Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Eculizumab

Proprietary Product Name: Soliris

Sponsor: Alexion Pharmaceuticals Australasia Pty Ltd

November 2020

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
ADA	Anti-drug antibody
aHUS	Atypical haemolytic uraemic syndrome
AQP4	Aquaporin-4
ARR	Annualised relapse rate
ARTG	Australian Register of Therapeutic Goods
ASA	Australian-specific Annex
AusPAR	Australian Public Assessment Report
C5	Complement protein C5
CI	Confidence interval
CMI	Consumer Medicines Information
COR A	Comparable Overseas Regulator approach A
CSF	Cerebrospinal fluid
C_{trough}	Trough concentration
DLP	Data lock point
EDSS	Expanded Disability Status Scale
EU	European Union
gMS	Generalised myasthenia gravis
GVP	Good Pharmacovigilance Practice
IST	Immunosuppressive therapy
IV	Intravenous
IVIg	Intravenous immunoglobulin
LLOQ	Lower limit of quantitation
Max	Maximum
Min	Minimum

Abbreviation	Meaning
mRS	Modified Rankin score
NA	Not applicable
NAb	Neutralising antibody
NMOSD	Neuromyelitis optica spectrum disorder
NNT	Number needed to treat
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PNH	Paroxysmal nocturnal haemoglobinuria
PSUR	Periodic safety update report
RCT	Randomised controlled trial
RMP	Risk management plan
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Extension of indication
Product name:	Soliris
Active ingredient:	Eculizumab
Decision:	Approved
Date of decision:	26 June 2020
Date of entry onto ARTG:	1 July 2020
ARTG number:	138885
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved
Sponsor's name and address:	Alexion Pharmaceuticals Australasia Pty Ltd Suite 401, 20 Rodborough Road Frenchs Forest NSW 2086
Dose form:	Concentrated solution
Strength:	300 mg
Container:	Glass vial
Pack size:	1 x 30 mL
Approved therapeutic use:	*Adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.* *Soliris is not intended for acute treatment of a NMOSD relapse.*
Route of administration:	Intravenous (IV) infusion
Dosage:	Patients must be administered a meningococcal vaccine at least two weeks prior to receiving Soliris therapy. Soliris should be administered by a healthcare professional and under appropriate medical supervision. The neuromyelitis optica spectrum disorder (NMOSD) dosing regimen for adult patients (≥ 18 years of age) consists of a 4

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

weeks initial phase followed by a maintenance phase:

- Initial phase: 900 mg of Soliris via a 25 to 45 minute intravenous infusion every week for the first 4 weeks.
- Maintenance phase: 1200 mg of Soliris administered via a 25 to 45 minute intravenous infusion on the fifth week, followed by 1200 mg of Soliris administered via a 25 to 45 minute intravenous infusion every 14 ± 2 days.

For patients with NMOSD, Soliris should be administered as an adjuvant therapy to their existing immunosuppressive therapy (IST). In clinical studies with Soliris, about76% of patients were on ISTs at Baseline.

Paediatric Patients (< 18 years of age): The safety and effectiveness of Soliris for the treatment of NMOSD in paediatric patients below the age of 18 years have not been established.

For further information regarding dosage, refer to the Product Information (PI)

Pregnancy category: B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Alexion Pharmaceuticals Australasia Pty Ltd (the sponsor) to register Soliris (eculizumab) 300 mg, concentrated solution for intravenous transfusion for the following extension of indication:

> *Adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.*
>
> *Soliris is not intended for acute treatment of a NMOSD relapse.*

Neuromyelitis optic spectrum disorder (NMOSD) is regarded as an extremely rare inflammatory disorder of the central nervous system, with an age and sex adjusted incidence ranging between 0.07 to 0.73 per 100,000 person-years and prevalence ranging between 3.9 and 10 per 100,000 person-years worldwide. NMOSD is more common in women than in men, with an average age at onset typically between 30 to 40 years. Female gender and race represent potential risk factors for NMOSD.

Risk factors for relapse of NMOSD are varied, however relapse appears to be more common in patients who are aquaporin-4 (AQP4) immunoglobulin G (IgG) auto-antibody seropositive than in patients who are seronegative.[2] Infection, severe pain, neutropaenia and neurological complications (bowel and bladder, neuropathy and blindness) are important co-morbidities for NMOSD. Worldwide, mortality rates in NMOSD range from 9% to 32%, depending on age, relapse rate, and recovery from attacks.

At the time this submission was under consideration, there were no other medicines approved in Australia for treatment of this group of patients.

The Product Information for Soliris outlines that:[3]

> 'Soliris (eculizumab rmc) is a genetically-engineered humanised monoclonal antibody directed against the α-chain of the C5 complement protein.
>
> […]
>
> In patients with NMOSD, the exact mechanism by which eculizumab rmc exerts its therapeutic effect is unknown but is presumed to involve inhibition of aquaporin-4 (AQP4) antibody induced terminal complement C5b-9 deposition and C5a-dependent inflammation.'

This application was submitted through the TGA's Comparable Overseas Regulator approach A (COR A);[4] using evaluation reports from Health Canada. The full dossier was also submitted to the TGA.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 March 2009 for the below indications.

Soliris is indicated for the treatment of patients with:

- *Paroxysmal Nocturnal Haemoglobinuria (PNH) to reduce haemolysis.*
- *atypical Haemolytic Uraemic Syndrome (aHUS).*

At the time the TGA considered this application, a similar application had been approved in United States of America (USA) (approved on 27 June 2019), European Union (EU) (approved on 26 August 2019) and Canada (approved on 24 September 2019).

[2] Aquarporin 4 immunoglobulin G antibody is also known as neuromyelitis optica immunoglobulin G (NMO-IgG).

[3] Product Information for Soliris (Eculizumab rmc) concentrated solution for intravenous infusion, sponsored by Alexion Pharmaceuticals Australasia Pty Ltd. Date of first approval 20 March 2009. Date of revision 1 July 2020.

[4] The TGA makes use of assessments from **comparable overseas regulators** (**COR**), where possible, in the evaluation of prescription medicines. Under the **COR-A** approach, the TGA regulatory decision will be based on a critical review of the COR assessment reports and an evaluation of the Australian label, Product Information (PI) and where required, the Risk Management Plan (RMP). The evaluation and decision timeframe for COR-A applications is 120 working days.
To meet this significantly shortened timeframe, the application must meet specific requirements. Key considerations for COR-A include: identical medicine and manufacturing to that approved by the COR, with evidence of compliance with Good Manufacturing Practice (GMP); the full overseas marketing approval for the medicine is no older than 1 year; and, aside from the label, PI and RMP (where required), no additional evaluation of Australian specific data is required.

Table 1: International regulatory status of Soliris

Region	Submission date	Status	Approved indications
USA	28 December 2018	Approved on 27 June 2019	*The treatment of Neuromyelitis Optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive*
EU	9 January 2019	Approved on 26 August 2019	*The treatment of Neuromyelitis Optica spectrum disorder (NMOSD) in patients who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease*
Canada	18 March 2019	Approved on 24 September 2019	*The treatment of Neuromylitis Optica Spectrum Disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.*
Japan	22 November 2019	Under consideration	Under consideration
Russia	10 September 2019	Under consideration	Under consideration
Switzerland	30 October 2020	Under consideration	Under consideration

Product Information

The 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 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-04825-1-1

Description	Date
Designation: Orphan[5]	16 September 2019
Submission dossier accepted and first round evaluation commenced	2 December 2019
First round evaluation completed	26 February 2020
Sponsor provides responses on questions raised in first round evaluation	27 March 2020
Second round evaluation completed	14 April 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	27 May 2020
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	26 June 2020
Completion of administrative activities and registration on the ARTG	1 July 2020
Number of working days from submission dossier acceptance to registration decision*	115

* The COR-A process has a 120 working day evaluation and decision timeframe.

III. Submission overview and risk/benefit assessment

This section is a TGA summary of wording used in the TGA's evaluation report, which discussed numerous aspects of overseas evaluation reports and included some information that was commercial in confidence.

[5] Orphan drugs are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier consisted of one Phase III clinical study and its open label extension study, Study ECU-NMO-301 and Study ECU-NMO-302 respectively.

- Study ECU-NMO-301: A Phase III, randomised (2:1), double blind, parallel group, placebo controlled, multicentre study. It evaluates the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of Soliris.
- Study ECU-NMO-302: A Phase III, open label, multicentre, extension study. It evaluates the efficacy, safety, PK, and PD of Soliris.

Pharmacology

The PK and PD of Soliris (eculizumab) in patients with relapsing NMOSD were studied in the Phase III trial, Study ECU-NMO-301.

Pharmacokinetics

94 patients with 2014 samples were analysed over the study period (up to 204 weeks). The PK data were then incorporated in a population pharmacokinetic modelling and exposure response analysis.

The threshold concentration (for example, concentration to achieve complete terminal complement inhibition) of 116 µg/mL was derived from the previous population PK/PD report for eculizumab in generalised myasthenia gravis (gMG) studies. The evaluator considered that '*based upon the characteristics of gMG and NMOSD, it is unlikely that this relationship would differ in patients with NMOSD'*. Thus, the approach to use a threshold concentration of 116 µg/mL as a benchmark to assess the relationship between eculizumab exposures and free complement protein C5 (C5) inhibition was considered as acceptable.

Median serum trough concentration (C_{trough}) was approximately 400 µg/mL.[6] The individual concentrations were mostly ranging between 100 and 700 µg/mL. The majority of trough eculizumab serum concentrations were well above the threshold of 116 µg/mL. Also, 88.4% of the patient population had serum eculizumab concentrations above the threshold for the full dosing interval.

Population PK analyses (based on Study ECU-NMO-301 data) estimated the terminal elimination half-life to be 414 ± 103 hours. Trough concentration (C_{trough}); was maintained above the threshold PK concentration (116 µg/mL) to achieve complete inhibition of terminal complement at all-time points in the majority of the patients (88.4%).

Anti-drug antibody (ADA) and neutralising antibody (NAb) formation was monitored in Study ECU-NMO-301. Immunogenicity associated with the use of eculizumab in NMOSD was not identified as a significant concern.

[6] **Trough concentration** (C_{trough}) is the lowest concentration of a drug immediately before the next dose is administered.

Overall, the final parameter estimates are roughly similar to the PK profiles of eculizumab in the previously reviewed aHUS and gMG populations.

Pharmacodynamics

Inhibition of terminal complement and serum free C5 concentrations were assessed for PD effects.

Complete and sustained inhibition of free C5 concentration (< 0.5 μg/mL) and of haemolytic activity were achieved in 95.8% and 92.6% of patients, respectively.

Cerebrospinal fluid (CSF) free C5 concentrations post-dose were all less than the lower limit of quantitation (LLOQ) of 3 ng/mL, with a mean baseline concentration value of 262 ng/mL for Soliris. This is suggestive of a complete terminal complement inhibition in CSF.

Efficacy

Rationale for dose selection

The eculizumab dosing regimen used in Study ECU-NMO-301 was 900 mg IV weekly for the first 4 weeks followed by 1200 mg IV starting at Week 5 and every 2 weeks thereafter. This is the same dosing regimen that has been demonstrated to achieve immediate, complete, and sustained inhibition of terminal complement activation and has been approved for the treatment of patients with aHUS and for the treatment of patients with gMG. This approach is in line with eculizumab's mechanism of action: targeting terminal complement mediated inflammation. Also, the conditions aHUS, PNH and NMOSD share '*complement mediated inflammation*' as the fundamental pathophysiology.

Study ECU-NMO-301.

Study design: Double blind, parallel group time to event randomised controlled trial (RCT).

Patients were randomised in a 2:1 ratio across eculizumab and placebo groups. There were 3 periods in this study: a screening period, study period, and safety follow-up period. Patients completed the study if they experienced an on trial relapse as per the treating physician or once the pre-specified number of patients had experienced a positively adjudicated on trial relapse, whichever occurred first.

An on-trial relapse was defined as a relapse that occurs during the study period; defined as a new onset of neurologic symptoms or worsening of existing neurologic symptoms with an objective change (clinical sign) on neurologic examination that persists for more than 24 hours as confirmed by the treating physician.

The primary objective of the study was to assess the efficacy of eculizumab in terms of relapse risk reduction, compared to placebo. Accordingly, the primary endpoint was time from randomisation to first occurrence of an adjudicated on trial relapse. Annualised relapse rate (ARR) was a key secondary efficacy endpoint.

Inclusion criteria: Diagnosis of NMOSD as defined by the 2006 or 2007 Wingerchuk criteria;[7,8] AQP4 autoantibody positivity, Expanded Disability Status Scale (EDSS) score ≤ 7;[9]and have experienced at least 2 relapses in the 12 months prior to screening or 3 relapses in the
24 months prior to screening (with at least 1 relapse in the 12 months prior to screening). Patients were permitted to continue to receive a stable dose of IST that they were taking at the time of screening. The use of concurrent corticosteroids was restricted to a maximum of 20 mg/day.

Key exclusion criteria: use of rituximab or mitoxantrone 3 months prior to screening. Use of intravenous immunoglobulin (IVIg) 3 weeks prior to screening. Unresolved meningococcal disease or other bacterial infection.

96 patients were randomised to eculizumab group and 47 patients to placebo group. A greater proportion of patients in eculizumab, compared to placebo group withdrew from the study (12 versus 1). None of the patients in eculizumab group withdrew due to treatment emergent adverse events (TEAE). Majority of patients in eculizumab group (80 out of 96) and placebo group (44 out of 47) completed the study.

The median age across groups was 45 years, with the youngest patient being 19 years of age and the eldest 75 years of age. Around 90% of patient population were females and the man age of disease onset was 37 years. The median (minimum, maximum) treatment duration was 89.43 (3.1, 211.1) weeks in the eculizumab group and 41.29 (6.1, 208.1) weeks in the placebo group. Patients in eculizumab group had a higher mean number of infusions per patient (n = 48.6), compared to placebo group (n = 31.7). Both patient groups had a mean treatment compliance of around 97%.

Primary endpoint

Time from randomisation to first occurrence of an adjudicated on trial relapse. 3.1% and 42.6% of patients in eculizumab and placebo groups respectively experienced a relapse during treatment period. The relative risk reduction was 94.2% for patients in eculizumab group, compared to placebo group. The absolute risk reduction was estimated by the Delegate as 39.5 and the number needed to treat (NNT) as 2.5. The hazard ratio was 0.058 (95% confidence interval (CI): 0.017 to 0.197); $p < 0.0001$).

[7] Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology*. 2006;66(10):1485-1489.
[8] Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.
[9] The **Expanded Disability Status Scale** (**EDSS**) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. It is widely used in clinical trials and in the assessment of people with MS. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. EDSS steps 1.0 to 4.5 refer to people with MS who are able to walk without any aid and is based on measures of impairment in eight functional systems (FS). EDSS steps 5.0 to 9.5 are defined by the impairment to walking.

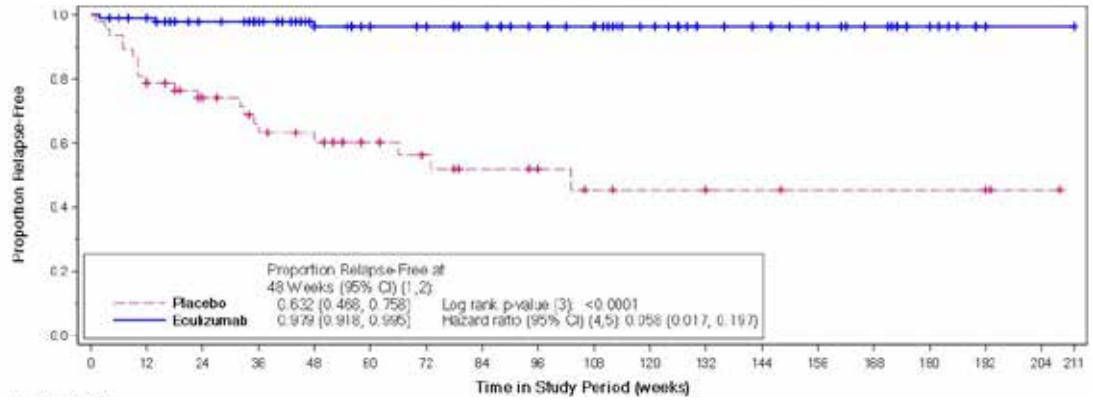
Table 3: Study ECU-NMO-301 Time from randomisation to first occurrence of an adjudicated on trial relapse

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)
Patients with a relapse	n (%)	20 (42.6)	3 (3.1)
Follow-up time (weeks)	Median (min, max)	36.00 (1.86, 208.57)	89.43 (2.57, 211.14)
Estimated proportion of patients relapse-free at:			
48 weeks	Cumulative probability[a] (95% CI[b])	0.632 (0.468, 0.758)	0.979 (0.918, 0.995)
96 weeks		0.519 (0.341, 0.670)	0.964 (0.891, 0.988)
144 weeks		0.454 (0.262, 0.628)	0.964 (0.891, 0.988)
Relapse-free time (weeks)	Percentile[a]		
	10th	7.71	NA
	25th	23.71	NA
	50th	103.14	NA
Treatment effect	p-value[c]	...	<0.0001
	Hazard ratio[d] (eculizumab/placebo)	...	0.058
	95% CI[e]	...	0.017, 0.197
	% reduction[d] (eculizumab/placebo)	...	94.2
	95% CI[e]	...	80.3, 98.3

Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomisation strata: (1) low EDSS at randomisation (≤ 2.0); (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomisation; (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomisation; (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomisation.

a Based on the Kaplan-Meier product limit method.; b Based on the complementary log-log transformation.; c Based on a stratified log-rank test.; d Based on a stratified Cox proportional hazards model.; e Wald confidence interval. max = maximum; min = minimum; NA = not applicable.

Figure 1: Study ECU-NMO-301 Kaplan-Meier Survival estimates for time to first adjudicated on trial relapse



Note: Patients who did not experience an adjudicated On-trial Relapse were censored at the end of the Study Period. Stratified analyses are based on 4 randomization strata: (1) low EDSS at randomisation (≤ 2.0), (2) high EDSS (≥ 2.5 to ≤ 7) and treatment naïve at randomisation, (3) high EDSS (≥ 2.5 to ≤ 7) and continuing on the same IST(s) since last relapse at randomisation, (4) high EDSS (≥ 2.5 to ≤ 7) and changes in IST(s) since last relapse at randomisation. 1 Based on the Kaplan-Meier product limit method. 2 Based on the complementary log-log transformation. 3 Based on a stratified log-rank test. 4 Based on a stratified Cox proportional hazards model. 5 Wald confidence interval.

Key secondary efficacy endpoint

The annualised relapse rate (ARR), adjusted for rate at Baseline were 0.016 (95% CI: 0.005, 0.050) and 0.350 (95% CI; 0.199, 0.616), respectively for eculizumab and placebo groups. ARR ratio was 0.045 (95% CI; 0.013, 0.151); $p < 0.0001$.

Table 4: Study ECU-NMO-301 Annualised relapse rate

Variable	Statistic	Placebo (N = 47)	Eculizumab (N = 96)
Number of patients with a total relapse count of			
0	n (%)	27 (57.4)	93 (96.9)
1	n (%)	19 (40.4)	3 (3.1)
2	n (%)	1 (2.1)	0
Patient relapse rate[a]	N	47	96
	Mean (SD)	1.14 (1.770)	0.09 (0.610)
	Median	0	0
	25th, 75th percentile	0, 1.71	0, 0.00
	Min, max	0, 6.52	0, 5.37
Total number of relapses	Sum	21	3
Total number of PY in study period	Sum	52.41	171.32
Adjusted adjudicated ARR[b]	Rate	0.350	0.016
	95% CI	0.199, 0.616	0.005, 0.050
Treatment effect[b]	Rate ratio (eculizumab/placebo)	...	0.045
	95% CI	...	0.013, 0.151
	p-value	...	<0.0001

a. The number of relapses for each patient divided by the number of years in the study period for that patient; summary statistics across all patients are presented.

b. Based on a Poisson regression adjusted for randomization strata and historical ARR in 24 months prior to screening.

There was no significant treatment difference for the EDSS between eculizumab and placebo groups. In line with the closed testing procedure, since no significant treatment difference for EDSS was observed, no further statistical testing was performed for other secondary endpoints that were measures of neurological disability, functional status and quality of life.

A significant improvement in modified Rankin scale (mRS);[10] score was reported with eculizumab group, compared to placebo group.

A statistically significant number of patients in placebo group (31.9%) required hospitalisation for treatment of a relapse, compared to 6.3% of patients in eculizumab group. The evaluator has highlighted that the statistical analysis of this end point was not pre-specified. Also, not controlled for multiplicity and the subjectivity in determination of need for hospitalisation for treatment of a relapse. The Delegate agrees with this conclusion.

Study ECU-NMO-302 (Interim analysis), open label extension of Study ECU-NMO-301

Patients who completed the Study ECU-NMO-301 due to either a relapse of NMOSD or reached the endpoint of the treatment period were enrolled in this open label extension study. The previous treatment should have been within 2 weeks prior to enrolment in this study.

Evaluation of long term safety was the primary objective. Secondary objective was to evaluate long term efficacy. Key efficacy endpoint was ARR.

No sample size or power calculations were performed. 43 patients had completed Study ECU-NMO-301 because they experienced an on trial relapse, of which 39 patients

[10] The **Modified Rankin Score** (**mRS**) is a 5 point disability scale with possible scores ranging from 0 to 5. The Modified Rankin Score (mRS) is the most widely used outcome measure in stroke clinical trials. 0: The patient has no residual symptoms. 1: The patient has no significant disability; able to carry out all pre-stroke activities. 2: The patient has slight disability; unable to carry out all pre-stroke activities but able to look after self without daily help. 3: The patient has moderate disability; requiring some external help but able to walk without the assistance of another individual. 4: The patient has moderately severe disability; unable to walk or attend to bodily functions without assistance of another individual. 5: The patient has severe disability; bedridden, incontinent, requires continuous care.

were enrolled in this study and included in this interim analysis. Subsequent interim analyses will include all enrolled patients, including those patients who did not experience an on trial relapse in Study ECU-NMO-301.

ARR was chosen as the primary endpoint for this interim analysis. EDSS, mRS scores were the key secondary endpoints.

39 patients who had previously experienced an on trial relapse in Study ECU-NMO-301 were included in the interim analysis. The majority of patients (n = 25) had received placebo.

The Delegate comments that the sponsor has done statistical calculation of the reduction in ARR. However, it was noted that this study was not powered for such a calculation. ARR was not pre-specified as a primary endpoint.

Safety

Safety data was based on exposure to 121 patients across Study ECU-NMO-301 and the ongoing Study ECU-NMO-302 over an average of 100 weeks of treatment.

Study ECU-NMO-301

Most common TEAEs in Study ECU-NMO-301 in the eculizumab group were upper respiratory tract infections (29.2%) and headache (22.9%). Other TEAEs with a greater rate of incidence versus placebo were influenza, dyspepsia and musculoskeletal pain. The rate of incidence of TEAEs was comparable between eculizumab and placebo groups.

No TEAE related discontinuations were reported in eculizumab group. 4.3% of withdrawals in placebo group were due to TEAEs.

There was no apparent difference in the incidence rate of TEAEs across placebo and eculizumab groups. There was around a 5 times increase in incidence of NMOSD in placebo group, compared to eculizumab group.

There were no cases of meningococcal infections across groups. Other serious infections were reported at comparable rates of around 11 to 12% across treatment groups. A higher incidence for infusion site reactions were noted in eculizumab group, compared to placebo group (6.3% versus 4.3%). A higher incidence of TEAE of special interest was reported in the first 6 months of the study and the incidence rate decreased as the study progressed in both treatment groups.

One death was reported in the eculizumab group. The cause of death was identified as infectious pleural effusion. This patient experienced serious TEAEs of congestive cardiac failure, pneumonia, respiratory failure, and sepsis. The serious TEAEs were determined as not related to the study drug. Infectious pleural effusion was determined as 'probably related to study drug'.

Two patients (2.1%) in eculizumab group were positive for ADA. Both patients were negative for neutralising antibodies against eculizumab.

Study ECU-NMO-302

The overall median duration of study in which the TEAEs were reported was around 85 weeks. The total eculizumab exposure was 62.4 patient-years.

The majority of TEAEs were mild to moderate in severity. 1 patient had four TEAEs leading to withdrawal of study drug (Sjogren's syndrome, autoimmune thyroiditis, and two events of worsening systemic lupus erythematosus). The most frequently reported TEAE was nasopharyngitis, headache, and urinary tract infection.

Risk management plan

The most recently evaluated EU-risk management plan (RMP) was version 18.3 (dated 14 June 2018; data lock point (DLP) 1 October 2017) and Australian specific Annex (ASA) version 5.1 (dated August 2019). In support of the extended indications, the sponsor has submitted EU-RMP version 19.3 (dated 22 July 2019; DLP 30 September 2018) and ASA version 6.0 (dated October 2019).

In the response to TGA questions, the sponsor has submitted ASA version 6.1 (dated 23 March 2020) and EU-RMP version 19.3 (dated 22 July 2019; DLP 30 September 2018).

In response to the recommendation in the second round RMP evaluation report, the sponsor has submitted updated additional risk minimisation materials for evaluation. No further updates to the ASA version 6.1 (dated 23 March 2020) and EU-RMP version 19.3 (dated 22 July 2019; DLP 30 September 2018) have been provided.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 5.[11]

Table 5: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Meningococcal infections	ü*	ü†‡	ü	ü∞¥βμφΩ§απ‖¶
	Serious infections (including sepsis)	ü	ü†‡	ü	ü∞¥βμφΩ§απ
	Aspergillus infection	ü	ü†‡	ü	ü∞¥§
	Severe TMA complications due to drug discontinuation in aHUS patients	ü	ü‡	ü	üμ¥
	Infusion reactions	ü	ü†‡	ü	ü∞¥βμφ§α
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients	ü	ü†	ü	ü∞β
	Malignancies and haematologic abnormalities in PNH patients	ü	ü†	ü	–
	Immunogenicity	ü	ü†‡	ü	ü∞¥§

[11] *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.

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
	Serious infections in neonates after maternal exposure to eculizumab	ü ^	ü †‡	ü	–
Missing information	None	–	–	–	–

Activities that apply to the extension of indications: *Targeted questionnaire for suspected and confirmed meningococcal infection reports. § Physician's Guide for NMOSD. α Patient Information Guide for NMOSD. Π Patient Safety Information Card. ‖ Controlled access program. ¶ Annual electronic vaccination reminder letters for HCPs. ^ Targeted questionnaire for newborns and infants exposed to Soliris during pregnancy (including 3 months follow-up after delivery and breastfeeding case reports).

Activities that do not apply to the extension of indications: † PNH registry. ‡ aHUS registry. ∞ Physician's guide for PNH. ¥ Physician's guide for aHUS. β Patient/Parent Guide for PNH. µ Patient/Parent guide for aHUS. ϕ Parent Information Brochure. Ω Patient Safety Information Card

The risk management plan (RMP) evaluator has concluded that the recommendation made in the RMP evaluation report has been resolved and there are no new recommendations for this submission.

Risk-benefit analysis

Delegate's considerations

NMOSD is a rare (orphan) immune mediated demyelinating disease with severe morbidity (frequent relapse) and mortality. There are no other medicines currently approved by the TGA for treatment of this group of patients.

The findings of the population PK study supports the rationale for dose selection of eculizumab for the treatment of NMOSD. The PD findings of near complete terminal complement inhibition in CSF is supported by the efficacy outcomes of the clinical study.

In the pivotal study, patients treated with eculizumab achieved a significant reduction in relative risk for relapses (94.2%). This outcome was clinically relevant as well. In patients with NMOSD, treatment with IST alone has shown a 33% reduction in relapse.[12] Also, around 57% of patients in placebo group did not experience a relapse. It needs to be considered that the reduction in relapse rate was achieved when eculizumab was administered as an adjuvant therapy. Statements to reflect this aspect of the study has been recommended to be inserted in the PI.

The relative risk reduction for relapse of NMOSD in eculizumab group was supported by the overall improvement in annualised relapse rate. A non-significant improvement in EDSS was reported. The duration of treatment period might not be sufficient enough to have a significant treatment difference in this measure. It could also be due to the undefined sensitivity and specificity of this measure in patients with NMOSD.

The Delegate recommends that the length of treatment with eculizumab should be individualised and based on the severity and frequency of attacks and disability. The Delegate has recommended statements to be include in the PI to reflect this approach of treatment. It was noted that around 57% of patients in placebo group did not experience a relapse. This suggests that a considerable proportion of patients with NMOSD and having frequent relapses and being positive for AQP4 antibodies may not require treatment with

[12] Palace, J., et al., Outcome prediction models in AQP4-IgG positive neuromyelitis optica spectrum disorders. *Brain*, 2019. 142(5): p. 1310-1323.

eculizumab during a relapse free time period.[13] This finding highlights the heterogeneous nature clinical progression of NMOSD;[13] and the determinants for relapse rate to be multi-factorial;[14] rather than solely dependent on AQP4 autoantibody status. The study was not designed to find the optimal use of eculizumab during the non-clustered period of relapses or a relapse free period of NMOSD. Considering the cluster phenomenon of frequency of relapses;[13] and the treatment algorithm for ISTs;[15] to treat NMOSD, an effective approach to define the duration of treatment with eculizumab need to be inserted in the PI. From a clinical perspective, it is important to ensure the optimal use of eculizumab to treat patients with NMOSD.

Patients on treatment with rituximab and mitoxantrone within 3 months prior to screening were excluded. The evaluator has stated that *'the sponsor stated that the rationale for not permitting rituximab or mitoxantrone as background therapies during the study was based on both having a potential impact on continuation of stable background doses during the study'*. The Delegate considers this rational acceptable. However, a statement is recommended in the PI to state that the efficacy and safety of eculizumab, when administered as an adjuvant therapy with rituximab and mitoxantrone has not been studied.

Overall, the adverse events were previously known with the use of eculizumab in already approved indications to treat patients with PNH and aHUS. The rate of incidence of most of the adverse events appear to be largely comparable across treatment groups. Higher incidence of infusion site reactions were reported in patients treated with eculizumab. These events do not appear to have resulted in discontinuations.

No cases of meningococcal infections were reported. Boxed warnings to indicate the increased risk of meningococcal infections with the use of eculizumab are on both PI and Consumer Medicines Information (CMI).

The evaluator recommended the proposed indication as:

> *Soliris is indicated for the treatment of patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive with a relapsing course of the disease.*

The Delegate has considered that those NMOSD patients who are AQP4 autoantibody positive will be at a greater risk of relapses. Also, the patients might have had relapses by the time the diagnosis of NMOSD has been confirmed.[12,13] However, an effective strategy to provide optimal duration of use of eculizumab for these patients need to be formulated. Based on the findings of clinical study, it appears that administering eculizumab reduces the relative risk of further relapses, compared to standard of care.

Proposed action

The findings of the Study ECU-NMO-301 suggest that use of eculizumab in the treatment of patients with NMOSD resulted in a significant reduction of relative risk for relapses, compared to placebo. Treatment regimen for patients with NMOSD needs to be well defined. Safety signals are largely in line with the known safety profile of eculizumab.

[13] Akaishi, T., et al., *Neuromyelitis optica spectrum disorders with unevenly clustered attack occurrence. Neurol Neuroimmunol Neuroinflamm*, 2020. 7(1).
[14] Kinoshita, M. and Y. Nakatsuji, Where Do AQP4 Antibodies Fit in the Pathogenesis of NMO? *Multiple Sclerosis International*, 2012. 2012: p. 862169.
[15] Crout, T.M., L.P. Parks, and V. Majithia, Neuromyelitis Optica (Devic's Syndrome): an Appraisal. *Curr Rheumatol Rep*, 2016. 18(8): p. 54.

This submission will be progressed based on sponsor's response to the recommended changes to the PI, response to clinical questions and the expert's opinion on the Delegate's clinical questions.

Questions for sponsor

1. ***It was noted that 57.4% of patients in the placebo group in the pivotal study did not experience a relapse during treatment period. This finding suggests that a considerable proportion of patients with frequent relapse as defined by the study protocol did not require eculizumab to be seizure free during the study period.***

All patients randomized in Study ECU-NMO-301 met the historical relapse inclusion criteria. Sponsor acknowledges that 57.4% of the patients randomized into the placebo arm of Study ECU-NMO-301 remained free from adjudicated on-trial relapse during the study period. In comparison, 96.9% of the patients randomized into the eculizumab arm remained free from adjudicated on-trial relapse during the study period ($p < 0.0001$).

While 57.4% of the patients in the placebo arm did not experience an adjudicated on-trial relapse during the study period, the literature indicates that patients with anti-AQP4 antibody positive NMOSD have a high likelihood of additional relapses following the first attack, which are unpredictable in timing and severity.[16] This uncertainty is particularly relevant as each new relapse can result in significant permanent morbidity that may include blindness or paralysis, and potentially death. In contrast to diseases such as multiple sclerosis, patients with NMOSD do not typically recover from their relapse-related neurologic deficits over time.[17]

As a direct result of the unpredictable nature of relapses and the significant, often permanent, morbidity associated with them, treatment guidelines recommend preventative treatment for all patients with anti-AQP4 antibodies. The current international recommendations conclude that '*patients who are AQP4-IgG-seropositive should be assumed to be at risk for relapse indefinitely and preventive treatment should be considered, even in the setting of a prolonged clinical remissio*n'.[18]

2. ***What was the mean and median total duration for which these patients remained seizure free, including the study period of Study ECU-NMO-302? What proportion of these patients remained seizure free?***

The mean and median duration for which patients in Study ECU-NMO-301 remained free from adjudicated On-trial Relapse is presented by treatment group in Table 6. In Study ECU-NMO-301, the mean duration that patients remained relapse-free in the placebo arm was 75.9 weeks (median 58.4 weeks), compared with a mean duration in the eculizumab arm of 95.2 weeks (median 94.0 weeks)

[16] Jarius S, Paul F, Franciotta D, et al. Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. *Mult Scler*. 2012;18(8):1135-1143.
[17] Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurol*. 2007;6(9):805-815.
[18] Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85(2):177-189.

Table 6: Study ECU-NMO-301 Summary of study period duration for patients free from adjudicated on-trial relapse (full analysis set free from adjudicated on-trial relapse)

	Statistic	Placebo (N=27)	Eculizumab (N=93)
Study period durations (weeks)	Mean (SD)	75.85 (56.967)	95.22 (55.894)
	Median	58.43	94.00
	Min, Max	12.57, 208.57	4.43, 211.14

Source: Study ECU-NMO-301, Table 350

In Study ECU-NMO-302, all patients were transitioned to open-label treatment with eculizumab. Of the 27 patients in the placebo arm of Study ECU-NMO-301who did not experience an adjudicated on-trial relapse, 23 enrolled in Study ECU-NMO-302 and 22 remained relapse free. Of the 93 patients in the eculizumab arm of Study ECU-NMO-301 who did not experience an adjudicated on-trial relapse, 75 enrolled in Study ECU-NMO-302 and 72 remained relapse free. The mean and median duration for which these patients remained free from adjudicated on-trial relapse in Study ECU-NMO-302 (data cut off 31 October 2018) is presented by treatment group (Table 7). In Study ECU-NMO-302, the mean duration that patients remained relapse-free in the placebo/eculizumab arm was 38.7 weeks (median 20.1 weeks), compared with a mean duration in the eculizumab/eculizumab arm of 33.3 weeks (median 20.1 weeks).

Table 7: Studies ECU-NMO-301/302 Summary of study period duration for patients free from adjudicated on-trial relapse (full analysis set free from adjudicated on-trial relapse)

	Statistic	Placebo/Eculizumab (N=22)	Eculizumab/Eculizumab (N=72)
Study period durations (weeks)	Mean (SD)	38.68 (43.252)	33.27 (39.843)
	Median	20.07	20.14
	Min, Max	1.43, 179.29	13.43, 198.43

Source: Studies ECU-NMO-301 and ECU-NMO-302, Table 354

At the end of Study ECU-NMO-301, 57.4% of the patients in the placebo arm were relapse free. As noted, upon entry into Study ECU-NMO-302, all patients were transitioned to open-label eculizumab. In this setting, as of the data-cut of 31 October 2018, 26 of 27 patients (96.3%) initially randomized to placebo who did not experience an adjudicated on-trial relapse in Study ECU-NMO-301 and who then transitioned to eculizumab in Study ECU-NMO-302 remained relapse free.

Table 8: Studies ECU-NMO-301/302 Summary of relapse experience for patients free from adjudicated on-trial relapse in Study ECU-NMO-301 (full analysis set free from adjudicated on-trial relapse)

	Treatment Group in Study ECU-NMO-301 Placebo (N=27)	Treatment Group in Study ECU-NMO-301 Eculizumab (N=93)
Patients enrolled in Study ECU-NMO-302	23	75
Patients free from adjudicated on-trial relapse in Study ECU-NMO-302	22	72
Proportion of patients enrolled in Study ECU-NMO-302 who remained free from adjudicated on-trial relapse in Study ECU-NMO-302 (1)	95.7%	96.0%
Patients free from adjudicated on-trial relapse in Studies ECU-NMO-301 and ECU-NMO-302 regardless of enrollment status of Study ECU-NMO-302	26	90
Proportion of patients who remained free from adjudicated on-trial relapse in Study ECU-NMO-302 (2)	96.3%	96.8%

Source: Studies ECU-NMO-301 and ECU-NMO-302, Table 352.

(1) Number of patients free from adjudicated on-trial relapse in ECU-NMO-302 divided by the number of patients enrolled in ECU-NMO-302

(2) Number of patients free from adjudicated on-trial relapse in both ECU-NMO-301 and ECU-NMO-302 regardless of enrollment status of ECU-NMO-302 divided by the number of patients free from adjudicated on-trial relapse in ECU-NMO-301.

3. ***In the pivotal study, 21.9% of patients in eculizumab group were not treated with immunosuppressive therapy at Baseline.***

   – ***What was the treatment regimen for these patients during study period?***

During the treatment period of Study ECU-NMO-301, Investigators were not permitted to make changes to the patients' background ISTs. As such, patients who were not treated with ISTs at Baseline were treated with eculizumab monotherapy for the study duration.

   – ***Were they treated with an immunosuppressive therapy during the study period? If so, which immunosuppressive therapy was used and what was the rationale for selection of immunosuppressive therapy?***

As noted, none of the patients who were not treated with an IST at Baseline were treated with an IST during the trial. They were all maintained on eculizumab alone.

   – ***Was the same rationale applied for patients in placebo group?***

In this randomized, double blind, placebo controlled trial, no patients in Study ECU-NMO-301 were permitted to have any changes to their background ISTs. Placebo patients who were not on background IST at Baseline were therefore considered to be 'pure placebo' patients and were maintained as such throughout the trial.

   – ***Similarly, 27.1% and 42.6% of patients in eculizumab and placebo groups respectively were treated with Rituximab at Baseline. What was the treatment regime for these patients when Rituximab was discontinued at Baseline?***

During Study ECU-NMO-301, rituximab was not permitted as background therapy based on the potential effects of eculizumab on the efficacy of rituximab. This criterion was not based on safety reasons related to concomitant use with eculizumab. Rituximab is not

approved for the treatment of patients with NMOSD. Rituximab has been used off-label in patients with NMOSD as it selectively depletes B-cells mainly through complement mediated cytotoxicity. In whole blood assays, rituximab mediated B cell lysis is inhibited by 90% in the presence of eculizumab.[19] There have been no clinical studies evaluating concomitant administration of eculizumab and rituximab. However, based on the potential inhibitory effect of eculizumab on complement-dependent cytotoxicity of rituximab, patients could be at risk of a reduction of the expected pharmacodynamics effects of rituximab. Sponsor agrees that rituximab had been discontinued for all patients prior to baseline. Patients who had previously been treated with rituximab had been transitioned to a number of different ISTs by their treating physicians prior to the trial, including some patients on no IST at trial baseline. IST subgroups are presented by treatment arm for patients with historical use of rituximab in Table 9.

Table 9: Subgroup of supportive immunosuppressive therapy use at Baseline for patients with historical use of rituximab (full analysis set with historical use of rituximab)

IST Subgroup	Statistic	Placebo (N=20)	Eculizumab (N=26)	Total (N=46)
Steroids Alone	n (%)	3 (15.0)	3 (11.5)	6 (13.0)
AZA SubGroup	n (%)	4 (20.0)	4 (15.4)	8 (17.4)
AZA alone	n (%)	3 (15.0)	4 (15.4)	7 (15.2)
AZA + Steroids	n (%)	1 (5.0)	0	1 (2.2)
MMF SubGroup	n (%)	5 (25.0)	11 (42.3)	16 (34.8)
MMF alone	n (%)	3 (15.0)	7 (26.9)	10 (21.7)
MMF + Steroids	n (%)	2 (10.0)	4 (15.4)	6 (13.0)
Other IST(s)	n (%)	1 (5.0)	1 (3.8)	2 (4.3)
Other IST(s) alone	n (%)	0	1 (3.8)	1 (2.2)
Other IST(s) + Steroids	n (%)	1 (5.0)	0	1 (2.2)
No IST Usage	n (%)	7 (35.0)	7 (26.9)	14 (30.4)

Source: Study ECU-NMO-301, Table 353.

Request for independent expert advice

The Delegate sought and received independent expert clinical advice on the following.

1. ***Rituximab and mitoxantrone were not permitted as background therapies in the pivotal study. Please comment on the external validity (whether this approach will have an implication on the treatment paradigm of NMOSD) of this approach.***

The approach of rituximab and mitoxantrone not being permitted as background therapies in the pivotal study is considered as externally valid. It would not have any implications on the study findings.

2. ***Please comment on the potential benefits of establishing registry for patients with NMOSD.***

Establishing a NMOSD patient registry would be a good initiatives. Potential benefits includes long term safety data.

[19] Bologna L, Gotti E, Manganini M, et al. Mechanism of action of type II, glycoengineered, anti-CD20 monoclonal antibody GA101 in B-chronic lymphocytic leukemia whole blood assays in comparison with rituximab and alemtuzumab. *J Immunol*. 2011;186(6):3762-3769.

3. ***Considering the incidence of NMOSD in children, what is your opinion to have the age limit (> 18 years) to be mentioned in the proposed indication (the pivotal study was conducted in adults)?***

It will be appropriate to have age limit (> 18 years) mentioned in the proposed indication.

4. ***What is your opinion regarding when and how to re-consider continued use of eculizumab for the treatment of AQP-4 autoantibody positive patients with NMOSD? Study ECU-NMO-301 was not designed to examine this aspect.***

It would be a case-by-case basis approach. Multiple factors such as treatment response, would need to be taken into consideration to determine when and how to re-consider the use of eculizumab for treatment of AQP-4 autoantibody positive patients with NMOSD.

Advisory Committee considerations[20]

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 Soliris (eculizumab rmc) for 300 mg intravenous infusion, indicated for the following extension of indications:

> *Adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.*
>
> *Soliris is not intended for acute treatment of a NMOSD relapse.*

As such, the full indications at this time were:

Soliris is indicated for the treatment of patients with:

- *Paroxysmal Nocturnal Haemoglobinuria (PNH) to reduce haemolysis.*
- *atypical Haemolytic Uraemic Syndrome (aHUS).*
- *Adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody-positive.*

Soliris is not intended for acute treatment of a NMOSD relapse.

Specific conditions of registration applying to these goods

- Soliris (eculizumab) is to be included in the Black Triangle Scheme. The PI, CMI and all additional risk minimisation materials for Soliris must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

[20] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

- The Soliris EU-Risk Management Plan (RMP) (version 19.3, dated 22 July 2019, data lock point 30 September 2018), with Australian Specific Annex (version 6.1, dated 23 March 2020), included with submission PM-2019-04825-1-1, and any subsequent revisions, as agreed with 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 the 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.
- For all injectable products the PI must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Soliris 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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