Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ravulizumab

Proprietary Product Name: Ultomiris

Sponsor: Alexion Pharmaceuticals Australasia Pty Ltd

November 2019

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
CMI	Consumer Medicine Information
CI	Confidence interval
CPD	Certified Product Details
CSR	Clinical study report
C5	Complement component 5
C5a	Complement component 5a
C5b	Complement component 5b
EMA	European Medicines Agency (EU)
EU	European Union
FcRn	Fc receptor
FDA	Food and Drug Administration (USA)
Hb	Haemoglobin
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IV	Intravenous
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAC	Membrane attacking complex
MI	Meningococcal infection
OR	Odds ratio
PD	Pharmacodynamic(s)
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal haemoglobinuria
PSUR	Periodic safety update report
RBC	Red blood cell
RMP	Risk management plan
SmPC	Summary Product Characteristics (EU)
TA	Transfusion avoidance
ULN	Upper limit of normal

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	8 October 2019
Date of entry onto ARTG:	17 October 2019
ARTG number:	311926
, *Black Triangle Scheme*	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Active ingredient:	Ravulizumab
Product name:	Ultomiris
Sponsor's name and address:	Alexion Pharmaceuticals Australasia Pty Ltd 20 Rodborough Road, Frenchs Forest NSW 2086
Dose form:	Injection, intravenous solution
Strength:	10 mg/mL
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Ultomiris is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).*
Route of administration:	Intravenous (IV)
Dosage:	The recommended dosing regimen for adult patients (≥ 18 years of age) with paroxysmal nocturnal haemoglobinuria (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. Maintenance doses should be administered at a once every 8 week interval, starting 2 weeks after loading dose administration. For further information refer to the Product Information

Product background

This AusPAR describes the application by Alexion Pharmaceuticals Austrasia Pty Ltd (the sponsor) to register the new biological entity ravulizumab as Ultomiris for the following indication:

> *Ultomiris is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).*

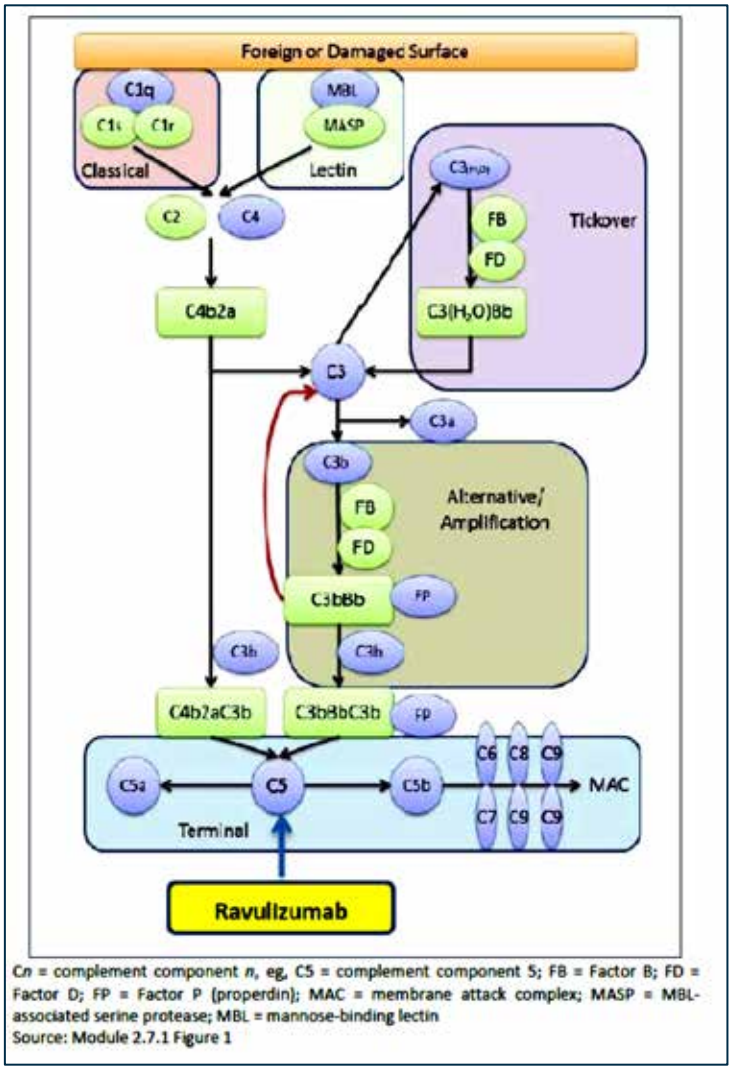
The sponsor has proposed the following dosage and administration:

> Weight based loading and maintenance doses. The maintenance doses are administered at 8-weekly intervals commencing 2 weeks after the loading dose.

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, debilitating and life threatening ultra-rare blood disorder characterised by haemolysis (destruction of red blood cells (RBC)) that is mediated by the uncontrolled activation of the complement system, a component of the body's immune system.

Ravulizumab a humanised antibody that specifically binds to the complement component 5 (C5) with high affinity, thereby inhibiting its cleavage to complement component 5a (C5a; the pro-inflammatory anaphylatoxin) and complement component 5b (C5b; the initiating subunit of the terminal complement complex (C5b-9, also known as the membrane attack complex (MAC))) preventing the generation of the C5b-9 or MAC (see Figure 1 for details). By binding specifically to C5, ravulizumab antagonises terminal complement-mediated inflammation, cell activation and cell lysis while preserving the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

Figure 1: Diagrammatic presentation of the effect of ravulizumab



Cn = complement component *n*, eg, C5 = complement component 5; FB = Factor B; FD = Factor D; FP = Factor P (properdin); MAC = membrane attack complex; MASP = MBL-associated serine protease; MBL = mannose-binding lectin
Source: Module 2.7.1 Figure 1

This action reduces complement mediated haemolysis in PNH as the disease is characterised by a lack of complement inhibitors (complement delay accelerating factor (CD55) and MAC inhibitory protein (CD59)) on cell surfaces and provides the clinical rationale for the use of Ultomiris in PNH.

Ravulizumab was specifically engineered to dissociate from C5 and associate with human neonatal Fc receptor (FcRn) at pH 6.0 (while minimising the impact in binding to C5 in intravascular space where the normal pH is 7.4). As a result, dissociation of antibody:C5 complexes in the acidified environment of the early endosome after pinocytosis is increased. Therefore, free antibody is recycled from the early endosome back into the vascular compartment by FcRn, resulting in an extended ravulizumab terminal elimination half-life.

The mechanism of action of ravulizumab is similar to eculizumab, an antibody which also binds to C5 to prevent activation of the complement cascade. Eculizumab (Soliris) is currently the only specific treatment for PNH on the Australian market. Eculizumab treatment requires frequent (biweekly) infusions which imposes a significant burden on patients.

The efficacy trials in this submission are non-inferiority comparisons against eculizumab.

Regulatory status

This is an application for a new chemical entity for Australian regulatory purposes.

Ravulizumab was approved for registration by the European Medicines Agency (EMA) in mid-2019, after the commencement of the Australian evaluation, and was approved for registration in the USA in December 2018. The EMA approval is conditional on the provision of the completed trials, Studies ALXN-1210-PHN-301 and 302 (referred to as Studies 301 and 302 respectively in this document).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table (Table 1) captures the key steps and dates for this application.

Table 1 Timeline for Submission PM-2018-05023-1-6

Description	Date
Submission dossier accepted and first round evaluation commenced	2 January 2019
First round evaluation completed	31 May 2019
Sponsor provides responses on questions raised in first round evaluation	27 June 2019
Second round evaluation completed	21 August 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	23 September 2019
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	8 October 2019
Completion of administrative activities and registration on ARTG	17 October 2019
Number of working days from submission dossier acceptance to registration decision*	180

*Statutory timeframe for standard applications is 255 working days.

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

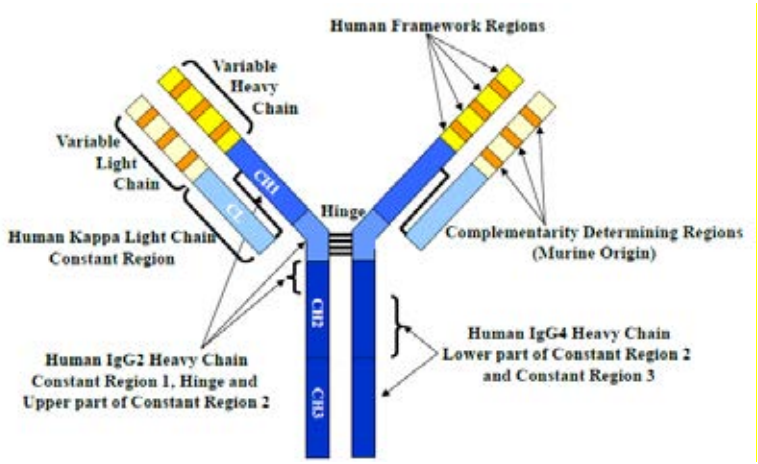
Quality

Structure

Ravulizumab is a recombinant humanised immunoglobulin (Ig) G2/4 monoclonal antibody (mAb) consisting of two identical heavy chains and two identical light chains linked by disulphide bonds (see Figure 2). The recombinant protein is expressed in Chinese hamster ovary cells.

The theoretical molecular weight is 148 kilo Dalton.

Figure 2: Structure of ravulizumab



Physical and chemical properties

The ravulizumab drug substance is a clear to translucent, slight whitish colour practically free from particles solution with a pH of 6.7 to 7.3.

The molecule is a humanised IgG2/4 kappa antibody consisting of two identical 448 amino acid heavy chains and two identical 214 amino acid light chains. The constant regions of ravulizumab include the human kappa light chain constant region and the chimeric human IgG2/G4 heavy chain constant region. The heavy chain CH1 domain, hinge region and the first 5 amino acids of the CH2 domain match human IgG2 amino acid sequence, residues 6 to 36 in the CH2 region are common to both human IgG2 and IgG4 amino acid sequence, while the remainder of the CH2 domain and the CH3 domain match human IgG4 amino acid sequence. The heavy and light chain variable regions that form the human C5 binding site consist of human framework regions grafted to murine complementarity-determining regions.

Biological properties

Ravulizumab is constructed by introducing four unique mutations into the heavy chain of eculizumab. These mutations increase the dissociation of ravulizumab:C5 complexes to free ravulizumab in the acidic environment of the early endosome increasing the fraction of free ravulizumab recycled from the early endosome back into the vascular compartment by FcRn thus extending the serum half-life of ravulizumab. Consequently, the increase in serum half-life translates to an extended patient dosing interval of 8 weeks

compared to eculizumab (biweekly) and therefore reduces the treatment burden for patients with PNH.

Manufacture

In process control testing and in process acceptance criteria testing are performed during drug substance manufacture. All manufacturing steps and analytical procedures of the drug substance are validated.

There are no issues pertaining to manufacture or manufacturer of the drug product.

Stability

Drug product

The sponsor proposed shelf life is 30 months at 2 to 8°C and protected from light.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product and a shelf life and the data supports a shelf life of 30 months stored at 2 to 8°C. Photostability data demonstrates that the product is not photostable and it is recommended that the product is stored protected from light.

Stability studies have been conducted in accordance with relevant International Council for Harmonisation (ICH) guidelines for the Technical Requirements for Pharmaceuticals for Human Use.

There are no outstanding issues pertaining to stability of the drug substance and drug product.

There are no objections to the registration of this product from sterility; endotoxin, container safety and viral safety related aspects.

Recommendation to the Delegate

There are no objections on quality grounds to the approval of Ultomiris ravulizumab 10 mg/mL concentrated solution for intravenous infusion. The following conditions of registration are recommended.

Proposed conditions of registration

Batch release testing and compliance with Certified Product Details (CPD)

- It is a condition of registration that all batches of Ultomiris ravulizumab 10 mg/mL imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- It is a condition of registration that each batch of Ultomiris ravulizumab 10 mg/mL imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.
- The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

- This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [(http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Nonclinical

The toxicology assessment noted that ravulizumab is highly related to eculizumab, but has higher affinity for the target at low pH (6.0) which promotes recycling of endocytosed antigen back into the vascular compartment. This increases the circulating half-life for ravulizumab and allows for the extended dosing interval compared to eculizumab.

Ravulizumab only recognises human C5 antigen and so direct trials in laboratory animals were not possible. Studies were performed in mice using a murine surrogate antibody. This did not indicate any safety or toxicity issues at 26 weeks.

The nonclinical evaluator concluded that there were no issues identified to preclude registration of ravulizumab pending amendments to the draft PI document the details of which are beyond the scope of this AusPAR.

Clinical

Pharmacology

Pharmacokinetics (PK) was examined in five studies, three of which were in healthy volunteers and two of which were in patients with PNH. Population pharmacokinetic analysis indicated that steady-state concentrations were achieved after an initial loading dose and sustained with an 8 weekly dosing interval. Plasma concentrations were dose proportional across then range studied (200 to 5400 mg) up to 12 weeks of therapy (see Table 2).

Table 2: Pharmacokinetic parameters for ravulizumab in healthy volunteers and PNH patients

Parameter		Healthy Volunteer (N = 38)	PNH Patient (N = 261)
CL (L/h)	Mean (SD)	0.00374 (0.000654)	0.00352 (0.00107)
	Geometric Mean (CV%)	0.00369 (17.4%)	0.00337 (29.9%)
	Median	0.00375	0.00335
	[2.5th – 97.5th percentile	[0.00275 – 0.00513]	[0.00199 – 0.00607]
Q (L/h)	Mean (SD)	0.0154 (0.00186)	0.0158 (0.00232)
	Geometric Mean (CV%)	0.0153 (12.0%)	0.0157 (14.7%)
	Median	0.0147	0.0158
	[2.5th – 97.5th percentile	[0.0128 – 0.0188]	[0.0118 – 0.0203]
Vc (L)	Mean (SD)	2.90 (0.475)	3.46 (0.651)
	Geometric Mean (CV%)	2.86 (16.7%)	3.40 (19.3%)
	Median	2.84	3.44
	[2.5th – 97.5th percentile	[2.22 – 3.78]	[2.36 – 4.78]
Vp (L)	Mean (SD)	1.88 (0.303)	1.93 (0.322)
	Geometric Mean (CV%)	1.85 (15.9%)	1.90 (16.9%)
	Median	1.75	1.90
	[2.5th – 97.5th percentile	[1.44 – 2.38]	[1.40 – 2.55]
Vss (L)	Mean (SD)	4.77 (0.741)	5.39 (0.915)
	Geometric Mean (CV%)	4.72 (15.6%)	5.31 (17.3%)
	Median	4.66	5.39
	[2.5th – 97.5th percentile	[3.67 – 6.11]	[3.78 – 7.16]
$t_{1/2\alpha}$ (days)	Mean (SD)	2.04 (0.104)	2.18 (0.138)
	Geometric Mean (CV%)	2.04 (5.1%)	2.18 (6.4%)
	Median	2.05	2.18
	[2.5th – 97.5th percentile	[1.87 – 2.26]	[1.90 – 2.47]
$t_{1/2\beta}$ (days)	Mean (SD)	38.6 (3.68)	47.8 (9.59)
	Geometric Mean (CV%)	38.4 (9.8%)	46.9 (20.5%)
	Median	39.1	47.2
	[2.5th – 97.5th percentile	[31.0 – 45.1]	[30.8 – 65.9]

CL = clearance; Q = intercompartmental clearance; Vc=volume of distribution in the central compartment; Vp=volume of distribution in the peripheral compartment; Vss = total volume of distribution; $t_{1/2\alpha}$ = distribution half-life, $t_{1/2\beta}$ = terminal elimination half-life.
Source: PopPK/PD report Appendix 3, Table 121.2

There was no relevant difference in pharmacokinetic variables between healthy volunteers and patients with PNH.

No specific studies were performed on drug interactions or in special populations.

A number of pharmacodynamic (PD) endpoints were examined in the efficacy studies. These included free C5 concentration, serum lactate dehydrogenase (LDH) concentration, and in vitro chicken RBC haemolysis. These all indicated improvements in patients receiving ravulizumab compared to their baseline.

Efficacy

Two pivotal studies, Studies ALXN1210-PNH-301 (Study 301) and ALXN1210-PNH-302 (Study 302) examined the efficacy of ravulizumab in treatment naïve and eculizumab treated patients respectively. Both trials were non-inferiority comparisons with eculizumab. A summary of the endpoints in the two studies are detailed in Table 3 below.

Table 3: Summary of endpoints in pivotal efficacy trials[1]

Study	Endpoint	Statistic for Treatment Comparison	NIM	Eculizumab Effect Preserved
ALXN1210-PNH-301	**Coprimary**			
	% Transfusion Avoidance	Difference in rate	-20%[a]	50%
	Normalization of LDH levels	Odds ratio	0.39[b,c]	50%
	Key Secondary			
	% Change in LDH	Difference in % change	20%[c]	75%
	Change in FACIT-Fatigue	Difference in change	-5[c]	50%
	% Breakthrough Haemolysis	Difference in rate	20%[c,d]	70%
	% Haemoglobin Stabilization	Difference in rate	-20%[c]	50%
ALXN1210-PNH-302	**Primary**			
	% Change in LDH	Difference in % change	15%[a]	89%
	Key Secondary			
	% Breakthrough Haemolysis	Difference in rate	20%[a,c]	51%
	Change in FACIT-Fatigue	Difference in change	-3[c]	50%
	% Transfusion Avoidance	Difference in rate	-20%[a]	60%
	% Haemoglobin Stabilization	Difference in rate	-20%[a]	56%

Note: The endpoints are presented in hierarchical testing order for non-inferiority (additional testing order for superiority is detailed in the SAP for each study).

[a] PNH Registry data were used to assess the non-inferiority margin (NIM).

[b] An NIM of 0.39 on the odds ratio scale which was derived from TRIUMPH clinical trial data where LDH-N was calculated to be 0.42 for eculizumab and 0.10 for placebo.

[c] TRIUMPH study data were used to assess NIM for Study ALXN1210-PNH-301. TRIUMPH and/or PNH registry data were used to assess NIM for Study ALXN1210-PNH-302.

[d] Phase 3 definition of breakthrough cannot be fully replicated in TRIUMPH due to incomplete collection of symptoms. NIM was established using LDH data from TRIUMPH and clinical judgment.

Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; NIM = non-inferiority margin; PNH = paroxysmal nocturnal haemoglobinuria; SAP = statistical analysis plan

Study 301

This study enrolled 214 patients randomised 1:1 to receive ravulizumab or eculizumab over a 26 week period of randomised therapy, followed by an open extension period of up to 2 years (ongoing). Enrolled patients were adults with PNH who had not received complement inhibitor therapy (eculizumab or ravulizumab) prior to the trial. The primary endpoints of the study were:

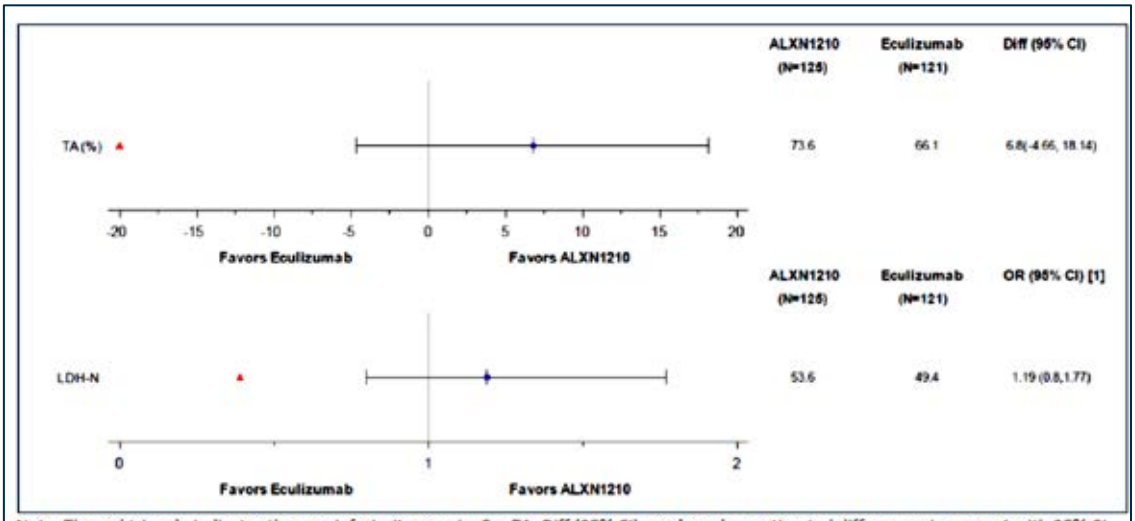
- transfusion avoidance (TA); and
- haemolysis.

TA was defined as the proportion of patients who remain transfusion free and do not require a RBC transfusion at Week 26. The need for transfusion was defined as haemoglobin (Hb) < 9 g/dL with symptoms; or < 7 g/dL regardless of symptoms. Haemolysis was measured through normalisation of plasma LDH.

Some 73.6% and 66.1% of the patients on ravulizumab and eculizumab respectively remained transfusion free over 26 weeks; a difference of 6.8% (95% confidence interval (CI) -4.66 to 18.14%) (see Figure 3). The prevalence of normalised LDH levels was 0.536 and 0.494 in the ravulizumab and eculizumab treated patients respectively; an odds ratio (OR) of 1.18 (95%CI 0.796 to 17.769) in favour of ravulizumab.

[1] European Public Assessment Report (EPAR) for Ultomiris https://www.ema.europa.eu/en/documents/assessment-report/ultomiris-epar-public-assessment-report_en.pdf

Figure 3: Comparative efficacy for primary endpoints in Study 301



Note: The red triangle indicates the non-inferiority margin. For TA, Diff (95% CI) was based on estimated differences in percent with 95% CI. For LDH-N, adjusted prevalence within each treatment was displayed. Treatment difference was estimated for ALXN1210 - eculizumab.

[1] To calculate the OR of ALXN1210 relative to eculizumab from the displayed adjusted prevalence rates, divide the odds of LDH-N on ALXN1210 (0.536/[1-0.536]) by the odds of LDH-N on eculizumab (0.494/[1-0.494]).

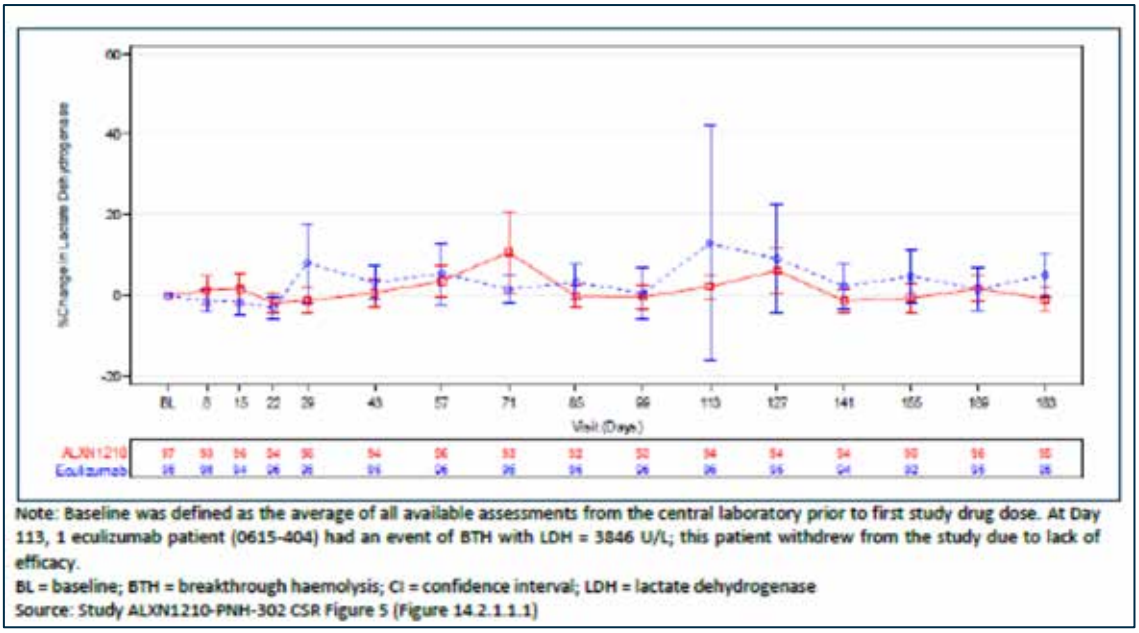
CI = confidence interval; Diff = difference; TA = transfusion avoidance; LDH-N = lactate dehydrogenase normalisation; OR = odds ratio

Source: Study ALXN1210-PNH-301 CSR Figure 4 (Figure 14.2.1.1.1)

Study 302

This was a similar 26 week study in which 208 patients were enrolled a randomised 1:1 to receive ravulizumab or eculizumab. Enrolled patients were stable (LDH < 1.5 upper limit of normal (ULN)) after six months of therapy with eculizumab. The primary endpoint was the percent change in LDH from Baseline (see Figure 4).

Figure 4: Change in LDH over treatment period for comparator therapies



Note: Baseline was defined as the average of all available assessments from the central laboratory prior to first study drug dose. At Day 113, 1 eculizumab patient (0615-404) had an event of BTH with LDH = 3846 U/L; this patient withdrew from the study due to lack of efficacy.

BL = baseline; BTH = breakthrough haemolysis; CI = confidence interval; LDH = lactate dehydrogenase

Source: Study ALXN1210-PNH-302 CSR Figure 5 (Figure 14.2.1.1.1)

Analysis of the LDH levels over the treatment period indicated non-inferiority to eculizumab; with a treatment difference of -9.21% (95% CI -18.84 to 0.42%) in favour of ravulizumab.

Safety

Safety data was primarily provided through the pivotal trials (detailed in Table 4).

Table 4: Summary of safety populations in submitted trials

Study Number	Number of Ravulizumab-treated Patients Contributing to the Safety Data	Clinical Database cutoff	Number of Pooled Patients Treated with Ravulizumab	Pooled Duration of Treatment with Ravulizumab
ALXN1210-PNH-301	125	26 weeks[a]	261 patients*	176.9 patient-years
ALXN1210-PNH-302	97	26 weeks[a]		
ALXN1210-PNH-103	13	07 Nov 2017		
ALXN1210-PNH-201	26	24 Nov 2017		

a In Study ALXN1210-PNH-103, up to Day 169; and in Study ALXN1210-PNH-201, up to Day 253 for Cohorts 1-3 and up to Day 281 for Cohort 4.
b Cohort 1a and 1b combined in Study ALXN1210-PNH-103.
* included 39 patients from the extension phases of Study ALXN1210-PNH-103 and ALXN1210-PNH-201
Max = maximum; Min = minimum; PNH = paroxysmal nocturnal haemoglobinuria

The most common treatment related adverse events and those of special interest reported are summarised below in Table 5 and Table 6.

Table 5: Treatment emergency adverse events occurring >5% of the trial population

System Organ Class Preferred Term	Total Ravulizumab (N = 261)	
	n (%)	E (rate)
Total patient-years of exposure (years)		**176.9**
Patients with at least one TEAE	**179 (68.6)**	**565 (319.3)**
Blood and lymphatic system disorders		
Anaemia	16 (6.1)	20 (11.3)
Gastrointestinal disorders		
Nausea	25 (9.6)	32 (18.1)
Diarrhoea	24 (9.2)	27 (15.3)
Abdominal pain	20 (7.7)	24 (13.6)
Vomiting	15 (5.7)	15 (8.5)
Constipation	14 (5.4)	15 (8.5)
General disorders and administration site conditions		
Fatigue	18 (6.9)	23 (13.0)
Pyrexia	18 (6.9)	21 (11.9)
Infections and infestations		
Upper respiratory tract infection	49 (18.8)	76 (43.0)
Nasopharyngitis	41 (15.7)	52 (29.4)
Musculoskeletal and connective tissue disorders		
Back pain	19 (7.3)	35 (19.8)
Pain in extremity	15 (5.7)	16 (9.0)
Arthralgia	14 (5.4)	19 (10.7)
Nervous system disorders		
Headache	90 (34.5)	141 (79.7)
Dizziness	16 (6.1)	17 (9.6)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	15 (5.7)	17 (9.6)
Cough	14 (5.4)	15 (8.5)

Notes: All PNH Patients population = ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301, and ALXN1210-PNH-302.
The data cut-off dates were 27 Nov 2017 for ALXN1210-PNH-103, 24 Nov 2017 for ALXN1210-PNH-201, and the end of randomised treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
E = number of events and rate = rate of AE adjusted by patient-years of exposure, defined as (number of events)/100 patient years
AEs are coded using MedDRA 20.1.
AE = adverse events; SOC = System Organ Class; TEAE = treatment-emergent adverse events.
Source: Module 2.7.4 Table 24 (ISS Table 2.7.4.2.7.03.2)

Table 6: Summary of adverse events of special interest pooled by treatment group in Phase III trials

Adverse Events of Interest Preferred Term	All Ravulizumab (N = 222)		All Eculizumab (N = 219)	
	n (%)	E	n (%)	E
Patients with at least one AESI	27 (12.2)	33	18 (8.2)	20
Angioedema	4 (1.8)	5	0	0
Urticaria	3 (1.4)	4	0	0
Gingival swelling	1 (0.5)	1	0	0
Cardiac Disorder	2 (0.9)	2	1 (0.5)	1
Left ventricular failure	1 (0.5)	1	0	0
Myocardial ischaemia	1 (0.5)	1	0	0
Palpitations	0	0	1 (0.5)	1
Infusion reaction	19 (8.6)	22	13 (5.9)	13
Rash	5 (2.3)	5	4 (1.8)	4
Rhinitis allergic	5 (2.3)	6	1 (0.5)	1
Infusion related reaction	4 (1.8)	5	1 (0.5)	1
Eczema	2 (0.9)	2	0	0
Rash pruritic	2 (0.9)	2	1 (0.5)	1
Dermatitis	1 (0.5)	1	0	0
Dermatitis allergic	1 (0.5)	1	0	0
Dermatitis atopic	0	0	1 (0.5)	1
Hypersensitivity	0	0	3 (1.4)	3
Rash erythematous	0	0	1 (0.5)	1
Rash maculo-papular	0	0	1 (0.5)	1
Other serious infection	4 (1.8)	4	5 (2.3)	
Influenza	1 (0.5)	1	0	6
Leptospirosis	1 (0.5)	1	0	0
Lower respiratory tract infection	1 (0.5)	1	0	0
Systemic infection	1 (0.5)	1	0	0
Abscess limb	0	0	1 (0.5)	0
Cellulitis	0	0	1 (0.5)	1
Infection	0	0	1 (0.5)	1
Pneumonia	0	0	1 (0.5)	1
Pyelonephritis acute	0	0	1 (0.5)	1
Viral upper respiratory tract infection	0	0	1 (0.5)	1

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomised treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
Under patient count columns, n (%), if a patient had more than one event for a particular SOC, the patient is counted only once for that SOC under n (%). If a patient had more than one event for a particular PT, the patient is counted only once for that PT.
AEs are coded using MedDRA 20.1.
AE = adverse event; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; PNH = paroxysmal nocturnal haemoglobinuria; PT = Preferred Term; SOC = System Organ Class
Source: Module 2.7.4 Table 31 (ISS Table 2.7.4.2.9.02.1)

The rates of adverse events were similar between the two complement inhibitors. There were two cases of meningococcal sepsis reported in ravulizumab treated patients.

Risk management plan[2]

The sponsor has submitted EU-RMP version 1.0 (date 18 June 2018; data lock point (DLP) 8 March 2018) and ASA version 1.0 (dated 13 November 2018) in support of this application. Following the first round RMP evaluation, the sponsor submitted an updated EU RMP version 1.4 (date 8 March 2018; DLP 2 May 2019) and an ASA version 2.0 (date 21 June 2019).

[2] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 7 below.

Table 7: Sponsor's summary of ongoing safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine (R)	Additional (A)	R	A
Important identified risks	**Meningococcal infection and sepsis**	✓§	✓*	✓	✓‡¶
Important potential risks	**Serious haemolysis after drug discontinuation in PNH patients**	✓	✓*	✓	✓‡
	Immunogenicity	✓	✓*	✓	✓‡
	Serious infections	✓	✓*	✓	✓‡
	Malignancies and haematologic abnormalities	✓	✓*	✓	✓‡
Missing information	**Use in pregnant and breast-feeding women**	✓§	✓*	✓	✓‡

*Clinical trials
‡Physician's guide, Patient's information brochure
¶Patient's safety card, Controlled distribution
§ Follow-up questionnaire

The risk management plan (RMP) evaluator has raised no objection to registration of ravulizumab, and has made a number of standard recommendations for the conditions of registration.

Risk-benefit analysis

Delegate's considerations

The data supports the safety and efficacy of ravulizumab in the treatment of PNH. It is non-inferior to standard of care treatment in relevant endpoints for controlling haemolysis, as shown in two trials.

The safety for ravulizumab appears, with limited patient exposure, to be comparable to eculizumab.

Paediatric data

The Delegate notes that the requested indication is for the treatment of PNH in adults, which is consistent with the US and EMA indications. However, 10% of PNH cases occur in children and, being very rare, there is a paucity of data in this group of patients. As the sponsor has noted in their response to the clinical evaluation report, a paediatric study, Study ALXN-1210-PNH-304, is ongoing in paediatric patients but this does not include

Australian sites. The sponsor's expectation is that once paediatric data is available, the indication will be extended to paediatric patients.

While the data in paediatric patients is clearly incomplete, the regulatory issue is whether it reasonable based on the information that is available to exclude the use of ravulizumab in children. The Delegate feels that given the pathophysiology of PNH is the same in adults as children, there is no reason to conclude it would not be effective in paediatric patients. Furthermore, as the sponsor has noted[3]:

> *Pharmacokinetic/pharmacodynamic (PK/PD) data are currently unavailable in pediatric patients with PNH. However, based on the similarity of PK/PD results between adult patients with PNH and adult and pediatric patients with complement-mediated TMA disease, including aHUS and between, similar PK/PD results are expected between adult and pediatric patients with PNH. This is further supported by the accumulated data from eculizumab in adult and pediatric patients.*

However, the Delegate has chosen not to pursue an age-non-specific indication for ravulizumab at this time as there is an existing therapy for PNH which is indicated in the paediatric population, and therefore there is not an unmet clinical need which would require pre-empting the availability of paediatric data for ravulizumab.

The Delegate intends to require the sponsor to provide the paediatric data for evaluation as soon as it is available as condition of registration of this product.

Risk of infection

Meningococcal infection (MI) is a serious risk in patients receiving ravulizumab and requires specific attention from prescribers.

The Delegate notes that the clinical evaluator requested the sponsor to amend reference to MI in the PI, to which the sponsor responded[4]

> *Alexion would like to clarify and confirm that to date there have been no fatal cases of meningococcal infections reported with ravulizumab. The intent of this sentence – 'Cases of serious or fatal meningococcal infections/sepsis have been reported in patients treated with other terminal complement inhibitors.' in Section 4.4 under Serious meningococcal infection is to inform of serious or fatal cases of meningococcal infections with other terminal complement inhibitors such as eculizumab. Therefore, Alexion believes that it's critical to retain the word "other" in the aforementioned sentence to differentiate the meningococcal cases with other terminal complement inhibitors from ravulizumab.*

The Delegate notes that the US prescribing information for ravulizumab states:

> *Life-threatening meningococcal infections/sepsis have occurred in patients treated with Ultomiris and may become rapidly life-threatening or fatal if not recognized and treated early (5.1).*
>
> - *Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in patients with complement deficiencies (5.1).*
> - *Immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of Ultomiris, unless the risks of delaying Ultomiris therapy outweigh the risks of developing a meningococcal infection. (See Warnings and Precautions (5.1) for additional guidance on the management of*

[3] Post-first round evaluation questions; response to Question 1.
[4] Post-first round evaluation response regarding tabulated changes to the Australian Ultomiris PI.

the risk of meningococcal infection.) Vaccination reduces, but does not eliminate, the risk of meningococcal infection.

- *Monitor patients for early signs of meningococcal infections, and evaluate immediately if infection is suspected.*

Ultomiris is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the Ultomiris REMS, prescribers must enroll in the program (5.1).

This appear to the Delegate difficult to reconcile with the conclusion that serious or fatal MI only occur in 'other' complement inhibitors.

The Delegate is of the view that the risk of MI is intrinsic to the mechanism of action of complement inhibitors and that the issue of whether an infection is fatal or merely serious is likely to be influenced by factors (such as time of presentation, suitable antibiotic therapy, age of patient andcomorbidities and so on) which are not relevant to the safety of the specific complement inhibitor received. All MI are serious and potentially life threatening as a consequence of the pathophysiology of the agent involved and so what is relevant for therapy is whether the risk of infection is increased.

The Delegate therefore proposes to amend the draft PI to include the US 'black box' statement as amended for the Australian context, specifically

- Refer to the 'Current Edition of the Australian Immunization Handbook' as the relevant guideline for vaccination
- Remove reference to the restricted access scheme operating in the USA.

The Delegate proposes to amend paragraph 2 of section 4.4 of the Australian PI to read:

Cases of life-threatening meningiococcal infections/sepsis have been reported in patients treated with terminal complement inhibitors.

Proposed action

The Delegate proposes to include ravulizumab in the Australian Register of Therapeutic Goods (ARTG) with the indication:

Ultomiris is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

With a PI document as amended from that provided in the sponsor's response to the TGA's consolidated request for further information as specified above, and with the additional condition of registration:

1. The sponsor will provide a study report of trial ALXN1210-PNH-304 to the Therapeutic Goods Administration for evaluation in support of a paediatric indication no later than this trial is first submitted to either the US FDA, EMA or Health Canada in support of a paediatric indication.

Request for ACM advice

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of ravulizumab 10 mg/mL concentrated solution for intravenous infusion, indicated for:

> *Ultomiris is indicated for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).*

Specific conditions of registration applying to these goods

1. Ultomiris (ravulizumab *rch*) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Ultomiris must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

2. The Ultomiris European Union (EU)-Risk Management Plan (RMP) (version 1.4, dated 8 March 2018; DLP 2 May 2019), with Australian Specific Annex (version 2.0, dated 21 June 2019), included with submission PM-2018-05023-1-6, to be revised to the satisfaction of the TGA, will be implemented in Australia.

   An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

   Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

   The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

3. Batch release testing & compliance with Certified Product Details (CPD)

   a. It is a condition of registration that all batches of Ultomiris ravulizumab 10 mg/mL imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

   b. It is a condition of registration that each batch of Ultomiris ravulizumab 10 mg/mL imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index.

   c. The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.

      This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

4. Certified Product Details

   The sCertified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

5. The sponsor will provide a study report of trial ALXN1210-PNH-304 to Therapeutic Goods Administration for evaluation in support of a paediatric indication no later than this trial is first submitted to either the US FDA, EMA or Health Canada in support of a paediatric indication.

6. For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Ultomiris approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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