ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/3 mL concentrate for solution for infusion
Ultomiris 1,100 mg/11 mL concentrate for solution for infusion
Ultomiris 300 mg/30 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ultomiris is a formulation of ravulizumab produced in Chinese hamster ovary (CHO) cell culture by recombinant DNA technology.

Ultomiris 300 mg/3 mL concentrate for solution for infusion

Each vial of 3 mL contains 300 mg of ravulizumab (100 mg/mL).
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Excipient(s) with known effect:
Sodium (4.6 mg per 3 mL vial)

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

Each vial of 11 mL contains 1,100 mg of ravulizumab (100 mg/mL).
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Excipient(s) with known effect:
Sodium (16.8 mg per 11 mL vial)

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Each vial of 30 mL contains 300 mg of ravulizumab (10 mg/mL).
After dilution, the final concentration of the solution to be infused is 5 mg/mL.

Excipient(s) with known effect:
Sodium (115 mg per 30 mL vial)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Translucent, clear to yellowish colour, pH 7.4 solution.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Clear to translucent, slight whitish colour, pH 7.0 solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ultomiris is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):
- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1).

Ultomiris is indicated in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab (see section 5.1).

4.2 Posology and method of administration

Ravulizumab must be administered by a healthcare professional and under the supervision of a physician experienced in the management of patients with haematological or renal disorders.

Posology

Adult patients with PNH and aHUS
The recommended dosing regimen 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. For adult patients (≥ 18 years of age), maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

Dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab, but the subsequent dose should be administered according to the original schedule).

For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab 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: Ravulizumab weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 40 to < 60	2,400	3,000	Every 8 weeks
≥ 60 to < 100	2,700	3,300	Every 8 weeks
≥ 100	3,000	3,600	Every 8 weeks

*Maintenance dose is administered 2 weeks after loading dose

There is no experience of concomitant PE/PI (plasmapheresis or plasma exchange, or fresh frozen plasma infusion) use with ravulizumab. Administration of PE/PI may reduce ravulizumab serum levels.

PNH is a chronic disease and treatment with ravulizumab is recommended to continue for the patient's lifetime, unless the discontinuation of ravulizumab is clinically indicated (see section 4.4).

In aHUS, ravulizumab treatment to resolve thrombotic microangiopathy (TMA) manifestations should be for a minimum duration of 6 months, beyond which length of treatment needs to be considered for each patient individually. Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy (see section 4.4).

Special populations

Elderly
No dose adjustment is required for patients with PNH and aHUS aged 65 years and over. There is no evidence indicating any special precautions are required for treating a geriatric population – although experience with ravulizumab in elderly patients is limited.

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Hepatic impairment
The safety and efficacy of ravulizumab have not been studied in patients with hepatic impairment; however pharmacokinetic data suggest that no dose adjustment is required in patients with hepatic impairment.

Paediatric population
Paediatric patients with PNH and aHUS with body weight ≥ 40 kg are treated in accordance with the adult dosing recommendations. The weight-based doses and dosing intervals for paediatric patients ≥ 10 kg to < 40 kg are shown in Table 2.

For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses should be administered per weight-based dosing regimen shown in Table 2, starting 2 weeks after loading dose administration.

Table 2: Ravulizumab weight-based dosing regimen for paediatric patient with PNH and aHUS below 40 kg

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 10 to < 20	600	600	Every 4 weeks
≥ 20 to < 30	900	2,100	Every 8 weeks
≥ 30 to < 40	1,200	2,700	Every 8 weeks

*Maintenance dose is administered 2 weeks after loading dose

Data to support safety and efficacy of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in section 4.8 but no recommendation on a posology can be made for patients below 10 kg body weight.

Ravulizumab has not been studied in paediatric patients with PNH who weigh less than 30 kg. The posology of ravulizumab for paediatric patients less than 30 kg is based on the posology used for paediatric patients with aHUS, on the basis of the pharmacokinetic/pharmacodynamic (PK/PD) data available in aHUS and PNH patients treated with ravulizumab.

Method of administration

For intravenous infusion only.
This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.

In the absence of compatibility studies, Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1,100 mg/11 mL concentrates for solution for infusion.

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Ultomiris concentrated at 100 mg/mL (3 mL and 11 mL vials) must be diluted to a final concentration of 50 mg/mL.

Ultomiris concentrate for solution for infusion presented as 3 mL and 11 mL vials (100 mg/mL) must be diluted prior to administration by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 0.4 to 1.3 hours (25 to 75 minutes) depending on body weight (see Table 3 below).

Table 3: Dose administration rate for Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30	900	35 (0.6)	2,100	75 (1.3)
≥ 30 to < 40	1,200	31 (0.5)	2,700	65 (1.1)
≥ 40 to < 60	2,400	45 (0.8)	3,000	55 (0.9)
≥ 60 to < 100	2,700	35 (0.6)	3,300	40 (0.7)
≥ 100	3,000	25 (0.4)	3,600	30 (0.5)

[a] Body weight at time of treatment.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Ultomiris concentrated at 10 mg/mL (30 ml vial) must be diluted to a final concentration of 5 mg/mL.

Ultomiris concentrate for solution for infusion presented as 30 mL vial (10 mg/mL) must be diluted prior to administration by intravenous infusion using a syringe-type pump or an infusion pump over a minimal period of 1.3 to 3.3 hours (77 to 194 minutes) depending on body weight (see Table 4 below).

Table 4: Dose administration rate for Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight range (kg)[a]	Loading dose (mg)	Minimum infusion duration minutes (hours)	Maintenance dose (mg)	Minimum infusion duration minutes (hours)
≥ 10 to < 20	600	113 (1.9)	600	113 (1.9)
≥ 20 to < 30	900	86 (1.5)	2,100	194 (3.3)
≥ 30 to < 40	1,200	77 (1.3)	2,700	167 (2.8)
⩾ 40 to < 60	2,400	114 (1.9)	3,000	140 (2.4)
⩾ 60 to < 100	2,700	102 (1.7)	3,300	120 (2.0)
⩾ 100	3,000	108 (1.8)	3,600	132 (2.2)

[a] Body weight at time of treatment.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with unresolved *Neisseria meningitidis* infection at treatment initiation (see section 4.4).
- Patients who are not currently vaccinated against *Neisseria meningitidis* unless they receive prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Serious meningococcal infection

Due to its mechanism of action, the use of ravulizumab 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 at least two weeks prior to initiating ravulizumab unless the risk of delaying ravulizumab therapy outweighs the risk of developing a meningococcal infection. Patients who initiate ravulizumab 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 where available, are recommended in preventing the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current national guidelines for vaccination use. If the patient is being switched from eculizumab treatment, physicians should verify that meningococcal vaccination is current according to 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 meningococcal infections/sepsis have been reported in patients treated with ravulizumab. Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated 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. Physicians should provide patients with a patient information brochure and a Patient card.

Immunization

Prior to initiating ravulizumab therapy, it is recommended that PNH and aHUS patients initiate immunizations according to current immunization guidelines.

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

Patients below the age of 18 years old must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, and strictly need to adhere to the national vaccination recommendations for each age group.

Other systemic infections

Ravulizumab therapy should be administered with caution to patients with active systemic infections. Ravulizumab blocks terminal complement activation; therefore, patients may have increased susceptibility to infections caused by *Neisseria* species and encapsulated bacteria. Serious infections with Neisseria species (other than *Neisseria meningitidis*), including disseminated gonococcal infections, have been reported.
Patients should be provided with information from the Package Leaflet to increase their awareness of potential serious infections and their signs and symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion reactions

Administration of ravulizumab may result in infusion reactions and allergic or hypersensitivity reactions (including anaphylaxis).
In clinical trials with PNH and aHUS, [(6 out of 487 patients with PNH), and (4 of 89 patients with aHUS)] patients experienced infusion reactions which were mild in severity and transient [e.g., lower

back pain, drop in blood pressure, elevation in blood pressure, limb discomfort, drug hypersensitivity (allergic reaction), and dysgeusia (bad taste)]. In case of infusion reaction, infusion of ravulizumab should be interrupted and appropriate supportive measures should be instituted if signs of cardiovascular instability or respiratory compromise occur.

Treatment discontinuation for PNH

If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of serious intravascular haemolysis, identified by elevated LDH (lactate dehydrogenase) levels along with sudden decrease in PNH clone size or haemoglobin, or re-appearance of symptoms such as fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. Any patient who discontinues ravulizumab should be monitored for at least 16 weeks to detect haemolysis and other reactions. If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consider restarting treatment with ravulizumab.

Treatment discontinuation for aHUS

There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment.
If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe TMA complications.
TMA complications post-discontinuation can be identified if any of the following is observed:

- At least two of the following laboratory results observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ravulizumab treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ravulizumab treatment; or, an increase in serum LDH of 25% or more as compared to baseline or to nadir during ravulizumab treatment (results should be confirmed by a second measurement)
- any one of the following symptoms of TMA: a change in mental status or seizures or other extra-renal TMA manifestations including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea; or thrombosis.

If TMA complications occur after ravulizumab discontinuation, reinitiation of ravulizumab treatment should be considered, beginning with the loading dose and maintenance dose (see section 4.2).

Sodium content

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 0.18 g sodium per 72 mL at the maximal dose, equivalent to 9.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicinal product contains 2.65 g sodium per 720 mL at the maximal dose, equivalent to 133% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Chronic intravenous human immunoglobulin (IVIg) treatment may interfere with the endosomal neonatal Fc receptor (FcRn) recycling mechanism of monoclonal antibodies such as ravulizumab and thereby decrease serum ravulizumab concentrations.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no clinical data from the use of ravulizumab in pregnant women.
Nonclinical reproductive toxicology studies were not conducted with ravulizumab (see section 5.3). Reproductive toxicology studies were conducted in mice using the murine surrogate molecule BB5.1, which assessed effect of C5 blockade on the reproductive system. No specific test-article related reproductive toxicities were identified in these studies. Human IgG are known to cross the human placental barrier, and thus ravulizumab may potentially cause terminal complement inhibition in the foetal circulation.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

In pregnant women the use of ravulizumab may be considered following an assessment of the risks and benefits.

Breast-feeding

It is unknown whether ravulizumab is excreted into human milk. 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.

A risk to infants cannot be excluded.
Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in nursing infants, breast-feeding should be discontinued during treatment with ravulizumab 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.

4.7 Effects on ability to drive and use machines

Ultomiris has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (very common frequency) are diarrhoea, nausea, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infection and meningococcal sepsis (see section 4.4).

Tabulated list of adverse reactions

Table 5 gives the adverse reactions observed from PNH and aHUS clinical trials and from post-marketing experience.
Adverse reactions are listed by MedDRA System Organ Class (SOC) and frequency, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 5: Adverse reactions

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis		Meningococcal infection [a]
Nervous system disorders	Headache	Dizziness	
Gastrointestinal disorders	Diarrhoea, Nausea	Abdominal pain, Vomiting, Dyspepsia	
Skin and subcutaneous tissue disorders		Rash, Pruritus	Urticaria [b]
Musculoskeletal and connective tissue disorders		Arthralgia, Back pain, Myalgia, Muscle spasms	
General disorders and administration site conditions	Pyrexia, Fatigue	Influenza like illness, Asthenia	Chills
Immune system disorders			Anaphylactic reaction [b], hypersensitivity
Injury, poisoning and procedural complications		Infusion related reaction	

[a] Meningococcal infection includes preferred terms of meningococcal infection and meningococcal sepsis
[b] Estimated from post-marketing experience

Description of selected adverse reactions

Meningococcal infection/sepsis
Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, 3 out of 261 adult PNH patients developed serious meningococcal infections/sepsis while receiving treatment with ravulizumab; all 3 had been vaccinated. All 3 recovered while continuing treatment with ravulizumab. In the study in paediatric patients with PNH, no meningococcal infections occurred among 13 patients receiving treatment with ravulizumab. In aHUS studies, no meningococcal infections occurred among 89 patients receiving treatment with ravulizumab. Please refer to section 4.4 for information on prevention and treatment of suspected meningococcal infection. In patients treated with ravulizumab, meningococcal infections presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek medical care immediately.

Immunogenicity
Treatment with any therapeutic protein may induce an immune response. In adult PNH patient studies (N = 261), paediatric PNH study (N = 13), and aHUS studies (N = 89), only 2 (0.55%) cases of development of treatment-emergent anti-drug antibody have been reported with ravulizumab (1 adult patient with PNH and 1 adult patient with aHUS). These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

Paediatric population

Paroxysmal nocturnal haemoglobinuria (PNH)
In paediatric PNH patients (aged 9 to 17 years old) enrolled in the paediatric PNH Study (ALXN1210-PNH-304), the safety profile appeared similar to that observed in adult PNH patients. The most common adverse reactions reported in paediatric PNH patients were abdominal pain and nasopharyngitis, which occurred in 2 patients (15.4%).

Atypical haemolytic uremic syndrome (aHUS)
In paediatric patients with evidence of aHUS (aged 10 months to less than 18 years) included in ALXN1210-aHUS-312 study, the safety profile of ravulizumab appeared similar to that observed in adult patients with evidence of aHUS. The safety profiles in the different paediatric subsets of age appear similar. The safety data for patient below 2 years of age is limited to four patients. The most common adverse reaction reported in paediatric patients was pyrexia (32.3%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported to date.
Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA43

Mechanism of action

Ravulizumab is a monoclonal antibody $IgG_{2/4K}$ that specifically binds to the complement protein C5, 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 C5b-9. Ravulizumab preserves the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Pharmacodynamic effects

Following ravulizumab treatment in both adult and paediatric complement inhibitor-naïve patients and eculizumab-experienced patients with PNH in Phase 3 studies, immediate, complete and sustained 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 patients. Immediate and complete inhibition of serum free C5 was also observed in adult and paediatric patients with aHUS by the end of the first infusion and throughout the 26-week treatment period.
The extent and duration of the pharmacodynamic response in patients with PNH and aHUS were exposure dependent for ravulizumab. Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Clinical efficacy and safety

Paroxysmal nocturnal haemoglobinuria
The safety and efficacy of ravulizumab in adult patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:
- a complement inhibitor-naïve study in adult patients with PNH who were naïve to complement inhibitor treatment,
- an eculizumab-experienced study in adult patients with PNH who were clinically stable after having been treated with eculizumab for at least the previous 6 months.

Ravulizumab was dosed in accordance with the recommended dosing described in section 4.2 (4 infusions of ravulizumab over 26 weeks) while eculizumab was administered according to the approved dosing regimen of eculizumab of 600 mg every week for the first 4 weeks and 900 mg every 2 weeks (15 infusions over 26 weeks).
Patients were vaccinated against meningococcal infection prior to or at the time of initiating treatment with ravulizumab or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.
There were no noteworthy differences in the demographic or baseline characteristics between the ravulizumab and eculizumab treatment groups in either of the Phase 3 studies. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 studies.

Study in complement inhibitor-naïve adult patients with PNH

The complement inhibitor-naïve study was a 26-week, multicentre, open-label, randomised, active-controlled, 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 demonstrate high disease activity, defined as LDH level ≥ 1.5 × upper limit of normal (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, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.

More than 80 % of patients in both treatment groups had a history of transfusion within 12 months of study entry. The majority of the complement inhibitor-naïve study population was highly haemolytic at baseline; 86.2 % of enrolled patients presented with elevated LDH ≥ 3 × ULN, which is a direct measurement of intravascular haemolysis, in the setting of PNH.

Table 6 presents the baseline characteristics of the PNH patients enrolled in the complement inhibitor-naïve study, with no apparent clinically meaningful differences observed between the treatment arms.

Table 6: Baseline characteristics in the complement inhibitor-naïve study

Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	37.9 (14.90) 34.0 15, 81	39.6 (16.65) 36.5 13, 82
Age (years) at first infusion in study	Mean (SD) Median	44.8 (15.16) 43.0	46.2 (16.24) 45.0

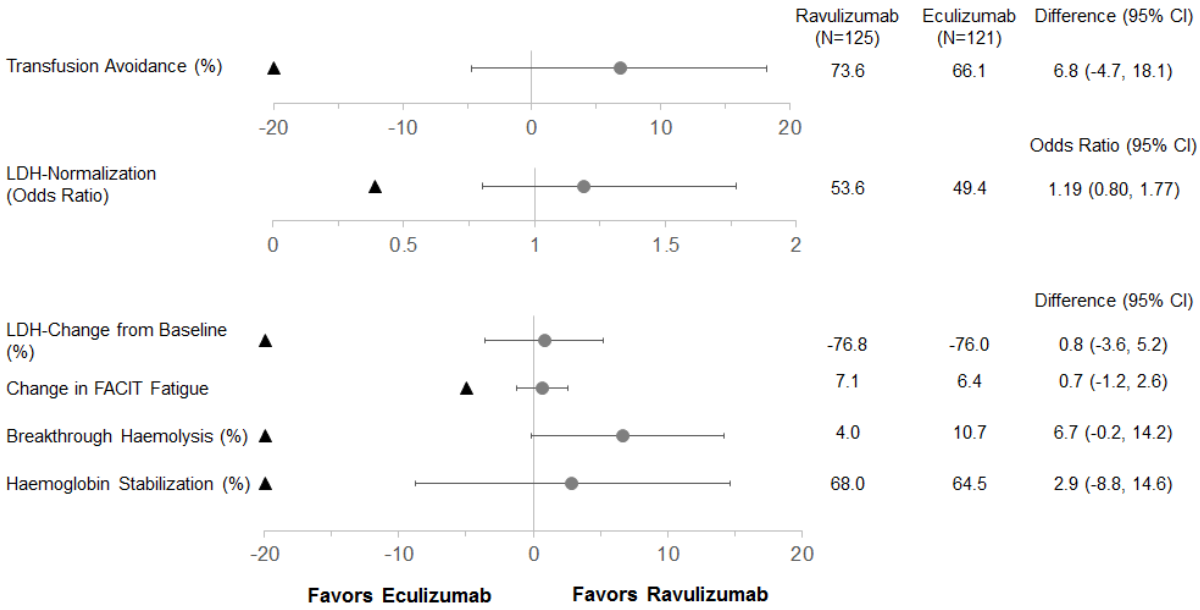
Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
	Min, max	18, 83	18, 86
Sex (n, %)	Male Female	65 (52.0) 60 (48.0)	69 (57.0) 52 (43.0)
Pre-treatment LDH levels	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0
Number of patients with packed red blood cell (pRBC) transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
Units of pRBC transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Total PNH RBC clone size	Median	33.6	34.2
Total PNH granulocyte clone size	Median	93.8	92.4
Patients with any PNH conditions[a] prior to informed consent	n (%)	121 (96.8)	120 (99.2)
Anaemia		103 (82.4)	105 (86.8)
Haematuria or haemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anaemia		41 (32.8)	38 (31.4)
Renal failure		19 (15.2)	11 (9.1)
Myelodysplastic syndrome		7 (5.6)	6 (5.0)
Pregnancy complication		3 (2.4)	4 (3.3)
Other[b]		27 (21.6)	13 (10.7)

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

The coprimary endpoints were transfusion avoidance, and haemolysis as directly measured by normalisation of LDH levels (LDH levels ≤ 1 × ULN; the ULN for LDH is 246 U/L). 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 haemolysis and proportion of patients with stabilized haemoglobin.

Ravulizumab was non-inferior compared to eculizumab for both coprimary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines and LDH normalisation from day 29 to day 183, and for all 4 key secondary endpoints (Figure 1).

Figure 1: Analysis of coprimary and secondary endpoints – full analysis set (complement inhibitor-naïve study)



Note: The black triangle indicates the non-inferiority margins, and grey dots indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

Study in adult PNH patients previously treated with eculizumab

The eculizumab-experienced study was a 26-week, multicentre, open-label, randomised, active-controlled Phase 3 study conducted in 195 patients with PNH who were clinically stable (LDH ≤ 1.5 x ULN) after having been treated with eculizumab for at least the past 6 months.

PNH medical history was similar between ravulizumab and eculizumab treatment groups. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups and more than 87 % of patients in both treatment groups had not received a transfusion within 12 months of study entry. The mean total PNH RBC clone size was 60.05 %, mean total PNH granulocyte clone size was 83.30 %, and the mean total PNH monocyte clone size was 85.86 %.

Table 7 presents the baseline characteristics of the PNH patients enrolled in the eculizumab-experienced study, with no apparent clinically meaningful differences observed between the treatment arms.

Table 7: Baseline characteristics in the eculizumab-experienced study

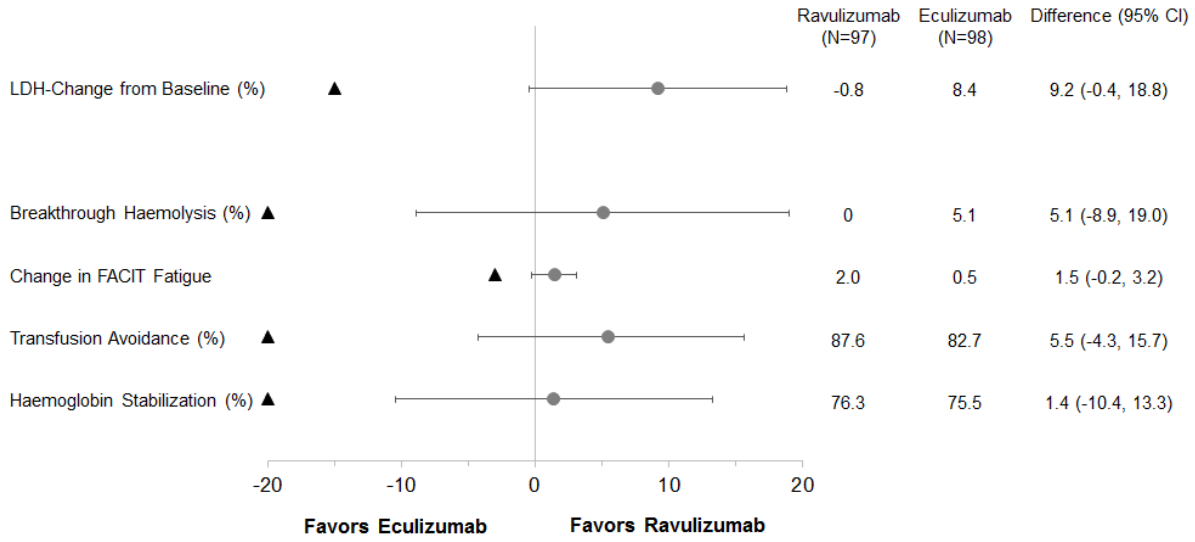
Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	50 (51.5) 47 (48.5)	48 (49.0) 50 (51.0)
Pre-treatment LDH levels	Mean (SD) Median	228.0 (48.71) 224.0	235.2 (49.71) 234.0
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose	n (%)	13 (13.4)	12 (12.2)
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	103 7.9 (8.78) 4.0	50 4.2 (3.83) 2.5
Patients with any PNH conditions[a] prior to informed consent Anaemia Haematuria or haemoglobinuria Aplastic anaemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[b]	n (%)	90 (92.8) 64 (66.0) 47 (48.5) 34 (35.1) 11 (11.3) 3 (3.1) 4 (4.1) 14 (14.4)	96 (98.0) 67 (68.4) 48 (49.0) 39 (39.8) 7 (7.1) 6 (6.1) 9 (9.2) 14 (14.3)

[a] Based on medical history.
[b] "Other" category included neutropenia, renal dysfunction, and thrombopenia, as well as a number of other conditions.

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

Ravulizumab was non-inferior compared to eculizumab for the primary endpoint, percent change in LDH from baseline to day 183, and for all 4 key secondary endpoints (Figure 2).

Figure 2: Analysis of primary and secondary endpoints – full analysis set (eculizumab-experienced study)



Note: The black triangle indicates the non-inferiority margins, and grey dot indicates point estimates.
Note: LDH = lactate dehydrogenase; CI = confidence interval.

Atypical haemolytic uremic syndrome (aHUS)

Study in adult patients with aHUS

The adult study was a multicentre, single arm, Phase 3 study conducted in patients with documented aHUS who were naïve to complement inhibitor treatment prior to study entry and had evidence of thrombotic microangiopathy (TMA). 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 58 patients with documented aHUS were enrolled. Enrolment criteria excluded patients presenting with TMA due to thrombotic thrombocytopenic purpura (TTP) or Shiga toxin *Escherichia coli* related haemolytic uremic syndrome (STEC-HUS). Two patients were excluded from the full analysis set due to a confirmed diagnosis of STEC-HUS. Ninety-three percent of patients had extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline.

Table 8 presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the full analysis set.

Table 8: Baseline characteristics in the adult study

Parameter	**Statistics**	**Ravulizumab (N = 56)**
Age at time of first infusion (years)	Mean (SD) Min, max	42.2 (14.98) 19.5, 76.6
Sex Male	 n (%)	 19 (33.9)
Race [a] Asian White Other	n (%)	 15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelets (10^9/L) blood	n Median (min,max)	56 95.25 (18, 473)
Haemoglobin (g/L) blood	n Median (min,max)	56 85.00 (60.5, 140)
LDH (U/L) serum	n Median (min,max)	56 508.00 (229.5, 3249)

Parameter	Statistics	Ravulizumab (N = 56)
eGFR (mL/min/1.73 m^2)	n (%) Median (min,max)	55 10.00 (4, 80)
Patients on dialysis	N (%)	29 (51.8)
Patients post partum	N (%)	8 (14.3)

Note: Percentages are based on the total number of patients.
Abbreviations: aHUS = atypical haemolytic uremic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum.

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet count ≥ 150 x 10^9/L and LDH ≤ 246 U/L) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week initial evaluation period as shown in Table 9.

Table 9: Complete TMA response and complete TMA response components analysis during the 26-week initial evaluation period (ALXN1210-aHUS-311)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	56	30	0.536 (0.396, 0.675)
Components of Complete TMA Response			
Platelet count normalisation	56	47	0.839 (0.734, 0.944)
LDH normalisation	56	43	0.768 (0.648, 0.887)
≥25% improvement in serum creatinine from baseline	56	33	0.589 (0.452, 0.727)
Haematologic normalisation	56	41	0.732 (0.607, 0.857)

[a] 95 % CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Four additional patients had a Complete TMA Response that was confirmed after the 26-week initial evaluation period (with a Complete TMA Response occurring at Days 169, 302, 401 and 407). resulting in an overall Complete TMA Response in 34 of 56 patients (60.7%; 95% CI: 47.0%, 74.4%). Individual component response increased to 48 (85.7%; 95% CI: 75.7%, 95.8%) patients for platelet count normalisation, 47 (83.9%; 95% CI: 73.4%, 94.4%) patients for LDH normalisation, and 35 (62.5%; 95% CI: 48.9%, 76.1%) patients for renal function improvement.

Complete TMA Response was achieved at a median time of 86 days (7 to 169 days). An increase in mean platelet count was observed rapidly after commencement of ravulizumab, 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). Similarly, mean LDH value decreased from baseline over the first 2 months of treatment and was sustained over the duration of the initial evaluation period (26 weeks).

Of the patients who presented at CKD Stage 5, 67.6% (23/34) showed an improvement of 1 or more CKD Stages. Chronic kidney disease stage continued to improve for many patients (19/30) after achieving Complete TMA Response during the 26-week initial evaluation period. 17 of the 29 patients who required dialysis at study entry were able to discontinue dialysis by the end of the available follow-up while 6 of 27 patients who were off dialysis at baseline were on dialysis at last available follow-up. Table 10 summarises the secondary efficacy outcomes for Study ALXN1210-aHUS-311.

Table 10: Secondary efficacy outcome for study ALXN1210-aHUS-311

Parameters	Study ALXN1210-aHUS-311 (N = 56)	
Haematologic TMA parameters, Day 183	Observed value (n=48)	Change from baseline (n=48)
Platelets (10^9/L) blood		
Mean (SD)	237.96 (73.528)	114.79 (105.568)
Median	232.00	125.00
LDH (U/L) serum		
Mean (SD)	194.46 (58.099)	-519.83 (572.467)
Median	176.50	-310.75
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/n	40/56	
proportion (95% CI)*	0.714 (0.587, 0.842)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	32/47	
Proportion (95% CI)*	0.681 (0.529, 0.809)	
Worsened[b]		
m/n	2/13	
Proportion (95% CI)*	0.154 (0.019, 0.454)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=48)	Change from baseline (n=47)
Mean (SD)	51.83 (39.162)	34.80 (35.454)
Median	40.00	29.00

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 5 is considered the worst category, while Stage 1 is considered the best category. Baseline is derived based on the last available eGFR before starting treatment.
Improved/Worsened: compared to CKD stage at baseline. *95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper-Pearson method. [a]Excludes those with CKD Stage 1 at baseline as they cannot improve. [b]Excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Paediatric population

Paroxysmal nocturnal haemoglobinuria (PNH)

Study in paediatric patients with PNH

The paediatric study (ALXN1210-PNH-304) is a multicentre, open-label, Phase 3 study conducted in eculizumab-experienced and complement inhibitor-naïve paediatric patients with PNH.
From interim results, a total of 13 PNH paediatric patients completed ravulizumab treatment during the primary evaluation period (26 weeks) of Study ALXN1210-PNH-304. Five of the 13 patients had never been treated with a complement inhibitor and 8 patients received treatment with eculizumab prior to study entry.
Most of the patients were between 12 years and 17 years of age at first infusion (mean: 14.4 years), with 2 patients under 12 years old (11 years and 9 years old). Eight of the 13 patients were female. Mean weight at baseline was 56 kg, ranging from 37 to 72 kg. Table 11 presents the baseline disease history and characteristics of the paediatric patients enrolled in Study ALXN1210-PNH-304.

Table 11: Disease History and Characteristics at Baseline (Full Analysis Set)

Variable	Complement Inhibitor-naïve Patients (N = 5)	Eculizumab-experienced Patients (N = 8)
Total PNH RBC clone size (%)	(N = 4)	(N = 6)
Median (min, max)	40.05 (6.9, 68.1)	71.15 (21.2, 85.4)
Total PNH granulocyte clone size (%)		
Median (Min, max)	78.30 (36.8, 99.0)	91.60 (20.3, 97.6)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	2 (40.0)	2 (25.0)
Number of pRBC/whole blood transfusions within 12 months prior to first dose		
Total	10	2
Median (min, max)	5.0 (4, 6)	1.0 (1, 1)
Units of pRBC/whole blood transfused within 12 months prior to first dose		
Total	14	2
Median (min, max)	7.0 (3, 11)	2.0 (2, 2)
Patients with any PNH-associated conditions prior to informed consent, n (%)	5 (100)	8 (100)
Anemia	2 (40.0)	5 (62.5)
Hematuria or hemoglobinuria	2 (40.0)	5 (62.5)
Aplastic anemia	3 (60.0)	1 (12.5)
Renal failure	2 (40.0)	2 (25.0)
Other[a]	0	1 (12.5)
Pre-treatment LDH levels (U/L)		
Median (min, max)	588.50 (444, 2269.7)	251.50 (140.5, 487)

[a] Other PNH-associated conditions were reported as "renal and splenic infarcts" and "multiple lesions concerning for embolic process".

Note: Percentages were based on the total number of patients in each cohort.

Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell.

Based on body weight, patients received a loading dose of ravulizumab 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 provided immediate, complete, and sustained inhibition of terminal complement throughout the 26-week primary evaluation period regardless of prior experience with eculizumab. Following initiation of ravulizumab treatment, steady-state therapeutic serum concentrations of ravulizumab were achieved immediately after the first dose and maintained throughout the 26-week primary evaluation period in both cohorts. There were no breakthrough haemolysis events in the study and no patients had post-baseline free C5 levels above 0.5 µg/mL. Mean percent change from baseline in LDH was -47.91% on Day 183 in the complement inhibitor-naïve cohort and remained stable in the eculizumab-experienced cohort during the 26-week primary evaluation period. Sixty percent (3/5) of complement inhibitor-naïve patients and 75% (6/8) of eculizumab-experienced patients achieved haemoglobin stabilisation by Week 26 respectively. Transfusion-avoidance was reached by 84.6% (11/13) of patients during the 26-week primary evaluation period.

These interim efficacy results are presented in table 12 below.

Table 12: Interim efficacy outcomes from the Paediatric study in PNH patients (ALXN1210-PNH-304) - 26-week primary evaluation period

End Point	Ravulizumab (Naïve, N = 5)	Ravulizumab (Switch, N = 8)
LDH- Percent change from Baseline Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion Avoidance Percentage (95% CI)	60.0 (14.66, 94.73)	100.0 (63.06, 100.00)
Haemoglobin Stabilisation Percentage (95% CI)	60.0 (14.66, 94.73)	75 (34.91, 96.81)
Breakthrough Haemolysis (%)	0	0

Abbreviations: LDH = lactate dehydrogenase

Based on data from these interim results, the efficacy of ravulizumab in paediatric PNH patients appears to be similar to that observed in adult PNH patients.

Atypical haemolytic uremic syndrome (aHUS)
Use of Ultomiris in paediatric patients for treatment of aHUS is supported by evidence from one paediatric clinical study (a total of 31 patients with documented aHUS were enrolled; 28 patients aged 10 months to 17 years were included in the full analysis set).

Study in paediatric patients with aHUS

The paediatric study is a 26-week ongoing, multicentre, single arm, Phase 3 study conducted in paediatric patients.
A total of 21 eculizumab-naïve patients with documented diagnosis of aHUS and evidence of TMA were enrolled, of which 18 were included in the Full Analysis set. Enrolment criteria excluded patients presenting with TMA due to TTP and STEC-HUS. Two patients were given a single dose, and one patient received 2 doses, but then discontinued and were excluded from the full analysis set because aHUS was not confirmed. The overall mean weight at baseline was 22.2 kg; majority of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients (72.2%) had pretreatment extra renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 33.3% (n = 6) of patients had CKD Stage 5.

A total of 10 patients, who switched from eculizumab to ravulizumab, had documented diagnosis of aHUS and evidence of TMA were enrolled. Patients had to have clinical response to eculizumab prior to enrolment (i.e LDH < 1.5 X ULN and platelet count ≥ 150,000/μL, and eGFR > 30 mL/min/1.73m2). Consequently, there is no information on the use of ravulizumab in patient refractory to eculizumab.

Table 13 presents the baseline characteristics of the paediatric patients enrolled in Study ALXN1210-aHUS-312.

Table 13: Demographics and baseline characteristics in study ALXN1210-aHUS-312

Parameter	Statistics	Ravulizumab (Naïve, N = 18)	Ravulizumab (Switch, N = 10)
Age at time of first infusion (years) category	n (%)		
Birth to < 2 years		2 (11.1)	1 (10.0)
2 to < 6 years		9 (50.0)	1 (10.0)
6 to < 12 years		5 (27.8)	1 (10.0)
12 to < 18 years		2 (11.1)	7 (70.0)
Sex	n (%)		
Male		8 (44.4)	9 (90.0)

Race[a]	n (%)		
American Indian or Alaskan Native		1 (5.6)	0 (0.0)
Asian		5 (27.8)	4 (40.0)
Black or African American		3 (16.7)	1 (10.0)
White		9 (50.0)	5 (50.0)
Unknown		1 (5.6)	0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelets (10^9/L) blood	Median (min, max)	51.25 (14, 125)	281.75 (207, 415.5)
Haemoglobin (g/L)	Median (min, max)	74.25 (32, 106)	132.0 (114.5, 148)
LDH (U/L)	Median (min, max)	1963.0 (772, 4985)	206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2)	Median (min, max)	22.0 (10, 84)	99.75 (54, 136.5)
Required dialysis at baseline	n (%)	6 (33.3)	0 (0.0)

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

The primary endpoint was Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalisation of haematological parameters (platelet ≥ 150 x 10^9/L and LDH ≤ 246 U/L) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Complete TMA Response was observed in 14 of the 18 naïve patients (77.8%) during the 26-week initial evaluation period as shown in Table 14.

Table 14: Complete TMA response and complete TMA response components analysis during the 26-week initial evaluation period (ALXN1210-aHUS-312)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	18	14	0.778 (0.524, 0.936)
Components of Complete TMA Response			
Platelet count normalisation	18	17	0.944 (0.727, 0.999)
LDH normalisation	18	16	0.889 (0.653, 0.986)
≥ 25% improvement in serum creatinine from baseline	18	15	0.833 (0.586, 0.964)
Haematologic normalisation	18	16	0.889 (0.653, 0.986)

Note: 1 patient withdrew from study after receiving 2 doses of ravulizumab.
[a] 95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
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 (15 to 97 days). All patients with Complete TMA Response maintained it through the initial evaluation period with continuous improvements seen in renal function. An increase in mean platelet count was observed rapidly after commencement of ravulizumab, 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).

Three additional patients had a Complete TMA Response that was confirmed after the 26-week initial evaluation period (with a Complete TMA Response occurring at Days 291, 297 and 353).; thus, 17 of 18 (94.4%) paediatric patients (95% CI: 72.7%, 99.9%) had a Complete TMA Response. Individual component response increased to 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for platelet count normalisation, 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for LDH normalisation, and 17 of 18 (94.4%; 95% CI: 72.7%, 99.9%) patients for renal function improvement.

All 6 of the patients who required dialysis at study entry were able to discontinue dialysis; 5 of which had already done so by Day 43. No patient started dialysis during the study. The majority of the patient population (15/17), improved by 1 or more CKD stages by Day 183; 14 patients improved by 2 or more stages. Table 15 summarises the secondary efficacy results for Study ALXN1210-aHUS-312.

Table 15: Secondary efficacy outcome for study ALXN1210-aHUS-312

Parameters	Study ALXN1210-aHUS-312 (N = 18)	
Haematologic TMA parameters, Day 183	Observed value (n = 17)	Change from baseline (n = 17)
Platelets (10^9/L) blood		
Mean (SD)	304.94 (75.711)	245.59 (91.827)
Median	318.00	247.00
LDH (U/L) serum		
Mean (SD)	262.41 (59.995)	-2044.13 (1328.059)
Median	247.00	-1851.50
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/N	16/18	
proportion (95% CI)*	0.889 (0.653, 0.986)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	15/17	
Proportion (95% CI)*	0.882 (0.636, 0.985)	
Worsened[b]		
m/n	0/11	
Proportion (95% CI)*	0.000 (0.000, 0.285)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n = 17)	Change from baseline (n = 17)
Mean (SD)	108.5 (56.87)	85.4 (54.33)
Median	108.0	80.0

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 1 is considered the best category, while Stage 5 is considered the worst category. Baseline is derived based on the last available eGFR before starting treatment. Improved/Worsened: Compared to CKD stage at baseline.
*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper Pearson method.
[a] Improved excludes patients with Stage 1 at baseline, as they cannot improve; [b]worsened excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

In eculizumab-experienced patients, switching to ravulizumab maintained disease control as evidenced by stable hematologic and renal parameters, with no apparent impact on safety.

The efficacy of ravulizumab for the treatment of aHUS appears similar in paediatric and adult patients.

5.2 Pharmacokinetic properties

Absorption

Because the route of ravulizumab administration is an intravenous infusion and the dosage form is a solution, 100 % of the administered dose is considered bioavailable. The time to maximum observed concentration (t_{max}) is expected at the end of infusion (EOI) or soon after EOI. Therapeutic steady-state drug concentrations are reached after the first dose.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state for adult patients with PNH and adult and paediatric patients with aHUS on the studied weight-based dose regimen was 5.35 (0.92) L and 5.22 (1.85) L respectively.

Biotransformation and elimination

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in adult patients with PNH and adult and paediatric patients with aHUS are 49.7 (8.9) days and 0.08 (0.022) L/day and 51.8 (16.2) days and 0.08 (0.04) L/day, respectively.

Linearity/non-linearity

Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear pharmacokinetics (PK).

Special populations

Weight
Body weight is a significant covariate in patients with PNH and aHUS, resulting in lower exposures in heavier patients. Weight-based dosing is proposed in section 4.2, Table 1 and Table 2.

No formal trial of the effect of sex, race, age (geriatric), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on population-PK assessment no impact of sex, age, race and hepatic or renal function on ravulizumab PK was identified in the studied healthy volunteers, subjects and patients with PNH or aHUS, and as a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab have been studied in aHUS patients with a range of renal impairment including patients receiving dialysis. There have been no observed differences in pharmacokinetic parameters noted in these subpopulations of patients including patients with proteinuria.

5.3 Preclinical safety data

Animal reproductive toxicology studies have not been conducted with ravulizumab, 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 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 (approximately 4 times the maximum recommended human ravulizumab dose, based on a body weight comparison); however, the exposure did not increase foetal loss or neonatal death.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of ravulizumab.

Non-clinical data reveal no special hazard for humans based on nonclinical studies using a murine surrogate molecule, BB5.1, in mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Polysorbate 80
Arginine
Sucrose
Water for injections

Ultomiris 300 mg/30 mL concentrate for solution for infusion
Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Sodium chloride
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

18 months.

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 4 hours at room temperature.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

30 months.

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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C)
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pack size of one vial.

Ultomiris 300 mg/3 mL concentrate for solution for infusion

3 mL of sterile concentrate in a vial (Type I glass) with a stopper and a seal.

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion

11 mL of sterile concentrate in a vial (Type I glass) with a stopper and a seal.

Ultomiris 300 mg/30 mL concentrate for solution for infusion

30 mL of sterile concentrate in a vial (Type I glass) with a stopper and a seal.

6.6 Special precautions for disposal and other handling

Each vial is intended for single use only.

Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

This medicinal product requires dilution to a final concentration of 50 mg/mL.

Aseptic technique must be used.

Prepare Ultomiris concentrate for solution for infusion 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.
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 50 mg/mL.
5. The prepared solution should be administered immediately following preparation unless it is stored at 2 °C-8 °C. If stored at 2 °C-8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to the Table 3 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C – 8 °C or 4 hours at room temperature taking into account the expected infusion time.

Table 16: Loading dose administration reference table for Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	6	6	12
≥ 20 to < 30	900	9	9	18
≥ 30 to < 40	1,200	12	12	24
≥ 40 to < 60	2,400	24	24	48
≥ 60 to < 100	2,700	27	27	54
≥ 100	3,000	30	30	60

[a] Body weight at time of treatment.
[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

Table 17: Maintenance dose administration reference table for Ultomiris 300 mg/3 mL and 1,100 mg/11 mL concentrates for solution for infusion

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	6	6	12
≥ 20 to < 30	2,100	21	21	42
≥ 30 to < 40	2,700	27	27	54
≥ 40 to < 60	3,000	30	30	60
≥ 60 to < 100	3,300	33	33	66
≥ 100	3,600	36	36	72

[a] Body weight at time of treatment.
[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

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

Ultomiris 300 mg/30 mL concentrate for solution for infusion

This medicinal product requires dilution to a final concentration of 5 mg/mL.

Aseptic technique must be used.

Prepare Ultomiris concentrate for solution for infusion 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.
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 unless it is stored at 2 °C-8 °C. If stored at 2 °C-8 °C, allow the diluted solution to warm to room temperature prior to administration. Do not administer as an intravenous push or bolus injection. Refer to the Table 4 for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C – 8 °C or 6 hours at room temperature taking into account the expected infusion time.

Table 18: Loading dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight range (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	900	90	90	180
≥ 30 to < 40	1,200	120	120	240
⩾ 40 to < 60	2,400	240	240	480
⩾ 60 to < 100	2,700	270	270	540
⩾ 100	3,000	300	300	600

[a] Body weight at time of treatment.
[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

Table 19: Maintenance dose administration reference table for Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight range (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 10 to < 20	600	60	60	120
≥ 20 to < 30	2,100	210	210	420
≥ 30 to < 40	2,700	270	270	540
⩾ 40 to < 60	3,000	300	300	600
⩾ 60 to < 100	3,300	330	330	660
⩾ 100	3,600	360	360	720

[a] Body weight at time of treatment.
[b] Ultomiris should only be diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection.

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

7. MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105 rue Anatole France
92300 Levallois-Perret
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/001
EU/1/19/1371/002

EU/1/19/1371/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02 July 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM Diosynth Biotechnologies U.S.A., Inc.
6051 George Watts Hill Drive
Research Triangle Park, North Carolina 27709
UNITED STATES

Patheon Biologics LLC
4766 La Guardia Drive
St. Louis, Missouri 63134
UNITED STATES

Lonza Biologics Porriño, S.L.
C/ La Relba, s/n.
Porriño
Pontevedra 36400
SPAIN

Name and address of the manufacturer(s) responsible for batch release

Alexion Pharma International Operations Unlimited Company
Alexion Dublin Manufacturing Facility (ADMF)
College Business and Technology Park
Blanchardstown Road North
Dublin 15
IRELAND

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth A91 P9KD
IRELAND

Almac Pharma Services Limited
22 Seagoe Industrial Estate
Craigavon, Armagh BT63 5QD
UNITED KINGDOM

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch/use of Ultomiris in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programmes, including communication media, distribution modalities, and any other aspects of the programmes, with the National Competent Authority.

The educational and controlled distribution programmes are aimed at education and instruction of healthcare professionals/patients about the detection, careful monitoring, and/or proper management of selected safety concerns associated with Ultomiris.

The MAH shall ensure that in each Member State where Ultomiris is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use Ultomiris have access to/are provided with the following educational package to be disseminated through professional bodies:

- Physician educational material
- Patient/parent information pack

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

- **The Guide for healthcare professionals** shall contain the following key elements:
  - To address the safety concerns of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and haematological abnormalities in in PNH patients, use in pregnant and breast-feeding women.
  - Treatment with ravulizumab increases the risk of *N. meningitidis* infections.
  - All patients must be monitored for signs of meningitis.
  - The need for patients to be vaccinated against *N. meningitidis* two weeks prior to receiving ravulizumab and/or to receive antibiotic prophylaxis.

- The risk of immunogenicity and advice on post-infusion monitoring.
- The risk of developing antibodies to ravulizumab.
- No clinical data on exposed pregnancies is available. Ravulizumab should be given to a pregnant woman only if clearly needed. The need for effective contraception in women of childbearing potential during and up to eight months after treatment. Male patients should not father a child or donate sperm up to eight months after treatment. Breast-feeding should be discontinued during and up to eight months after treatment.
- Risk of serious haemolysis following ravulizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- Risk of severe TMA complications following ravulizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only).
- The need to explain to and ensure understanding of by patients:
  - the risk of treatment with ravulizumab (including potential risks of malignancies and haematologic abnormalities in PNH patients and serious infections)
  - the signs and symptoms of meningococcal infection and what action to take
  - the patient's/parent's guides and their contents
  - the need to carry the Patient card and to tell any healthcare practitioner that he/she is receiving treatment with ravulizumab
  - the requirement for pre-treatment vaccinations/antibiotic prophylaxis
  - the enrolment in the PNH and aHUS registries
- Details of the PNH registry, aHUS registry and how to enter patients

The patient/parent's information pack should contain:

- Package leaflet
- A patient guide
- A parent guide
- A Patient card

- **The patient guide** shall contain the following key messages:
  - To address the safety concerns of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and haematological abnormalities in PNH patients, use in pregnant and breast-feeding women.
  - Treatment with ravulizumab increases the risk of *N. meningitidis* infections.
  - Signs and symptoms of meningococcal infection and the need to obtain urgent medical care.
  - The patient alert card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with ravulizumab.
  - The importance of meningococcal vaccination prior to treatment and/or to receive antibiotic prophylaxis.
  - The risk of immunogenicity with ravulizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
  - The need for effective contraception in women of childbearing potential during and up to eight months after treatment, and that breast-feeding should be discontinued during and up to eight months after treatment. Male patients should not father a child or donate sperm up to eight months after treatment.
  - Risk of severe haemolysis following discontinuation/postponement of ravulizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administrations (PNH only).

- Risk of severe TMA complications following discontinuation/postponement of ravulizumab administration, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administration (aHUS only)
- Potential risks of severe, non-neisserial infections and malignancies and haematologic abnormalities in PNH patients treated with ravulizumab.
- Enrolment in the PNH and aHUS registries.

- **The parent guide** (provided together with patient guide) shall contain the following key messages:
  - To address the risks of meningococcal infection and serious infections in infants and children.
- **The Patient card** shall contain the following key messages:
  - Signs and symptoms of meningococcal infection
  - Warning to seek immediate medical care if above are present
  - Statement that the patient is receiving ravulizumab
  - Contact details where a healthcare professional can receive further information
  - Patient card should be retained for 8 months after last dose of ravulizumab

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense ravulizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on ravulizumab.

The MAH shall ensure that in each Member State where Ultomiris is marketed, a system aimed to control distribution of Ultomiris beyond the level of routine risk minimisation measures is in place. The following requirements need to be fulfilled before the product is dispensed:

- Submission of written confirmation of the patient`s vaccination against all available meningococcal infection serotypes *N. meningitidis* and/or prophylactic antibiotic treatment according to national vaccination guideline.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 300 mg/30 mL

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/30 mL concentrate for solution for infusion
ravulizumab
(10 mg/mL)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 30 mL contains 300 mg of ravulizumab.

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 5 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium chloride, polysorbate 80, and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 1,100 mg/11 mL (100 mg/mL) or Ultomiris 300 mg/3 mL (100 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 300 mg/30 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 300 mg/30 mL Sterile concentrate
ravulizumab
(10 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 1,100 mg/11 mL

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion
ravulizumab
(100 mg/mL)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 11 mL contains 1,100 mg of ravulizumab.

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 50 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 300 mg/30 mL (10 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 1,100 mg/11 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 1,100 mg/11 mL Sterile concentrate
ravulizumab
(100 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton Label 300 mg/3 mL

1. NAME OF THE MEDICINAL PRODUCT

Ultomiris 300 mg/3 mL concentrate for solution for infusion
ravulizumab
(100 mg/mL)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 3 mL contains 300 mg of ravulizumab.

After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the final concentration of the solution is 50 mg/mL.

3. LIST OF EXCIPIENTS

Sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose and water for injections.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.
Do not mix with Ultomiris 300 mg/30 mL (10 mg/mL).

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1371/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Single use Type I glass vial 300 mg/3 mL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ultomiris 300 mg/3 mL Sterile concentrate.
ravulizumab
(100 mg/mL)
IV after dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ultomiris 300 mg/30 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

2. What you need to know before you use Ultomiris

Do not use Ultomiris
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always 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 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

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 is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 2.65 g sodium (main component of cooking/table salt) in 720 mL at the maximal dose. This is equivalent to 133 % of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.

If you were previously receiving another medicine for PNH and aHUS called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20	600	600
20 to less than 30	900	2,100
30 to less than 40	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 2 hours.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
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 for PNH
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:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),
- 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 stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,
- Shortness of breath,

- Abdominal pain, diarrhoea, 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection/sepsis.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Nausea, diarrhoea,
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Fever (pyrexia), feeling tired (fatigue)

Common (may affect up to 1 in 10 people):
- Dizziness
- Abdominal pain, vomiting, stomach discomfort after meals (dyspepsia)
- Rash, itchy skin (pruritus)
- Back pain, joint pain (arthralgia), muscle pain (myalgia) and muscle spasms
- Influenza like illness, feeling tired (asthenia)
- Infusion related reaction

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Chills
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity
- Hives

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

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.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 6 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 300 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, sodium chloride, polysorbate 80, water for injections.

This medicine contains sodium (see section 2 “Ultomiris contains sodium”).

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (30 mL in a vial – pack size of 1).
Ultomiris is a clear to translucent, slight whitish colour, practically free from particles solution.

Marketing Authorisation Holder
Alexion Europe SAS
103-105, rue Anatole France
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France

Manufacturer
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Dublin 15 R925
Ireland

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris

1- How is Ultomiris supplied?
Each vial of Ultomiris contains 300 mg of active substance in 30 mL of product solution.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

2- Before administration
Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1,100 mg/11 mL concentrates for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 5 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)
≥ 10 to < 20	600	60	60	120	113 (1.9)
≥ 20 to < 30	900	90	90	180	86 (1.5)
≥ 30 to < 40	1,200	120	120	240	77 (1.3)
≥ 40 to < 60	2,400	240	240	480	114 (1.9)
≥ 60 to < 100	2,700	270	270	540	102 (1.7)
≥ 100	3,000	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 for injection

Table 2: 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)
≥ 10 to < 20	600	60	60	120	113 (1.9)
≥ 20 to < 30	2,100	210	210	420	194 (3.3)
≥ 30 to < 40	2,700	270	270	540	167 (2.8)
≥ 40 to < 60	3,000	300	300	600	140 (2.4)
≥ 60 to < 100	3,300	330	330	660	120 (2.0)
≥ 100	3,600	360	360	720	132 (2.2)

[a] Body weight at time of treatment
[b] Ultomiris should be only diluted using sodium chloride 9 mg/mL (0.9 %) solution for injection

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.

- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 6 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 2 hours using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2 °C–8 °C). Do not freeze. Store in the original package in order to protect from light.
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.

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

Package leaflet: Information for the user

Ultomiris 1,100 mg/11 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

2. What you need to know before you use Ultomiris

Do not use Ultomiris:
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always 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 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

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 is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 0.18 g sodium (main component of cooking/table salt) in 72 mL at the maximal dose. This is equivalent to 9.1% of the recommended maximum daily dietary intake of sodium for an adult.
You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be calculated by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.

If you were previously receiving another medicine for PNH and aHUS called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20	600	600
20 to less than 30	900	2,100
30 to less than 40	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 45 min.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
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 for PNH
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:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),
- 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 stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision

- Chest pain, or angina,
- Shortness of breath,
- Abdominal pain, diarrhoea, 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection/sepsis.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Nausea, diarrhoea,
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Fever (pyrexia), feeling tired (fatigue)

Common (may affect up to 1 in 10 people):
- Dizziness
- Abdominal pain, vomiting, stomach discomfort after meals (dyspepsia)
- Rash, itchy skin (pruritus)
- Back pain, joint pain (arthralgia), muscle pain (myalgia) and muscle spasms
- Influenza like illness, feeling tired (asthenia)
- Infusion related reaction

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Chills
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity
- Hives

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

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.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 4 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 1,100 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, water for injections

This medicine contains sodium (see section 2 "Ultomiris contains sodium").

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (11 mL in a vial – pack size of 1).
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

Marketing Authorisation Holder
Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

Manufacturer
Alexion Pharma International Operations Unlimited Company
Alexion Dublin Manufacturing Facility
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Blanchardstown Rd North
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Ireland

Almac Pharma Services (Ireland) Limited
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Almac Pharma Services Limited
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris

1- How is Ultomiris supplied?
Each vial of Ultomiris contains 1,100 mg of active substance in 11 mL of product solution.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

2- Before administration
Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 1,100 mg/11 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/30 mL concentrate for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.
- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 50 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	900	9	9	18	35 (0.6)
≥ 30 to < 40	1,200	12	12	24	31 (0.5)
≥ 40 to < 60	2,400	24	24	48	45 (0.8)
≥ 60 to < 100	2,700	27	27	54	35 (0.6)
≥ 100	3,000	30	30	60	25 (0.4)

[a] Body weight at time of treatment

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

Table 2: 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)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	2,100	21	21	42	75 (1.3)
≥ 30 to < 40	2,700	27	27	54	65 (1.1)
≥ 40 to < 60	3,000	30	30	60	55 (0.9)
≥ 60 to < 100	3,300	33	33	66	40 (0.7)
≥ 100	3,600	36	36	72	30 (0.5)

[a] Body weight at time of treatment

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

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 4 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 45 min using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2 °C–8 °C). Do not freeze. Store in the original package in order to protect from light.

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.

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

Package leaflet: Information for the user

Ultomiris 300 mg/3 mL concentrate for solution for infusion
ravulizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ultomiris is and what it is used for

What is Ultomiris
Ultomiris is a medicine that contains the active substance ravulizumab and it belongs to a class of medicines called monoclonal antibodies, that attach to a specific target in the body. Ravulizumab has been designed to attach to the C5 complement protein, which is a part of the body's defence system called the 'complement system'.

What is Ultomiris used for
Ultomiris is used to treat adult and children patients 10 kg and over with a disease called paroxysmal nocturnal haemoglobinuria (PNH), including patients untreated with complement inhibitor and patients who have received eculizumab for at least the past 6 months. In patients with PNH, the complement system is overactive and attacks their red blood cells, which can lead to low blood counts (anaemia), tiredness, difficulty in functioning, pain, abdominal pain, dark urine, shortness of breath, difficulty swallowing, erectile dysfunction and blood clots. By attaching to and blocking the C5 complement protein, this medicine can stop complement proteins from attacking red blood cells and so control symptoms of the disease.

Ultomiris is also used to treat patients 10 kg and over with a disease affecting the blood system and kidney called atypical haemolytic uremic syndrome (aHUS), including patients untreated with complement inhibitor and patients who have received eculizumab for at least 3 months. In patients with aHUS, their kidneys and blood vessels, including platelets, can be inflamed which can lead to low blood counts (thrombocytopenia and anaemia), reduced or lost kidney function, blood clots, tiredness and difficulty in functioning. Ultomiris can block the body's inflammatory response, and its ability to attack and destroy its own vulnerable blood vessels and so control symptoms of the disease including injury to the kidneys.

2. What you need to know before you use Ultomiris

Do not use Ultomiris:
- If you are allergic to ravulizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have not been vaccinated against meningococcal infection.
- If you have meningococcal infection.

Warnings and precautions
Talk to your doctor before using Ultomiris.

Meningococcal and other *Neisseria* infections symptoms
Because the medicine blocks the complement system, which is part of the body's defences against infection, the use of Ultomiris increases your risk of meningococcal infection caused by *Neisseria meningitidis*. These are severe infections affecting the linings of the brain and can spread throughout the blood and body (sepsis).

Consult your doctor before you start Ultomiris to be sure that you receive vaccination against *Neisseria meningitidis* at least 2 weeks before beginning therapy. If you cannot be vaccinated 2 weeks beforehand, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated. Ensure that your current meningococcal vaccination is up to date. You should also be aware that vaccination may not always 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 'Patient card' to carry with you at all times, listing relevant signs and symptoms of meningococcal infection/sepsis.
If you experience any of the following symptoms, you should immediately inform your doctor:
- headache with nausea or vomiting
- headache and fever
- headache with a stiff neck or stiff back
- fever
- fever and rash
- confusion
- muscle aches with flu-like symptoms
- eyes sensitive to light

Treatment for meningococcal infection while travelling

If you are travelling in a region where you are unable to contact your doctor or will be temporarily unable to receive medical treatment, your doctor may prescribe an antibiotic against *Neisseria meningitidis* to bring with you. If you experience any of the symptoms described above, you should take the course of antibiotics as prescribed. You should bear in mind that you should still see a doctor as soon as possible, even if you feel better after having taken the antibiotics.

Infections
Before starting Ultomiris, inform your doctor if you have any infections.

Infusion reactions
When Ultomiris is given, you may experience reactions to the infusion (drip) (infusion reaction) such as headache, lower back pain, and infusion-related pain. Some patients may experience allergic or hypersensitivity reactions (including anaphylaxis, a serious allergic reaction which causes difficulty breathing or dizziness).

Children and adolescents
Patients less than 18 years of age must be vaccinated against *Haemophilus influenzae* and pneumococcal infections.

Other medicines and Ultomiris
Tell your doctor or pharmacist if you are using or have recently used or might use any other medicines.

Pregnancy, breast-feeding, and fertility

Women of childbearing potential

The effects of the medicine on an unborn child are not known. Therefore, effective contraception during treatment and up to 8 months after treatment should be used in women who are able to get pregnant.

Pregnancy/ Breast-feeding

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 is not recommended during pregnancy and in women of childbearing potential not using contraception.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines.

Ultomiris contains sodium
Once diluted with sodium chloride 9 mg/mL (0.9%) solution for injection, this medicine contains 0.18 g sodium (main component of cooking/table salt) in 72 mL at the maximal dose. This is equivalent to 9.1% of the recommended maximum daily dietary intake of sodium for an adult. You should take this into consideration if you are on a controlled sodium diet.

3. How to use Ultomiris

At least 2 weeks before you start treatment with Ultomiris, your doctor will give you a vaccine against meningococcal infections if you have not previously had one or if your vaccination is outdated. If you cannot be vaccinated at least 2 weeks before you start treatment with Ultomiris, your doctor will prescribe antibiotics to reduce the risk of infection until 2 weeks after you have been vaccinated.
If your child is less than 18 years, your doctor will administer a vaccine (if not yet done) against *Haemophilus influenzae* and pneumococcal infections according to the national vaccination recommendations for each age group.

Instructions for proper use
Your dose of Ultomiris will be worked out by your doctor, based on your body weight, as shown in Table 1. Your first dose is called the loading dose. Two weeks after receiving your loading dose, you will be given a maintenance dose of Ultomiris, and this will then be repeated once every 8 weeks for patient above 20 kg and every 4 weeks for patient less than 20 kg.

If you were previously receiving another medicine for PNH and aHUS called eculizumab, the loading dose should be given 2 weeks after the last eculizumab infusion.

Table 1: Ultomiris weight-based dosing regimen

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)
10 to less than 20	600	600
20 to less than 30	900	2,100
30 to less than 40	1,200	2,700
40 to less than 60	2,400	3,000
60 to less than 100	2,700	3,300
above 100	3,000	3,600

Ultomiris is given by infusion (drip) into a vein. The infusion will take approximately 45 min.

If you receive more Ultomiris than you should
If you suspect that you have been accidentally given a higher dose of Ultomiris than prescribed, please contact your doctor for advice.

If you forget an appointment to receive Ultomiris
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 for PNH
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:
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- A significant fall in your red blood cell counts (anaemia),
- Dark urine,
- Fatigue,
- Abdominal pain,
- Shortness of breath,
- Difficulty swallowing,
- Erectile dysfunction (impotence),
- 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 stop using Ultomiris for aHUS
Interrupting or ending treatment with Ultomiris may cause your aHUS symptoms to come back. Your doctor will discuss the possible side effects with you and explain the risks. Your doctor will want to monitor you closely.

The risks of stopping Ultomiris include an increase in small blood vessel damage, which may cause:
- A significant fall in your platelets (thrombocytopenia),
- A significant rise in destruction of your red blood cells,
- An increase in your lactate dehydrogenase (LDH) levels, a laboratory marker of destruction of red blood cells,
- Decreased urination (problems with your kidneys),
- An increase in your serum creatinine level (problems with your kidneys),
- Confusion or change in how alert you are,
- Change in your vision
- Chest pain, or angina,

- Shortness of breath,
- Abdominal pain, diarrhoea, 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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Your doctor will discuss the possible side effects with you and explain the risks and benefits of Ultomiris with you prior to treatment.

The most serious side effect is meningococcal infection/sepsis.
If you experience any of the meningococcal infection symptoms (see section 2 Meningococcal infection symptoms), you should immediately inform your doctor.

If you are not sure what the side effects below are, ask your doctor to explain them to you.

Very common (may affect more than 1 in 10 people):
- Headache
- Nausea, diarrhoea,
- Upper respiratory tract infection
- Common cold (nasopharyngitis)
- Fever (pyrexia), feeling tired (fatigue)

Common (may affect up to 1 in 10 people):
- Dizziness
- Abdominal pain, vomiting, stomach discomfort after meals (dyspepsia)
- Rash, itchy skin (pruritus)
- Back pain, joint pain (arthralgia), muscle pain (myalgia) and muscle spasms
- Influenza like illness, feeling tired (asthenia)
- Infusion related reaction

Uncommon (may affect up to 1 in 100 people):
- Meningococcal infection
- Chills
- Serious allergic reaction which causes difficulty in breathing or dizziness (anaphylactic reaction), hypersensitivity
- Hives

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ultomiris

Keep this medicine out of the sight and reach of children.

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.

Store in the original package in order to protect from light.
After dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection, the medicine should be used immediately, or within 24 hours if refrigerated or within 4 hours at room temperature.

Do not throw away any medicines via wastewater. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ultomiris contains

- The active substance is ravulizumab. Each vial of solution contains 300 mg of ravulizumab.
- The other ingredients are: sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate, polysorbate 80, arginine, sucrose, water for injections

This medicine contains sodium (see section 2 “Ultomiris contains sodium”).

What Ultomiris looks like and contents of the pack
Ultomiris is presented as a concentrate for solution for infusion (3 mL in a vial – pack size of 1).
Ultomiris is a translucent, clear to yellowish colour, practically free from particles solution.

Marketing Authorisation Holder
Alexion Europe SAS
103-105, rue Anatole France
92300 Levallois-Perret
France

Manufacturer
Alexion Pharma International Operations Unlimited Company
Alexion Dublin Manufacturing Facility
College Business and Technology Park
Blanchardstown Rd North
Dublin 15 R925
Ireland

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth A91 P9KD
Ireland

Almac Pharma Services Limited
22 Seagoe Industrial Estate
Craigavon, Armagh BT63 5QD
United Kingdom

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Instructions for Use for Healthcare Professionals
Handling Ultomiris

1- How is Ultomiris supplied?

Each vial of Ultomiris contains 300 mg of active substance in 3 mL of product solution.

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

2- Before administration

Dilution should be performed in accordance with good practices rules, particularly for the respect of asepsis.

In the absence of compatibility studies, Ultomiris 300 mg/3 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/30 mL concentrate for solution for infusion.

Ultomiris should be prepared for administration by a qualified healthcare professional using aseptic technique.

- Visually inspect Ultomiris solution for particulate matter and discolouration.
- Withdraw the required amount of Ultomiris from the vial(s) using a sterile syringe.
- Transfer the recommended dose to an infusion bag.
- Dilute Ultomiris to a final concentration of 50 mg/mL (initial concentration divided by 2) by adding the appropriate amount of sodium chloride 9 mg/mL (0.9%) solution for injection to the infusion as per the instructions provided in table below.

Table 1: 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)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	900	9	9	18	35 (0.6)
≥ 30 to < 40	1,200	12	12	24	31 (0.5)
≥ 40 to < 60	2,400	24	24	48	45 (0.8)
≥ 60 to < 100	2,700	27	27	54	35 (0.6)
≥ 100	3,000	30	30	60	25 (0.4)

[a] Body weight at time of treatment

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

Table 2: 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)
≥ 10 to < 20	600	6	6	12	45 (0.8)
≥ 20 to < 30	2,100	21	21	42	75 (1.3)
≥ 30 to < 40	2,700	27	27	54	65 (1.1)
≥ 40 to < 60	3,000	30	30	60	55 (0.9)
≥ 60 to < 100	3,300	33	33	66	40 (0.7)
≥ 100	3,600	36	36	72	30 (0.5)

[a] Body weight at time of treatment

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

- Gently agitate the infusion bag containing the diluted Ultomiris solution to ensure thorough mixing of the medicinal product and diluent. Ultomiris should not be shaken.
- The diluted solution should be allowed to warm to room temperature (18 °C–25 °C) prior to administration by exposure to ambient air during approximately 30 min.
- The diluted solution must not be heated in a microwave or with any heat source other than the prevailing room temperature.
- Discard any unused portion left in a vial as the medicinal product contains no preservatives.
- The prepared solution should be administered immediately following preparation. Infusion must be administered through a 0.2 µm filter.
- If the medicinal product is not used immediately after dilution, storage times must not exceed 24 hours at 2 °C–8 °C or 4 hours at room temperature taking into account the expected infusion time.

3- Administration

- Do not administer Ultomiris as an intravenous push or bolus injection.
- Ultomiris should only be administered via intravenous infusion.
- The diluted solution of Ultomiris should be administered by intravenous infusion over approximately 45 min using a syringe-type pump or an infusion pump. It is not necessary to protect the diluted solution of Ultomiris from light during administration to the patient.

The patient should be monitored for one hour following infusion. If an adverse event occurs during the administration of Ultomiris, the infusion may be slowed or stopped at the discretion of the physician.

4- Special handling and storage

Store in a refrigerator (2 °C–8 °C). Do not freeze. Store in the original package in order to protect from light.

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.

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for ravulizumab, the scientific conclusions of CHMP are as follows:

In view of available data on urticaria from spontaneous reports including in some cases with a close temporal relationship, a positive re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between ravulizumab and urticaria is established. The PRAC concluded that the product information of products containing ravulizumab should be amended accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for ravulizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing ravulizumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.