Date: 16 September 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Ultomiris

International non-proprietary name: ravulizumab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength: 300 mg/30 ml

Route(s) of administration: intravenous use

Marketing Authorisation Holder: Alexion Pharma GmbH

Marketing Authorisation No.: 67278

Decision and Decision date: extension of therapeutic indication approved on 24.08.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a[decies] no. 1 of the TPA.
The Orphan Status was granted on 13 July 2020

Authorisation human medical product under Art. 13 TPA
The applicant requested a reduced assessment procedure in accordance with Art. 13 TPA.

Extension(s) of the therapeutic indication(s)
The applicant requested to add or change the indication in accordance with Article 23 TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Ultomiris is used in the treatment of patients with a body weight of 10 kg and over 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

2.2.2 Approved Indication

Ultomiris is used in the treatment of patients weighing 10 kg and over with atypical haemolytic uraemic syndrome (aHUS) who have not previously been treated with complement inhibitors (complement inhibitor-naïve patients) or have received eculizumab for at least 3 months, with evidence of a response to eculizumab.

2.2.3 Requested Dosage

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

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	2 December 2020
Formal control completed	31 December 2020
Predecision	29 April 2021
Answers to Predecision	12 May 2021
Labelling corrections	5 July 2021
Answers to Labelling corrections:	14 July 2021
Final Decision	24 August 2021
Decision	approval

Swissmedic has not assessed the primary data of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR refers to the publicly available Assessment Report Ultomiris, EMEA/H/C/004954/II/0002 dated 15 July 2020 issued by the European Medicines Agency EMA

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report Ultomiris, EMEA/H/C/004954/II/0002 dated 15 July 2020 issued by the European Medicines Agency EMA.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority European Medicines Agency EMA. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report Ultomiris, EMEA/H/C/004954/II/0002 dated 15 July 2020 issued by the European Medicines Agency EMA

4.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Appendix

6.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ultomiris, concentrate for solution for infusion was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ULTOMIRIS 300 MG/30 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

ULTOMIRIS 300 MG/3 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

ULTOMIRIS 1100 MG/11 ML, CONCENTRATE FOR SOLUTION FOR INFUSION

Composition

Active substances

Ravulizumab, produced from genetically modified ovarian cells from the Chinese hamster.

Excipients

Sodium dihydrogen phosphate monohydrate
Disodium phosphate heptahydrate
Ultomiris 300 mg/3 mL and 1100 mg/11 mL: L-arginine
Ultomiris 300 mg/3 mL and 1100 mg/11 mL: sucrose
Ultomiris 300 mg/30 mL: 115 mg sodium chloride per 30 mL vial
Ultomiris 300 mg/3 mL: 4.6 mg sodium chloride per 3 mL vial
Ultomiris 1100 mg/11 mL: 16.8 mg sodium chloride per 11 mL vial
Polysorbate 80
Water for injection q.s. to 30 mL

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
Ultomiris 300 mg/30 mL:
Clear to translucent solution, slight whitish colour, pH 7.0.
One 30 mL vial contains 300 mg of ravulizumab (10 mg/mL) and 115 mg of sodium.
After dilution, the final concentration of the solution to be infused is 5 mg/mL.
Ultomiris 300 mg/3 mL:
Translucent, clear to yellowish solution, pH 7.4.
One 3 mL vial contains 300 mg of ravulizumab (100 mg/mL) and 4.6 mg of sodium.
After dilution, the final concentration of the solution to be infused is 50 mg/mL.
Ultomiris 1100 mg/11 mL:
Translucent, clear to yellowish solution, pH 7.4.

One 11 mL vial contains 1100 mg of ravulizumab (100 mg/mL) and 16.8 mg of sodium.
After dilution, the final concentration of the solution to be infused is 50 mg/mL.

Indications/Uses

Ultomiris is used in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):
- in patients with haemolysis with one or more 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 "Properties/Effects").

Ultomiris is used in the treatment of patients weighing 10 kg and over with atypical haemolytic uraemic syndrome (aHUS) who have not previously been treated with complement inhibitors (complement inhibitor-naïve patients) or have received for eculizumab for at least 3 months, with evidence of a response to eculizumab.

Dosage/Administration ons

Ravulizumab must be administered by healthcare professionals and under the supervision of a physician experienced in the treatment of patients with haematological disorders or kidney diseases. In order to improve the traceability of bio-technological medicinal products, recording of the name and the batch number of each treatment is recommended.

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. In adult patients (≥ 18 years of age), the maintenance doses should be administered at 8-week intervals, starting 2 weeks after administration of the loading dose. The dosing regimen may occasionally vary by ± 7 days from 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 being switched from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion. Maintenance doses are then administered once every 8 weeks, starting 2 weeks after administration of the loading dose, as shown in Table 1.

Table 1: Ravulizumab weight-based dosing regimen

Body weight (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dose 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

*The maintenance dose is administered 2 weeks after the loading dose.

Ravulizumab has not been studied in patients with PNH who weigh less than 40 kg.

No clinical data are available for the concomitant use of ravulizumab and PE/PI (plasmapheresis or plasma exchange, or infusion of fresh frozen plasma). The use of PE/PI could reduce the serum ravulizumab levels.

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

In aHUS, treatment with ravulizumab should be administered for at least 6 months to eliminate the manifestations of thrombotic microangiopathy (TMA). After that, the duration of treatment should be decided individually for each patient. In patients who have a higher risk of recurrence of TMA, in the treating doctor’s opinion (or according to the clinical indication), long-term treatment may be necessary (see section “Warnings and precautions”).

Patients with impaired hepatic function

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.

Patients with impaired renal function

No dose adjustment is required for patients with renal impairment (see section "Pharmacokinetics").

Elderly patients

No dose adjustment is required for patients with PNH and aHUS aged 65 years and over. There is no evidence indicating that special precautions are required for treating geriatric patients. However, experience with ravulizumab in this patient population is still limited.

Children and adolescents

Atypical haemolytic uraemic syndrome (aHUS)
Children and adolescents with aHUS weighing ≥ 40 kg are treated according to the dosage recommendations for adults. Table 2 shows the doses and dose intervals calculated by body weight for children and adolescents weighing ≥ 10 kg to < 40 kg.

Table 2: Weight-based ravulizumab dosage regimen in children and adolescents weighing less than 40 kg

Body weight (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dose 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

*The maintenance dose is administered 2 weeks after the loading dose.

There is only limited evidence of the safety and efficacy of ravulizumab in patients weighing under 10 kg. The currently available data are described in section 4.8, but no dosage recommendations can be given for patients weighing under 10 kg.

Paroxysmal nocturnal haemoglobinuria (PNH)
The safety and efficacy of ravulizumab in children with PNH aged 0 to < 18 years have not been established. No data are available.

Mode 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.
As no compatibility studies have been conducted, Ultomiris 300 mg/30 mL concentrate for solution for infusion must not be mixed with Ultomiris 300 mg/3 mL or 1100 mg/11 mL concentrate for solution for infusion.

Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion
Ultomiris 100 mg/mL concentrate (vials of 3 mL and 11 mL) must be diluted to a final concentration of 50 mg/mL.
Ultomiris concentrate for solution for infusion in 3 mL and 11 mL vials (100 mg/mL) must be diluted before it is administered as an intravenous infusion using a syringe pump or infusion pump over a minimum period of 25 to 75 minutes (0.4 to 1.3 hours), depending on body weight; see Table 3 below.

Table 3: Infusion rate for doses of Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion

Body weight (kg)a	Loading dose (mg)	Minimum infusion time Minutes (hours)	Maintenance dose (mg)	Minimum infusion time Minutes (hours)
≥ 10 to < 20	600	45 (0.8)	600	45 (0.8)
≥ 20 to < 30	900	35 (0.6)	2100	75 (1.3)
≥ 30 to < 40	1200	31 (0.5)	2700	65 (1.1)
≥ 40 to < 60	2400	45 (0.8)	3000	55 (0.9)
≥ 60 to < 100	2700	35 (0.6)	3300	40 (0.7)
≥ 100	3000	25 (0.4)	3600	30 (0.5)

[a] Body weight at the time of treatment.

Ultomiris 300 mg/30 mL concentrate for solution for infusion
Ultomiris 10 mg/mL concentrate (vial of 30 mL) must be diluted to a final concentration of 5 mg/mL.
Ultomiris concentrate for solution for infusion in 30 mL vials (10 mg/mL) must be diluted before it is administered by intravenous infusion with a syringe pump or infusion pump over a minimum period of 77 to 194 minutes (1.3 to 3.3 hours), depending on body weight (see Table 4 below).

Table 4: Infusion rate for doses of Ultomiris 300 mg/30 mL concentrate for solution for infusion

Body weight[a] (kg)	Loading dose (mg)	Minimum duration of infusion Minutes (hours)	Maintenance dose (mg)	Minimum duration of infusion 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 "Instructions for handling".

Contraindications

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

Warnings and precautions

Serious meningococcal infection

Due to its mechanism of action, 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 starting treatment with ravulizumab. Patients who start 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 for prevention of the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to the official guidelines for vaccination use. If the patient is being switched from eculizumab treatment, physicians should verify that there is adequate protection against meningococcal disease according to the official guidelines for vaccination use.

Vaccination may not be sufficient to prevent meningococcal infection. Attention should be paid to official guidance on the appropriate use of antibiotics. 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 seek immediate medical care. Physicians should provide patients with the patient information brochure and patient safety card.

Immunisation

It is recommended that before the start of treatment with ravulizumab, patients with PNH and aHUS start their vaccinations according to the current vaccination guidelines.
Vaccination may further activate the 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. Patients should therefore be closely monitored for disease symptoms after the recommended vaccination.
Patients aged under 18 years must be vaccinated against *Haemophilus influenzae* and pneumococcal infections, with rigorous adherence 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; patients may therefore 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 observed.
Patients should be informed about potential serious infections and their symptoms. Physicians should advise patients about gonorrhoea prevention.

Infusion reactions

Administration of ravulizumab may result in infusion reactions. In clinical trials in PNH and aHUS, patients (4 out of 296 PNH patients and 4 out of 89 aHUS patients) experienced infusion reactions which were mild in severity and transient (e.g., lower back pain, drop in blood pressure, rise in blood pressure, limb symptoms, drug sensitivity [allergic reaction] and dysgeusia [altered sense of taste]). In cases of infusion reaction and signs of cardiovascular instability or respiratory compromise, the infusion of ravulizumab should be interrupted and appropriate supportive measures should be taken.

Discontinuation of treatment in PNH

If patients with PNH discontinue treatment with ravulizumab, they should be closely monitored for signs and symptoms of serious intravascular haemolysis. This is identified by elevated LDH (lactate dehydrogenase) levels along with the following: 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.

Patients who discontinue ravulizumab therapy should be monitored for at least 16 weeks for haemolysis and other reactions. If signs and symptoms of haemolysis occur after discontinuation, including elevated LDH, consideration should be given to restarting treatment with ravulizumab.

Discontinuation of treatment in aHUS

No specific data on the cessation of ravulizumab are available. In a long-term, prospective observational study, discontinuation of treatment with the complement C5 inhibitor (eculizumab) led to a 13.5 times higher rate of TMA recurrence, and there was a tendency towards a decline in kidney function compared with patients who continued the treatment.

If patients need to discontinue treatment with ravulizumab, they should be continuously and closely monitored for signs and symptoms of TMA. However, it is possible that monitoring is not sufficient for predicting or preventing serious TMA complications.

Complications of TMA after cessation of treatment can be identified by any of the following observations:

(i) At least two of the following laboratory findings are simultaneously present: a decrease of at least 25% in the platelet count from either the baseline count or the highest platelet count during ravulizumab treatment; increase of at least 25% in serum creatinine from the baseline value or from the lowest value during ravulizumab treatment; or increase of at least 25% in serum LDH from the baseline value or from the lowest value during ravulizumab treatment (the results should be confirmed by a second measurement) or

(ii) any of the following symptoms of TMA: change in mental state or seizures or other extrarenal manifestations of TMA, including cardiovascular abnormalities, pericarditis, gastrointestinal symptoms/diarrhoea or thrombosis.

If complications of TMA occur after cessation of ravulizumab, resumption of ravulizumab treatment with the loading and maintenance doses described in section 4.2 should be considered.

Patients with Shiga toxin-producing *E. coli* haemolytic uraemic syndrome (STEC-HUS)

No data are available on the use of Ultomiris in patients with STEC-HUS.

Sodium content

Ultomiris 300 mg/30 mL concentrate for solution for infusion

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

Ultomiris 300 mg/3 mL and 1100 mg/11 mL concentrate for solution for infusion

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

Interactions

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.

Pregnancy, lactation

Pregnancy

Women of child-bearing potential
Women of childbearing potential must use effective contraception methods during treatment and for up to 8 months afterwards.

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

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

Lactation

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 the young resulting from consuming milk from treated dams.

A risk to infants cannot be excluded.

Since many medicinal products and immunoglobulins are excreted 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 studies on fertility have been conducted with ravulizumab.

Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on the fertility of the treated females or males.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The most common adverse drug reactions (with the frequency statement “very common”) are diarrhoea, nausea, vomiting, nasopharyngitis and headache. The most serious adverse reactions in patients in clinical trials are meningococcal infections and meningococcal sepsis (see section "Warnings and precautions").

Tabulated list of adverse reactions

Table 5 gives the adverse reactions observed in clinical trials on PNH and aHUS.
Adverse reactions are listed by MedDRA system organ class 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 (frequency cannot be estimated from available data).

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

Table 5: Adverse reactions

MedDRA system organ class	Very common* (≥ 1/10)	Common (≥ 1/100, < 1/10)	Uncommon ((≥ 1/1000, < 1/100)
Infections and infestations	Infection of the upper respiratory tract (18.8%), nasopharyngitis (15.7%)		Meningococcal infection*
Nervous system disorders	Headache (34.5%)	Dizziness	
Gastrointestinal disorders	Diarrhoea, nausea	Abdominal pain, vomiting, dyspepsia	
Skin and subcutaneous tissue disorders		Rash, pruritus	
Musculoskeletal and connective tissue disorders		Arthralgia, back pain, myalgia, muscle spasms	
General disorders and administration site conditions	Fever, fatigue	Influenza-like illness, asthenia	Chills

Meningococcal infection covers the following group of preferred terms (PTs): meningococcal infection and meningococcal sepsis

Description of selected undesirable effects

Meningococcal infection/sepsis

Vaccination reduces, but does not eliminate, the risk of meningococcal infections. In clinical trials, 3 out of 261 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 clinical studies of aHUS, no meningococcal infections occurred in any of the 89 patients who received treatment with ravulizumab. Please refer to section "Warnings and precautions" for information on prevention and treatment of suspected meningococcal infection. Meningococcal infections in patients treated with ravulizumab presented as meningococcal sepsis. Patients should be informed of the signs and symptoms of meningococcal septicaemia and advised to seek immediate medical care.

Immunogenicity
Treatment with any therapeutic protein may induce an immune response. In PNH patient studies (N = 261) and in aHUS studies (N = 89), only two cases (0.57%) of development of treatment-related anti-drug antibody has been reported with ravulizumab. These anti-drug antibodies were transient in nature with low titre and did not correlate with clinical response or adverse events.

Children and adolescents
In children and adolescents with signs of aHUS (aged 10 months to under 18 years) who took part in the study ALXN1210-aHUS-312, the safety profile of ravulizumab seemed similar to that in adult patients with signs of aHUS. The safety profiles in the different paediatric age groups seem to be similar. The safety data for patients aged under 2 years are confined to four patients. The most commonly reported adverse effect in paediatric patients was fever (32.3%).
The safety of ravulizumab has not been proved in children with PNH aged 0 to < 18 years. No data are available.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.
Patients who experience overdose should have their infusion interrupted immediately and be closely monitored.

Properties/Effects

ATC-Code

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

Mechanism of action

Ravulizumab is a monoclonal antibody IgG2/4K 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 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.

Pharmacodynamics

Following ravulizumab treatment in patients with PNH not previously treated with complement-inhibitors and patients with PNH previously treated with eculizumab in Phase 3 trials, immediate and complete inhibition of serum free C5 (concentration of < 0.5 µg/mL) was observed by the end of the first infusion and sustained throughout the entire 26-week treatment period in all 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 with ravulizumab.
Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Clinical efficacy

Paroxysmal nocturnal haemoglobinuria
The safety and efficacy of ravulizumab in patients with PNH were assessed in two open-label, randomised, active-controlled Phase 3 trials:

- a trial in adult patients with PNH who had not previously received complement inhibitor treatment,
- a trial in patients with PNH who were clinically stable after having been treated with eculizumab for at least the previous 6 months.

Ravulizumab was administered in accordance with the recommended dosing regimen described in the section "Dosage/Administration" (4 infusions of ravulizumab over 26 weeks) while eculizumab was administered according to the approved dosing regimen for 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 start of treatment with ravulizumab or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.
There were no noteworthy differences in demographics or in characteristics present at start of the trial between the ravulizumab and eculizumab treatment groups in either of the Phase 3 trials. The 12-month transfusion history was similar between ravulizumab and eculizumab treatment groups within each of the Phase 3 trials.

Trial in patients with PNH who had not previously received complement inhibitor treatment
The trial of patients not previously treated with complement inhibitors was a 26-week multicentre open-label randomised active-controlled Phase 3 trial, conducted in 246 patients who had not received complement inhibitor treatment prior to study entry. Patients eligible for 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 transfusion due to PNH.

More than 80% of patients in both treatment groups had a history of transfusion within 12 months prior to study entry. The majority of the trial population from the trial with patients not previously treated with complement inhibitors was highly haemolytic at baseline; 86.2% of enrolled patients presented, in the setting of PNH, with elevated LDH ≥ 3 × ULN, a direct measurement of intravascular haemolysis.

Table 6 presents the baseline characteristics of the PNH patients enrolled in the trial of patients not previously treated with complement inhibitors. No apparent clinically meaningful differences were observed between the treatment arms.

Table 6: Baseline characteristics in trial of patients not previously treated with complement inhibitors

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 trial	Mean (SD) Median Min; Max.	44.8 (15.16) 43.0 18; 83	46.2 (16.24) 45.0 18; 86
Sex (n, %)	Male Female	65 (52.0) 60 (48.0)	69 (57.0) 52 (43.0)
Pre-treatment LDH	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0

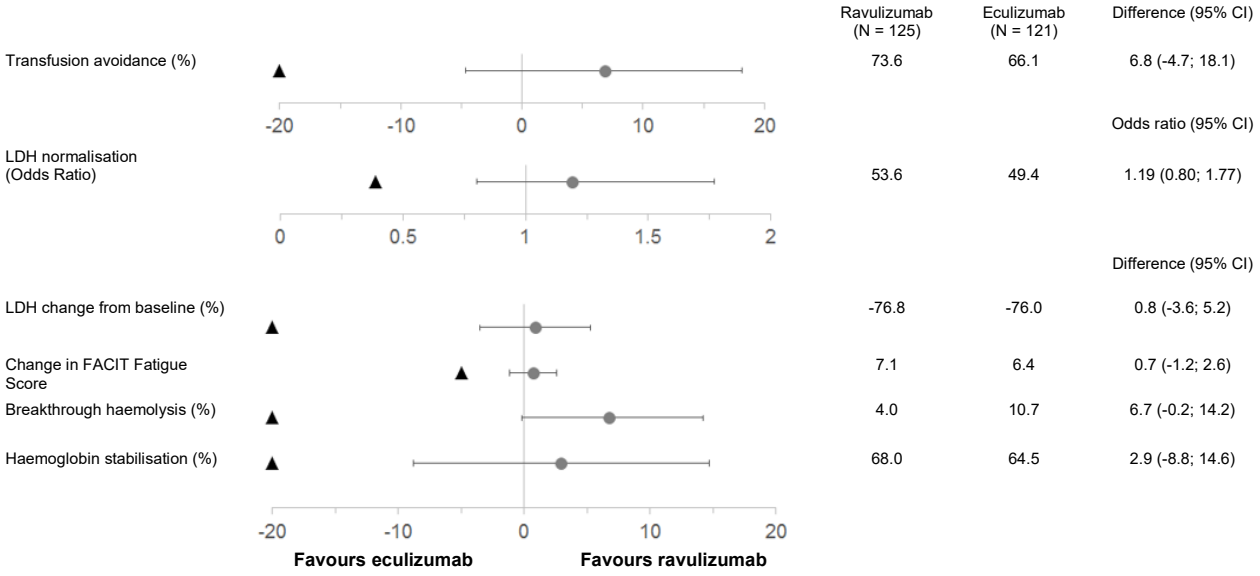
Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Number of patients with packed red blood cell transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
Units of packed red blood cells transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Total PNH red blood cell clone size	Median	33.6	34.2
Total PNH granulocyte clone size	Median	93.8	92.4
Patients with PNH-related symptoms and disorders[a] before trial start	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 symptoms and disorders.

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 percentage change from baseline in LDH levels, change in quality of life (FACIT Fatigue Score), the proportion of patients with breakthrough haemolysis and proportion of patients with stabilised haemoglobin.

Ravulizumab was non-inferior compared to eculizumab for both coprimary endpoints, avoidance of packed red blood cell transfusion in accordance with 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 (trial with patients not previously treated with complement inhibitors)



NB: Black triangles indicate the non-inferiority margins; grey dots indicate point estimates.
NB: LDH = lactate dehydrogenase; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy.

Trial of PNH patients previously treated with eculizumab

The trial of patients previously treated with eculizumab was a 26-week multicentre open-label randomised active-controlled Phase 3 trial conducted with 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.

The PNH medical history was similar for ravulizumab and eculizumab treatment groups. The 12-month transfusion history was similar for ravulizumab and eculizumab treatment groups and more than 87% of patients in both treatment groups had not received a transfusion within 12 months prior to study entry. The mean total PNH red blood cell 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 trial of patients previously treated with eculizumab. No apparent clinically meaningful differences were observed between the treatment arms.

Table 7: Baseline characteristics in trial of patients previously treated with eculizumab

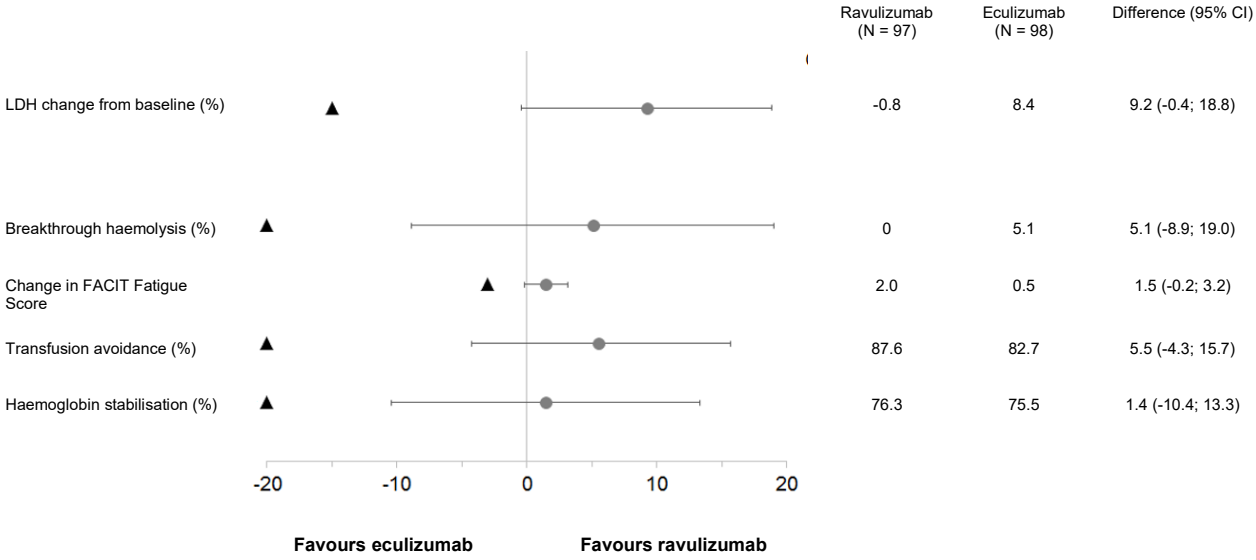
Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min; Max.	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in trial	Mean (SD) Median Min; Max.	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	50 (51.5) 47 (48.5)	48 (49.0) 50 (51.0)
Pre-treatment LDH	Mean (SD) Median	228.0 (48.71) 224.0	235.2 (49.71) 234.0
Number of patients with packed red blood cell/whole blood transfusions within 12 months prior to first dose	n (%)	13 (13.4)	12 (12.2)
Units of packed red blood cells/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 PNH-related symptoms and disorders[a] before trial start	n (%)	90 (92.8)	96 (98.0)
Anaemia		64 (66.0)	67 (68.4)
Haematuria or haemoglobinuria		47 (48.5)	48 (49.0)
Aplastic anaemia		34 (35.1)	39 (39.8)
Renal failure		11 (11.3)	7 (7.1)
Myelodysplastic syndrome		3 (3.1)	6 (6.1)
Pregnancy complication		4 (4.1)	9 (9.2)
Other[b]		14 (14.4)	14 (14.3)

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

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

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

Figure 2: Analysis of coprimary and secondary endpoints – full analysis set (trial with patients previously treated with eculizumab)



NB: Black triangles indicate the non-inferiority margins; grey dots indicate point estimates.
NB: LDH = lactate dehydrogenase; CI = confidence interval.

Atypical haemolytic uraemic syndrome (aHUS)

Study in adult patients with aHUS

The study in adults was a multicentre, single arm, phase 3 clinical study in patients with documented aHUS who had not had any treatment with a complement inhibitor prior to inclusion in this study and showed signs of thrombotic microangiopathy (TMA). The study consisted in a 26-week period for the first assessment, and the patients had the option of participating in an extension of up to 4.5 years.
A total of 58 patients with documented aHUS were included. The inclusion criteria excluded patients who had TMA resulting from thrombotic thrombocytopenic purpura (TTP) or Shiga toxin-producing *Escherichia coli* haemolytic uraemic syndrome (STEC-HUS). Two patients were excluded from the complete analysis set because of a confirmed diagnosis of STEC-HUS. At the start of the study, 93% of the patients showed extrarenal (cardiovascular, pulmonary, central nervous, gastrointestinal, cutaneous or musculoskeletal) signs or symptoms of aHUS.
Table 8 shows the demographic characteristics and baseline characteristics of 56 adult patients who were included in study ALXN1210-aHUS-311 and formed the complete analysis set.

Table 8: Baseline characteristics in the study in adults

Parameter	Statistics	Ravulizumab (N = 56)
Age at first infusion (years)	Mean (SD) Min., Max.	42.2 (14.98) 19.5; 76.6
Sex male	 n (%)	 19 (33.9)
Ethnicity a Asian White Other	n (%)	 15 (26.8) 29 (51.8) 12 (21.4)
History of transplant	n (%)	8 (14.3)
Platelet count (× 109/L)	n Median (min., max.)	56 95.25 (18; 473)
Blood haemoglobin (g/L)	n Median (min., max.)	56 85.00 (60.5; 140)
Serum LDH (U/L)	n Median (min., max.)	56 508.00 (229.5; 3,249)
eGFR (mL/min/1.73 m2)	n (%) Median (min., max.)	55 10.00 (4; 80)
Dialysis patients	N (%)	29 (51.8)
Post-partum patients	N (%)	8 (14.3)

Note: the percentages are based on the total number of patients.

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; Max. = maximum; Min. = minimum.

The primary endpoint was the complete response of the TMA during the 26-week period for the first assessment, proved by normalisation of the haematological parameters (platelet count ≥ 150 x 10^9/L and LDH ≤ 246 U/l) and an improvement in serum creatinine by ≥ 25% compared with the baseline value. Patients had to fulfil each criterion for a complete response of the TMA at 2 different assessments separated by an interval of at least 4 weeks (28 days) and at each measurement in between.

A complete response of the TMA was observed in 30 of the 56 patients (53.6%) during the 26-week period for the first assessment, as shown in Table 9.

Table 9: Analysis of the complete response of the TMA and the components of the complete response of the TMA during the 26-week period for the first assessment (ALXN1210-aHUS-311)

	Total	Responders	
		n	Fraction (95% CI)a
Complete response of the TMA	56	30	0.536 (0.396; 0.675)
Components of the complete response of the TMA			
Normalisation of the platelet count	56	47	0.839 (0.734; 0.944)
Normalisation of LDH	56	43	0.768 (0.648; 0.887)
≥25% improvement in the serum creatinine compared with baseline	56	33	0.589 (0.452; 0.727)
Normalisation of the blood values	56	41	0.732 (0.607; 0.857)

[a] The 95% CIs for the fraction were based on the asymptotic Gaussian approximation method with continuity correction.

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Four further patients showed a complete response of the TMA, which was confirmed after the 26-week period for the first assessment (the complete response of the TMA was observed on days 169, 302, 401 and 407). Thus, a total of 34 out of 56 patients showed a complete response of the TMA (60.7%; 95% CI: 47.0%, 74.4%). The number for the response of individual components increased to 48 patients (85.7%; 95% CI: 75.7%, 95.8%) for the normalisation of the platelet count, to 47 patients (83.9%; 95% CI: 73.4%, 94.4%) for the normalisation of LDH, and to 35 patients (62.5%; 95% CI: 48.9%, 76.1%) for improvement in kidney function.

A complete response of the TMA was achieved within a median period of 86 days (7 to 169 days). An increase in the mean platelet count was observed soon after the start of ravulizumab treatment, a rise from 118.52 × 10^9/L at the start of the study to 240.34 × 10^9/L on day 8 being observed. The value remained above 227 × 10^9/L at all subsequent visits during the period for the first assessment (26 weeks). Similarly, the mean LDH value decreased from the baseline value during the first 2 months of treatment, and the decrease was maintained throughout the period for the first assessment (26 weeks).

Of the patients who presented with stage 5 chronic kidney disease, 67.6% (23/34) showed an improvement in the chronic kidney disease of 1 or more stages. The stage of the chronic kidney disease continued to improve in many patients (19/30) after a complete response of the TMA was achieved during the 26-week period for the first assessment. Of the 29 patients who were dialysis-dependent at the time of inclusion in the study, 17 were able to discontinue dialysis treatment by the end of the available follow-up period, while 6 out of 27 patients who were not receiving any dialysis treatment at the start of the study were receiving dialysis treatment at the last available follow-up examination. Table 10 summarises the secondary efficacy results from study ALXN1210-aHUS-311.

Table 10: Secondary effficacy result for study ALXN1210-aHUS-311

Parameter	Study ALXN1210-aHUS-311 (N = 56)	
Haematological parameters in TMA, day 183 Platelet count (109/L) Mean (SD) Median Serum LDH (U/L) Mean (SD) Median	Observed value (n = 48) 237.96 (73.528) 232.00 194.46 (58.099) 176.50	Change from baseline (n = 48) 114.79 (105.568) 125.00 -519.83 (572.467) -310.75
≥ 20 g/L increase in haemoglobin from baseline with a confirmatory result by the end of the period for the first assessment m/n Fraction (95% CI)**	40/56 0.714 (0.587; 0.842)	
Change from baseline in CKD stage, day 183 Improvementa m/n Fraction (95% CI)* Deteriorationb m/n Fraction (95% CI)*	32/47 0.681 (0.529; 0.809) 2/13 0.154 (0.019; 0.454)	
eGFR (mL/min/1.73 m2), day 183 Mean (SD) Median	Observed value (n = 48) 51.83 (39.162) 40.00	Change from baseline (n = 47) 34.80 (35.454) 29.00

Note: n: number of patients with available data for a defined examination at the visit on day 183. m: number of patients who meet a defined criterion. The stage of the chronic kidney disease (CKD) is determined using the chronic kidney disease stage classification of the National Kidney Foundation. Stage 5 is the worst category, whereas stage 1 is the best category. The baseline value is determined using the last available eGFR before the start of treatment. Improvement/deterioration: compared with the CKD stage at the start of the study. *The 95% confidence intervals (95% CI) are based on the exact Clopper-Pearson confidence interval. [a]Excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them. [b]Excludes patients with stage 5 at the start of the study, as no deterioration is possible in them.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Safety and efficacy in paediatric patients

Paroxysmal nocturnal haemoglobinuria

Ultomiris has not been studied in paediatric patients with PNH.

Swissmedic, the Swiss regulator for medicinal products, has deferred the obligation to submit the results of trials with Ultomiris in one or more paediatric age groups for paroxysmal nocturnal haemoglobinuria (see section "Dosage/Administration" for information on use in children and teenagers).

Atypical haemolytic uraemic syndrome (aHUS)

The use of Ultomiris in paediatric patients for the treatment of aHUS is supported by the results of a clinical study in children and adolescents (in total, 31 patients with documented aHUS were included. 28 patients aged 10 months to 17 years were included in the complete analysis set).

Study in paediatric patients with aHUS

This paediatric study was a 26-week, continuous, multicentre, single arm, phase 3 study in children and adolescents.

In total, 21 patients without previous eculizumab treatment with the documented diagnosis of aHUS and evidence of TMA were included in the study; of these, 18 were included in the complete analysis set. The inclusion criteria excluded patients who had TMA resulting from TTP and STEC-HUS. Two patients received one single dose and one patient received two doses; the patients then stopped the treatment and were excluded from the complete analysis set, because the aHUS was not confirmed.

The mean body weight at the start of the study was 22.2 kg; the majority of the patients were in the weight category ≥ 10 to < 20 kg at the start of the study. Most patients (72.2%) showed extrarenal (cardiovascular, pulmonary, central nervous, gastrointestinal, cutaneous or musculoskeletal) signs or symptoms of aHUS before treatment at the start of the study. 33.3% (n = 6) of the patients had stage 5 CKD at the start of the study.

A total of 10 patients who were switching from eculizumab to ravulizumab and had a documented aHUS diagnosis and signs of TMA were included in the study. A clinical response to eculizumab had to be present before the patients were included in the study (i.e. LDH < 1.5 x ULN and platelet count ≥ 150,000/µL and eGFR > 30 mL/min/1.73 m^2). Consequently, there are no data on the use of ravulizumab in patients who do not respond to eculizumab.

Table 11 shows the baseline characteristics of paediatric patients who were included in study ALXN1210-aHUS-312.

Table 11: Demographic characteristics and baseline characteristics in study ALXN1210-aHUS-312

Parameter	Statistics	Ravulizumab (no previous treatment, N = 18)	Ravulizumab (treatment switch, N = 10)
Age group at first infusion (years) Birth to < 2 years 2 to < 6 years 6 to < 12 years 12 to < 18 years	n (%)	 2 (11.1) 9 (50.0) 5 (27.8) 2 (11.1)	 1 (10.0) 1 (10.0) 1 (10.0) 7 (70.0)
Sex male	n (%)	 8 (44.4)	 9 (90.0)
Ethnicitya Native American (Indian) or Alaskan Asian Black or African American White Unknown	n (%)	 1 (5.6) 5 (27.8) 3 (16.7) 9 (50.0) 1 (5.6)	 0 (0.0) 4 (40.0) 1 (10.0) 5 (50.0) 0 (0.0)
History of transplant	n (%)	1 (5.6)	1 (10.0)
Platelet count (× 109/L)	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.)	1,963.0 (772; 4,985)	206.5 (138.5; 356)
eGFR (mL/min/1.73 m2)	Median (min., max.)	22.0 (10; 84)	99.75 (54; 136.5)
Dialysis dependence at the start of the study	n (%)	6 (33.3)	0 (0.0)

Note: the percentages are based on the total number of patients.

[a] The patients may have several ethnicities.

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; Max. = maximum; Min. = minimum.

The primary endpoint was the complete response of the TMA during the 26-week period for the first assessment, determined on the basis of the normalisation of the haematological parameters (platelet count ≥ 150 x 10^9/L and LDH ≤ 246 U/l) and an improvement in serum creatinine by ≥ 25% compared with the baseline value. Patients had to fulfil all criteria for a complete response of the TMA at 2 different assessments separated by an interval of at least 4 weeks (28 days) and at each measurement in between.

A complete response of the TMA was observed during the 26-week period for the first assessment in 14 of the 18 patients without previous treatment (77.8%), as shown in Table 12.

Table 12: Complete response of the TMA and analysis of the components of the complete response of the TMA during the 26-week period for the first assessment (ALXN1210-aHUS-312)

	Total	Responders	
		n	Fraction (95% CI)a
Complete response of the TMA	18	14	0.778 (0.524; 0.936)
Components of the complete response of the TMA			
Normalisation of the platelet count	18	17	0.944 (0.727; 0.999)
Normalisation of LDH	18	16	0.889 (0.653; 0.986)
≥25% improvement in the serum creatinine compared with baseline	18	15	0.833 (0.586; 0.964)
Normalisiation of the blood values	18	16	0.889 (0.653; 0.986)

Note: 1 patient withdrew from the study after treatment with 2 doses of ravulizumab.
[a] The 95% confidence intervals (95% CI) for the fraction were based on the asymptotic Gaussian approximation method with continuity correction.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

The complete response of the TMA during the period for the first assessment was achieved in a median time of 30 days (15 to 97 days). In all patients with a complete response of the TMA, the response was maintained throughout the period for the first assessment, continuous improvements in kidney function being observed. After the start of the ravulizumab treatment, a rise in the mean platelet count was soon detectable, with an increase from 60.50 × 10^9/L at the start of the study to 296.67 × 10^9/L on day 8; it was above 296 × 10^9/L at all subsequent visits in the period for the first assessment (26 weeks).

Three further patients showed a complete response of the TMA, which was confirmed after the 26-week period for the first assessment (the complete response of the TMA was observed on days 291, 297 and 353). Thus, 17 of the 18 paediatric patients (94.4%) (95% CI: 72.7%; 99.9%) showed a complete response of the TMA. The response of individual components increased to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for the normalisation of the platelet count, to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for the normalisation of LDH, and to 17 of 18 patients (94.4%; 95% CI: 72.7%, 99.9%) for improvement in kidney function.

All 6 patients who were dialysis-dependent at inclusion in the study were able to discontinue the dialysis treatment. In five of these patients, this was possible on day 43 at the latest. No patient started dialysis treatment during the study. Most of the patient population (15/17) showed an improvement in the CKD of one or more stages by day 183; 14 patients showed an improvement of 2 or more stages. Table 13 summarises the secondary efficacy results for study ALXN1210-aHUS-312.

Table 13: Secondary efficacy results of study ALXN1210-aHUS-312

Parameter	Study ALXN1210-aHUS-312 (N = 18)	
Haematological parameters in TMA, day 183 Platelet count (109/L) Mean (SD) Median Serum LDH (U/L) Mean (SD) Median	Observed value (n = 17) 304.94 (75.711) 318.00 262.41 (59.995) 247.00	Change from baseline (n = 17) 245.59 (91.827) 247.00 -2,044.13 (1,328.059) -1,851.50
≥ 20 g/L increase in haemoglobin from baseline with confirmed result during the period for the first assessment m/N Fraction (95% CI)*	16/18 0.889 (0.653; 0.986)	
Change from baseline in CKD stage, day 183 Improvementa m/n Fraction (95% CI)* Deteriorationb m/n Fraction (95% CI)*	15/17 0.882 (0.636; 0.985) 0/11 0.000 (0.000; 0.285)	
eGFR (mL/min/1.73 m2), day 183 Mean (SD) Median	Observed value (n = 17) 108.5 (56.87) 108.00	Change from baseline (n = 17) 85.4 (54.33) 80.00

Note: n: number of patients with available data for a defined examination at the visit on day 183. m: number of patients who meet a defined criterion. The stage of the chronic kidney disease (CKD) is determined using the chronic kidney disease stage classification of the National Kidney Foundation. Stage 1 is regarded as the best category, whereas stage 5 is the worst category. The baseline value is determined using the last available eGFR before the start of treatment. Improvement/deterioration: compared with the CKD stage at the start of the study.

*The 95% confidence intervals (95% CI) are based on the exact Clopper-Pearson confidence interval.

[a] Improvement excludes patients with stage 1 CKD at the start of the study, because no improvement is possible in them.

[b] Deterioration excludes patients with stage 5 at the start of the study, as no deterioration is possible in them.

Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

In patients who were previously treated with eculizumab, the switch to ravulizumab led to maintenance of control of the disease, as can be seen from the stable haematological and renal parameters, without any evident impact on safety.

The efficacy of ravulizumab in the treatment of aHUS seems to be similar in paediatric patients to that in adult patients.

Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolised 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 naturally occurring amino acids and has no known active metabolites.

Elimination

The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with PNH and 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 range of dosing and dosing regimens, ravulizumab exhibited dose-proportional and time-linear pharmacokinetics (PK).

Kinetics in specific patient groups

Body weight

Body weight is a significant co-variable in patients with PNH and aHUS, which leads to lower bioavailability in heavier patients. Weight-based dosing is given in section "Dosage/Administration", Table 1.

No formal trial of the effect of sex, ethnic background, age (geriatric patients), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on a pharmacokinetic population analysis, no impact of sex, age, ethnic background and hepatic or renal function on the pharmacokinetic properties of ravulizumab was identified in the studied healthy volunteer subjects and patients with PNH or aHUS. As a result, no dosing adjustment is considered necessary.

The pharmacokinetics of ravulizumab were investigated in aHUS patients with different degrees of kidney function impairment, including dialysis-dependent patients. In these patient subpopulations, including patients with proteinuria, no differences in the pharmacokinetics were observed.

Preclinical 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 reproductive toxicology studies in mice using murine surrogate antibodies. 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.

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

Other information

Incompatibilities

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

Shelf life

The medicinal product may be used only up to the date marked with "EXP" on the container.

Shelf life after opening

Ultomiris 300 mg/3 mL and 1100 mg/11 mL

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 2–8 °C and up to 5 hours at room temperature.

Ultomiris 300 mg/30 mL
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 2–8 °C and up to 6 hours at room temperature.

Special precautions for storage

Store in a refrigerator (2–8ºC).
Do not freeze.
Keep the container in the outer carton to protect contents from light (and/or moisture).
Keep out of the reach of children.

For storage conditions after dilution of the medicinal product, see section "Shelf life after opening".

Instructions for handling

Each vial is intended for single use only.

Ultomiris 300 mg/3 mL and 1100 mg/11 mL
Ultomiris must be diluted to a final concentration of 50 mg/mL.
The usual aseptic conditions must be observed.

Prepare Ultomiris as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section "Dosage/Administration".
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. Mix the product carefully. Do not shake.
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 2–8 °C. If stored at 2–8 °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 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 2–8 °C or 5 hours at room temperature, taking into account the expected infusion time.

Table 14: Loading dose administration reference table for Ultomiris 300 mg/3 mL and 1100 mg/11 mL

Body weight (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 15: Maintenance dose administration reference table for Ultomiris 300 mg/3 mL and 1100 mg/11 mL

Body weight (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.

Ultomiris 300 mg/30 mL

Ultomiris must be diluted to a final concentration of 5 mg/mL.

The usual aseptic conditions must be observed.

Prepare Ultomiris as follows:

1. The number of vials to be diluted is determined based on the individual patient's weight and the prescribed dose, see section "Dosage/Administration".
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. Mix the product carefully. Do not shake.
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 2–8°C. If stored at 2–8°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 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 2–8°C or 6 hours at room temperature, taking into account the expected infusion time.

Table 16: Loading dose administration reference table for Ultomiris 300 mg/30 mL

Body weight (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 17: Maintenance dose administration reference table for Ultomiris 300 mg/30 mL

Body weight (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 national requirements.

Authorisation number

67278 (Swissmedic)

Packs

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

3 mL sterile concentrate in a type I glass vial contains 300 mg ravulizumab (A)

Ultomiris 1100 mg/11 mL (100 mg/mL) concentrate for solution for infusion

11 mL sterile concentrate in a type I glass vial contains 1100 mg ravulizumab (A)

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

30 mL sterile concentrate in a type I glass vial contains 300 mg ravulizumab (A)

Marketing authorisation holder

Alexion Pharma GmbH

Giesshübelstrasse 30

8045 Zurich

Switzerland

Date of revision of the text

May 2021