Date: 2 March 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ultomiris

International non-proprietary name: ravulizumabum
Pharmaceutical form: concentrate for solution for infusion
Dosage strength: 300 mg
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Alexion Pharma GmbH
Marketing Authorisation No: 67278
Decision and Decision date: approved on 20 January 2020

Note:

Assessment Report as adopted by Swissmedic with all information of 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 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 Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to 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

1 Terms, Definitions, Abbreviations 4
2 Background Information on the Procedure 5
2.1 Applicant's Request(s) 5
2.2 Indication and Dosage 5
2.2.1 Requested Indication 5
2.2.2 Approved Indication 5
2.2.3 Requested Dosage 5
2.2.4 Approved Dosage 6
2.3 Regulatory History (Milestones) 6
3 Quality Aspects 7
4 Nonclinical Aspects 7
5 Clinical and Clinical Pharmacology Aspects 7
6 Risk Management Plan Summary 7
7 Appendix 8
7.1 Approved Information for Healthcare Professionals 8

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 antibodies
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
Max	Maximum
MAH	Marketing Authorisation Holder
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PSP	Pediatric Study Plan (US-FDA)
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 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)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 19 September 2019.

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

2.2 Indication and Dosage

2.2.1 Requested Indication

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).

2.2.2 Approved Indication

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).

2.2.3 Requested Dosage

The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. Maintenance doses should be administered once every 8 weeks, starting 2 weeks after loading dose administration. The 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; subsequently, 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)
≥ 40 - < 60	2.400	3.000
≥ 60 - < 100	2.700	3.300
≥ 100	3.000	3.600

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

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

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 Warnings and precautions section).

Special populations

Elderly population (> 65 years old)

No dose adjustment is required for patients with PNH aged 65 years and over. There is no evidence indicating a need for special precautions 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 Pharmacokinetics section.

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

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

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	15 May 2019
Formal control completed	8 July 2019
Predecision	11 September 2019
Answers to Predecision	22 October 2019
Final Decision	20 January 2020
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/004954/0000, dated 26 April 2019 of 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 Quality Aspects

Swissmedic has not assessed the primary data relating to quality 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 quality aspects refers to the publicly available Assessment Report Ultomiris, EMEA/H/C/004954/0000, dated 26 April 2019 of the European Medicines Agency EMA.

4 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/004954/0000, dated 26 April 2019 of the European Medicines Agency EMA.

5 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 Ultomiris, EMEA/H/C/004954/0000, dated 26 April 2019 of the European Medicines Agency EMA.

6 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

7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Ultomiris 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 documents, which are valid and relevant for the effective and safe use of medicinal products in Switzerland, are 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, 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 hydrogen phosphate heptahydrate
Sodium chloride
Polysorbate 80
Water for injection q.s. to 30 mL
Corresp. to sodium 124.9 mg

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.
Clear to translucent solution, slight whitish colour, pH 7.0.
One 30 mL vial contains 300 mg of ravulizumab.
After dilution, the final concentration of the solution to be infused is 5 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").

Dosage/Administration

Ravulizumab must be administered by healthcare professionals and under the supervision of a physician experienced in the treatment of patients with haematological disorders.
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

The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in Table 1. 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 switching 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 range (kg)	Loading dose (mg)	Maintenance dose (mg)
≥ 40 to < 60	2,400	3,000
≥ 60 to < 100	2,700	3,300
≥ 100	3,000	3,600

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

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").

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 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

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.
Ultomiris must be diluted to a final concentration of 5 mg/mL.
This medicinal product must be administered through a 0.2 µm filter and should not be administered as an intravenous push or bolus injection.
Ultomiris must be diluted prior to administration by intravenous infusion over a minimum period of 1.7 to 2.4 hours depending on body weight (see Table 2 below).

Table 2: Infusion rate

Body weight range (kg)	Loading dose (mg)	Minimum duration of infusion Minutes (hours)	Maintenance dose (mg)	Minimum duration of infusion Minutes (hours)
≥ 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, 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 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

Vaccination may further activate the complement. As a result, patients with complement-mediated diseases, including PNH, 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.

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 reported in patients treated with other terminal complement inhibitors. 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, some patients with PNH experienced infusion reactions which were mild in severity and transient (e.g., lower back pain and drop in blood pressure). 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

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.

Sodium content

The maximum dose of this medicinal product when diluted with sodium chloride 9 mg/mL (0.9 %) solution for injection 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.

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 should use effective contraception methods during treatment and 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 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 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 are upper respiratory tract infections (very common), nasopharyngitis (very common) and headache (very common). 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 3 gives the adverse reactions observed from clinical trials.
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 3: Adverse reactions

MedDRA system organ class	**Very frequent* (≥ 1/10)**	**Frequent (≥ 1/100, < 1/10)**
Infections and parasitic diseases	Infection of the upper respiratory tract (18.8%), nasopharyngitis (15.7%)	Meningococcal infection**
Nervous system disorders	Headache (34.5%)	Dizziness

MedDRA system organ class	Very frequent* (≥ 1/10)	Frequent (≥ 1/100, < 1/10)
Gastrointestinal disorders		Vomiting, nausea, diarrhoea, abdominal pain, dyspepsia
Skin and subcutaneous tissue disorders		Rash, pruritus
Musculoskeletal, connective tissue and bone disorders		Back pain, arthralgia, myalgia, muscle spasms
General disorders and administration site conditions		Pyrexia, influenza-like illness, fatigue, chills, asthenia

* Clinical trials ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, ALXN1210-PNH-302
** Including 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. 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), only 1 (0.38%) case of development of treatment-related anti-drug antibody has been reported with ravulizumab. This anti-drug antibody was transient in nature with low titre and did not correlate with clinical response or adverse events.

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.
Free C5 levels less than 0.5 µg/mL were correlated with maximal intravascular haemolysis control and complete terminal complement inhibition.

Clinical efficacy

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 4 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 4: 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
Number of patients with packed red blood cell transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
	Total Mean (SD)	925 9.0 (7.74)	861 8.6 (7.90)

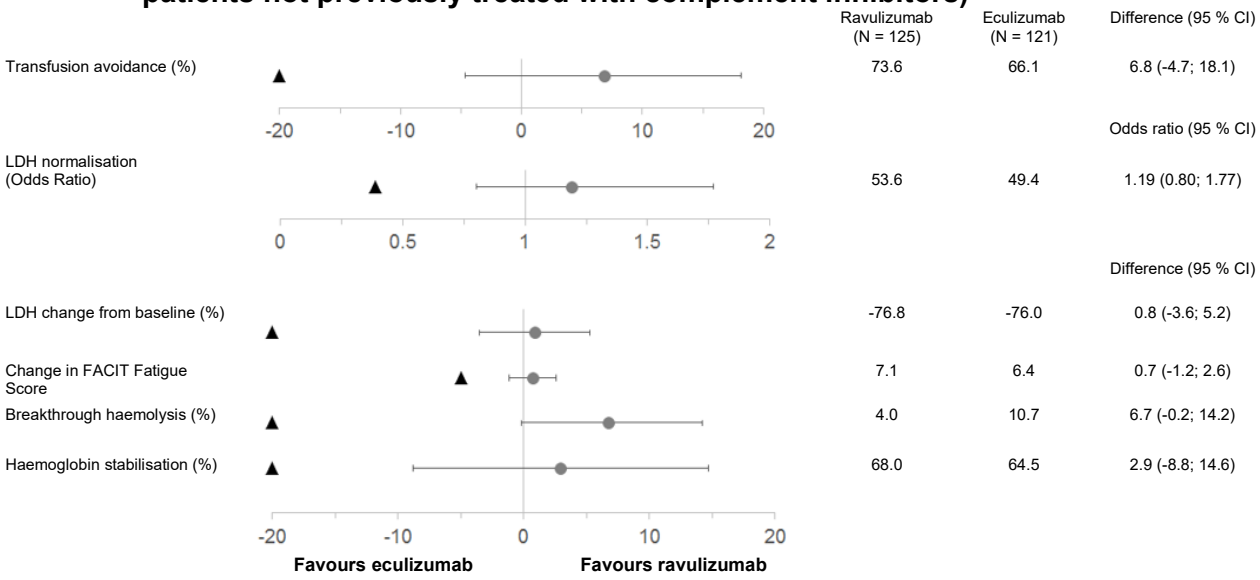
Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Units of packed red blood cells transfused within 12 months prior to first dose	Median	6.0	6.0
Total PNH red blood cell clone size	Median	33.6	34.2
Total PNH granulocyte clone size	Median	93.8	92.4
Patients with PNH-related symptoms and 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.

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 5 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 5: 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)

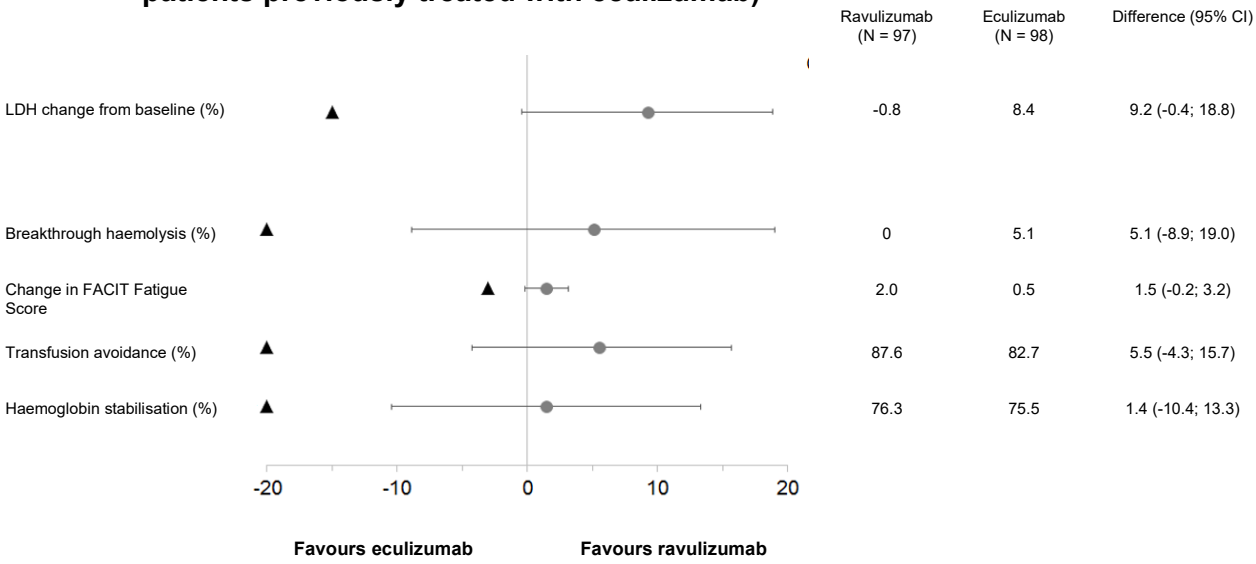
[a] Based on medical history.

[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.

Safety and efficacy in paediatric patients

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).

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 treated in accordance with the studied weight-based dose regimen was 5.34 (0.92) 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 are 49.7 (8.9) days and 0.003 (0.001) L/h, 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
When given the same dose, heavier patients with PNH had lower median serum ravulizumab concentrations compared to lighter 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. As a result, no dosing adjustment is considered necessary.

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

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 must be diluted to a final concentration of 5 mg/mL.
Aseptic precautions 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. The product should be mixed carefully. 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 2–8°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 the administration reference tables below for minimum infusion duration. Infusion must be administered through a 0.2 µm filter.
6. If the medicinal product is not used immediately after 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 6: Loading dose administration reference table

Body weight (kg)[a]	Loading dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 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 7: Maintenance dose administration reference table

Body weight (kg)[a]	Maintenance dose (mg)	Ultomiris volume (mL)	Volume of NaCl diluent[b] (mL)	Total volume (mL)
≥ 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

1 Vial (A)

Marketing authorisation holder

Alexion Pharma GmbH
Giesshübelstrasse 30

8045 Zurich

Switzerland

Date of revision of the text

September 2019