's systems from attacking and destroying vulnerable blood cells.

What are the ingredients in ULTOMIRIS?
Medicinal ingredients: Ravulizumab
Non-medicinal ingredients: Polysorbate 80 (vegetable origin), sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, water for injections.

ULTOMIRIS comes in the following dosage forms:
Single use vial of 300 mg concentrate for solution for infusion

Do not use ULTOMIRIS if:
- you are allergic to ravulizumab, or any of the other ingredients of this medicine
- you have not received a meningococcal vaccine before or at the time of starting therapy
- you have unresolved meningococcal infection before therapy initiation

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ULTOMIRIS. Talk about any health conditions or problems you may have, including if you:
- have an infection (including if you have or are at risk for gonorrhea infection)

Other warnings you should know about:
Allergic Reactions
ULTOMIRIS contains a protein than may cause allergic reactions in some people. Tell your doctor or nurse right away if you get any of these symptoms during your ULTOMIRIS infusion:
- chest pain
- trouble breathing or shortness of breath
- swelling of your face, tongue, or throat
- feel faint or pass out

Infusion reactions
When ULTOMIRIS is given, you may experience reactions to the infusion (drip) such as headache, lower back pain, and infusion-related pain. Some patients may experience infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness). Tell your doctor or nurse right away if you develop these symptoms, or any other symptoms during your ULTOMIRIS infusion.

Pregnancy and Nursing
ULTOMIRIS should not be used during pregnancy unless the potential benefit justifies the potential risk to the mother and the fetus.
The use of effective contraception during treatment and up to 8 months after treatment should be considered in women who are able to get pregnant.
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

ULTOMIRIS contains sodium
This medicinal product contains 265 mg sodium chloride per vial. You should take into consideration if you are on a controlled sodium diet.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ULTOMIRIS:
The treatment will be given by your doctor or other health care provider by infusing a dilution of the ULTOMIRIS vial from a drip bag through a tube directly into one of your veins. It is recommended that the beginning of your treatments, called the loading phase, will extend over 2 weeks, followed by a maintenance phase. The doses administered are based on your body weight, as shown in the Table 1, your doctor will calculate this. Two weeks after receiving your loading dose, you will be administered ULTOMIRIS once every 8 weeks.
If you were receiving Soliris prior to receiving ULTOMIRIS, the loading dose should be administered 2 weeks after the last Soliris infusion. The infusion will take approximately 2 hours.

Usual dose:
Table 1: ULTOMIRIS Weight-Based Dosing Regimen

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60	2400	3000
≥ 60 to < 100	2700	3300
≥ 100	3000	3600

Overdose:
If you think you, or a person you are caring for, have taken too much ULTOMIRIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget an appointment, please contact your doctor immediately for advice, and see section below "If you stop using ULTOMIRIS."

If you stop using ULTOMIRIS
Interrupting or ending treatment with ULTOMIRIS may cause your PNH symptoms to return with greater severity. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely for at least 16 weeks.
The risks of stopping ULTOMIRIS include an increase in the destruction of your red blood cells, which may cause:

- A significant fall in your red blood cell counts (anemia),
- Confusion or change in how alert you are,
- Chest pain, or angina,
- An increase in your serum creatinine level (problems with your kidneys), or
- Thrombosis (blood clotting).

If you have any of these symptoms, contact your doctor.
If you have any further questions on the use of this medicine, ask your doctor.

What are possible side effects from using ULTOMIRIS?
These are not all the possible side effects you may have when taking Ultomiris. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effect in people with PNH treated with ULTOMIRIS is headache.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON Upper respiratory tract infection	x		
Common cold	x		
Headache		x	
COMMON Dizziness	x		
Vomiting	x		
Diarrhea	x		
Nausea	x		
Abdominal pain	x		
Dyspepsia	x		
Rash	x		
Pruritus	x		
Back Pain	x		
Joint Pain	x		
Muscle Pain	x		
Muscle Spasm	x		
Fever		x	
Influenza-like illness		x	
Fatigue	x		
Chills		x	
Feeling tired	x		
RARE Meningococcal infection		x	
Meningococcal sepsis		x	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Do not use this medicine after the expiry date which is stated on the carton after "EXP". The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C).
Do not freeze. Do not shake.

Store in the original package in order to protect from light.
After dilution with 0.9% sodium chloride, the product should be used within 24 hours if refrigerated or within 6 hours at room temperature.
Keep out of reach and sight of children.

If you want more information about ULTOMIRIS:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.alexion.com, or by calling 1-888-765-4747.

Alexion Pharmaceuticals, Inc. has established a PNH registry in order to continue to monitor and evaluate the safety and effectiveness of ULTOMIRIS. Please speak to your physician if you are interested in participating in the study. For further information on the PNH Registry, please contact medinfo.ca@alexion.com.

This leaflet was prepared by Alexion Pharma GmbH.
Last Revised: 22-SEP-2021