7.05 ECULIZUMAB, Solution concentrate for I.V. infusion 300 mg in 30 mL, Soliris®, Alexion Pharmaceuticals Australasia Pty Ltd

1 Purpose of submission

1.1 The Standard Re-Entry submission requested a Section 100 (Highly Specialised Drug) PBS listing for eculizumab for the treatment of patients with neuromyelitis optica spectrum disorder (NMOSD) who are aquaporin-4 positive (AQP4+) with an Expanded Disability Status Scale (EDSS) score ≤ 7, and who have either frequent relapses, or a prior immunosuppressive event. The PBAC previously considered eculizumab for NMOSD in November 2020.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus best supportive care.

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Patients with neuromyelitis optica spectrum disorder who are AQP4 positive and have an EDSS score of 0-7[a] and who have either frequent relapses or a prior immunosuppressive event
Intervention	Eculizumab (900 mg intravenous infusion weekly for first 4 weeks followed by fortnightly 1,200 mg intravenous infusions from Week 5) with best supportive care
Comparator	Best supportive care alone
Outcomes	Reduction in relapse frequency leading to a reduction in disability progression and mortality
Clinical claim	Eculizumab is superior in terms of efficacy and non-inferior in terms of safety compared to placebo

Source: Table 1-1 (p 3) of the resubmission

Abbreviations: AQP4, aquaporin 4 antibody; EDSS, Expanded Disability Status Scale

[a] A criterion for patients to have an EDSS score 0-7 was included in the proposed restriction to better align with the PREVENT trial criteria

2 Background

Registration status

2.1 Eculizumab was approved by the TGA on 1 July 2020 for the following indication:

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

2.2 Eculizumab is also currently TGA approved for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome.

Previous PBAC consideration

2.3 The matters of concern from the November 2020 PBAC meeting are summarised in Table 2.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
The PBAC noted that the proposed PBS restriction was broader than the inclusion criteria of the key trial (PREVENT)… The PBAC considered that the restriction should align with the inclusion criteria of the trial in terms of EDSS score, frequency and number of prior relapses (para 7.4, eculizumab Public Summary Document [PSD], November 2020)	The proposed restriction has been amended to align with the PREVENT trial in terms of frequency and number of prior relapses, and EDSS score. The ESC considered that this was appropriate.
The PBAC noted that the submission nominated best supportive care as the primary comparator. The PBAC considered that rituximab, which is funded through some public hospitals as a preventative treatment for relapse, is a relevant comparator…The PBAC considered exclusion of rituximab from the trial population may affect the generalisability of the results to clinical practice (para 7.6, eculizumab PSD, November 2020)	The resubmission maintained that rituximab was not an appropriate comparator as eculizumab would be used after rituximab. A systematic review was included summarising the evidence for the use of rituximab in the treatment of NMOSD, but no treatment comparison was conducted, and no claim was made against rituximab. The Pre-Sub-Committee Response (PSCR) stated that the exchangeability between the rituximab trials and the eculizumab trial was problematic and the rituximab evidence was not applicable to the Australian setting.
The PBAC noted that there were no statistically significant differences in disability or quality of life measures, but that the results generally favoured eculizumab. The PBAC agreed with ESC that because patients completed the PREVENT trial six weeks after relapse, it was unclear whether the changes in disability progression represented temporary differences or permanent effects (para 7.10, eculizumab PSD, November 2020)	The resubmission included new post hoc analyses of PREVENT and the open label extension study including a longer (120 day) follow-up post relapse, regardless of treatment assignment. The change in EDSS of 0.3 per relapse based on the change in EDSS at 120 days was used to inform disability progression in the economic model. The ESC noted that the longer follow up was more informative; however, the change in EDSS score did not reach significance ($p = 0.137$), likely due to small patient numbers, and remained uncertain. No additional comparative data were provided.
The PBAC also noted that the submission presented no evidence that eculizumab reduced mortality or extended life for patients with NMOSD (para 7.10, eculizumab PSD, November 2020)	Not addressed in the resubmission
In addition, the PBAC considered that the impact of reducing relapses remained unclear in terms of the magnitude of the effect on disability progression and quality of life due to the limited follow-up in the PREVENT trial (para 7.11, eculizumab PSD, November 2020)	Not addressed in the resubmission
The PBAC noted that the submission did not present an economic analysis for the use of eculizumab in patients who have had a prior immunosuppressive event, therefore the cost effectiveness of eculizumab in this population could not be assessed. (para 7.13, eculizumab PSD, November 2020)	Not addressed in the resubmission

Matter of concern	How the resubmission addresses it
The relapse definition used in the model was based on adjudication by an independent committee, which may underestimate the frequency of relapses in clinical practice which would be assessed by the treating physician (para 7.15, eculizumab PSD, November 2020)	The economic model applies relapse rates as determined by the treating physician
The economic model applied a 53 year time horizon compared to 1-2 years in the PREVENT trial, which the PBAC considered increased the uncertainty of the model. The PBAC noted that the majority of the incremental benefits, which included patients treated with eculizumab averaging 1.6 fewer relapses and gaining 4.6 life years compared to those treated with placebo, occurred in the extrapolated period (para 7.15, eculizumab PSD, November 2020)	Not addressed in the resubmission
The submission assumed 7% of relapses were fatal based on Mealy 2018, an observational study. The PBAC noted that removing mortality from the economic model resulted in a 27% increase in the ICER. The PBAC considered the assumption of a survival benefit with eculizumab treatment, due to a reduction in fatal relapses, was not demonstrated in the trial data and was not supported by the observational data presented in the submission (para 7.15, eculizumab PSD, November 2020)	An alternative source of NMOSD mortality data was identified (Kitley 2012), and a relapse-specific mortality rate of 2.3% was applied in the economic model
Utility values were based on a limited number of observations from the PREVENT trial (para 7.15, eculizumab PSD, November 2020)	Not addressed in the resubmission
The PBAC considered that a substantial price reduction would aid in mitigating the uncertainties in the model and potentially achieve an ICER in an acceptable range (para 7.16, eculizumab PSD, November 2020)	The resubmission included a proposed special pricing arrangement, with an effective DPMQ consisting of a [redacted]% rebate on the published price
The PBAC considered that, at the proposed price, the cost of eculizumab to the PBS/RPBS of $[redacted][1] over the first six years (updated PSCR estimates) for less than < 500 patients was very high. The PBAC considered that the restriction should more closely align with the inclusion criteria of the trial (para 7.17, eculizumab PBAC PSD, November 2020).	The resubmission applied an alternative methodology (prevalence-based approach rather than mixed incidence/prevalence approach), which resulted in a higher estimated prevalence compared with the November 2020 submission, and corrected a number of logical inconsistencies that occurred with the mixed incidence/prevalence approach used in the previous submission. The resubmission also applied changes to the majority of inputs used in the analysis, including eligibility criteria (new EDSS criterion and narrower definition of frequent relapses), uptake rates, compliance, and price.
The sponsor in its pre-PBAC response proposed a RSA. The PBAC noted that the proposed RSA was based on patient numbers that were substantially higher that the estimated number of treated patients and considered this was inappropriate. Further, the pre-PBAC response did not provide any details on the proportion of the rebate for any utilisation above the cap offered in the RSA (para 7.18, eculizumab PSD, November)	The resubmission included a proposal for a RSA with an updated patient number cap, based on the total number of patients on treatment. This reduces the cap compared to the first submission

Source: the resubmission

Abbreviations: DPMQ, dispensed price for maximum quantity; EDSS, Expanded Disability Status Scale; ICER, incremental cost-effectiveness ratio; NMOSD, neuromyelitis optica spectrum disorders; PSCR, pre-subcommittee response; RSA, risk share agreement

The redacted values correspond to the following ranges: [1] $200 million to < $300 million

2.4 Eculizumab is currently subsidised under the PBS for the treatment of atypical haemolytic uraemic syndrome (aHUS). Eculizumab is currently subsidised under the Life Saving Drugs Program (LSDP) for the treatment of paroxysmal nocturnal haemoglobinuria.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 The resubmission presented a revised restriction to align with the PREVENT trial – additions to the November 2020 restriction are in italics and deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Published (effective) Dispensed Price for Maximum Quantity	Proprietary name and manufacturer
Initial treatment					
Eculizumab, 300 mg/30 mL injection, 30 mL vial	12	12	0	Public hospital: $[redacted] ($[redacted]) Private hospital: $[redacted] ($[redacted])	Soliris® Alexion
Continuing treatment					
Eculizumab, 300 mg/30 mL injection, 30 mL vial	8	8	5	Public hospital: $[redacted] ($[redacted]) Private hospital: $[redacted] ($[redacted])	Soliris® Alexion

Episodicity:	Relapsing
Condition:	Neuromyelitis optica spectrum disorder (NMOSD)
PBS Indication:	Patients with NMOSD
Treatment phase:	Initial
Restriction:	☒Authority Required - In Writing
Treatment criteria:	Patient must be treated by a neurologist
Clinical criteria:	Patient must have a confirmed diagnosis of NMOSD with AQP4-IgG *AND* *An Expanded Disability Status Scale (EDSS) score of 0–7* AND ~~Patient must have had at least one relapse in the last 12 months with at least two relapses in the last 24 months~~ *Patient must have had at least two relapses in the last 12 months or three relapses in the last 24 months with at least one relapse in the previous 12 months despite treatment with immunosuppressive therapy* OR Patient must have experienced immunosuppression associated serious adverse event that requires treatment discontinuation and when switching to another immunosuppression therapy is clinically inappropriate
Definitions	NMOSD with AQP4-IgG defined as: positive test for AQP4-IgG using best available detection method
Prescriber Instructions	*This drug is not PBS-subsidised if it is prescribed to a public hospital inpatient*

3.2 The resubmission proposed a special pricing arrangement (SPA) with an effective price based on a [redacted]% reduction from the published price. The published price per vial remained unchanged from the previous submission.

3.3 The requested restriction is narrower than the current TGA indication, which covers a broad population of patients with AQP4+ NMOSD and does not specify the number of required relapses, EDSS, or adverse events from immunosuppressive therapies. Although the TGA indication is limited to adult patients, the requested restriction does not include an age limit. A study of weight-based eculizumab dosing in paediatric patients with NMOSD is due for completion in November 2021 (ECU-NMO-303).

3.4 The requested restriction was revised to align with the PREVENT eligibility criteria in terms of frequency and number of prior relapses despite treatment with immunosuppressive therapies, and in terms of EDSS score requiring a score between 0 and 7. These changes were consistent with PBAC's consideration of the November 2020 submission (paragraph 7.4, eculizumab Public Summary Document (PSD), November 2020). The proposed restriction would allow treatment of patients who had experienced prior immunosuppression-related serious adverse events, without needing to meet any relapse criteria, which is not consistent with the eligibility criteria of the PREVENT trial (all patients were required to have frequent relapses regardless of prior treatment history).

3.5 If eculizumab is positioned as a last line therapy (see paragraphs 5.4 and 5.5) the ESC considered that the restriction would need to define the proposed patient population more clearly. The ESC noted that the restriction presented above potentially allows for relapses to occur in the context of suboptimal immunosuppressive therapies (e.g. glucocorticoids alone) and is therefore not explicit in the intent that patients need to fail all other potentially efficacious treatments (e.g. rituximab, other immunosuppressive therapies) before accessing eculizumab. In addition, the ESC noted that the proposed restriction should consider that (i) relapse in the context of rituximab use where there has been repopulation of B cells; and (ii) relapse soon after initiating any immunosuppression, does not always indicate drug failure.

3.6 The ESC also considered that the definitions of 'immunosuppression associated serious adverse event' and 'clinically appropriate' should be clarified.

3.7 The pre-PBAC response provided revisions to the proposed restriction positioning eculizumab as a last-line treatment in patients who relapsed 'despite an adequate trial of other accessible preventative treatment for NMOSD including rituximab azathioprine and mycophenolate'. The revisions also defined immunosuppressive associated adverse events as including:

- Immunosuppression associated recurrent skin cancer and other malignancies;
- recurrent immunosuppression associated infections such as shingles or cytomegalovirus; and

- hypogammaglobulinaemia resulting in recurring and/or serious bacterial infections such as those requiring intravenous antibiotics (in hospital treatment).

3.8 The requested restriction did not include any specific criteria for continuation of therapy.

3.9 Eculizumab is only being considered for outpatient use. Treatment of admitted patients (public and private) in public hospitals remains the responsibility of the states and territories. The PBAC noted that the statement that 'This drug is not PBS-subsidised in it is prescribed to a public hospital in-patient' was added to the proposed restriction as advised in November 2020.

3.10 The Pre-Sub-Committee Response (PSCR) provided a reference source for the EDSS which is freely available for use in the restriction.[1]

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Neuromyelitis optica spectrum disorders (NMOSD) are a collection of inflammatory disorders of the central nervous system that predominantly target the optic nerves and spinal cord and are associated with severe, immune-mediated demyelination and axonal damage.

4.2 Patients with NMOSD typically have a disease course characterised by acute clinical attacks (relapses) followed by partial/full recovery and periods of clinical stability (remissions). Relapses are unpredictable with respect to timing, frequency and severity and incomplete recovery can result in the accumulation of disability. The symptoms associated with relapse vary based on the location of the attack and can include visual loss/blindness, loss of colour vision, pain with eye movement, central scotoma, bilateral motor weakness, loss of sensation, paraesthesia, tonic spasms, neuropathic pain, bladder/bowel dysfunction, nausea, vomiting, vertigo, respiratory failure and prolonged hiccoughs.

4.3 Relapses may be managed in the community setting or require hospitalisation depending on the severity of relapse. Acute management typically involves the use of high dose corticosteroids (oral or intravenous) with more severe or treatment-resistant relapses treated with plasma exchange. Intravenous immunoglobulin (IVIg) may also be used in patients failing other therapies.

4.4 There is disease-specific mortality associated with NMOSD, however rates vary substantially between studies. The mortality associated with NMOSD has substantially decreased over time with the inclusion of less severe patients under the diagnostic

[1] Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology. 1983;33(11):1444-1452.

umbrella of NMOSD and the use of immunosuppressive therapy and plasma exchange. In November 2020 the PBAC considered current mortality associated with NMOSD was unclear but appears to be low (paragraph 4.6, eculizumab PSD, November 2020).

4.5 NMOSD was previously considered a variant of relapsing-remitting multiple sclerosis (RRMS) due to its similar clinical presentations but is now generally recognised as a separate clinical entity. Key differences between NMOSD and RRMS include the presence of AQP4 antibodies (observed in most NMOSD patients but not RRMS patients), the risk of converting to a secondary progressive disease course (rare in NMOSD but common in RRMS patients) and the efficacy of immunomodulatory treatments (many treatments used for RRMS appear to be non-effective or harmful in NMOSD).

4.6 Patients with NMOSD who are AQP4+ represent the largest subgroup of patients with NMOSD (70-90% of cases). This subgroup is characterised by a high female to male ratio (up to 9:1) and a mean age at onset of approximately 40 years.

4.7 The resubmission noted that antibody testing is currently reimbursed on the Medicare Benefits Schedule via item 71119 (detection of antibodies to tissue antigens not otherwise specified). However, a separate item number for AQP4 and MOG testing was supported by MSAC in July 2020 as the existing item subsidises AQP4/MOG testing at a lower level than charged by providers (MSAC Application 1582).

4.8 The worldwide prevalence of NMOSD ranges from approximately 0.5 to 4 patients per 100,000 population. However, these estimates are highly variable given observed racial associations with NMOSD (higher in African and Asian [particularly Japanese] populations) and evolving diagnostic criteria.

4.9 The resubmission included a Personal Experience Expectation Knowledge (PEEK) study into NMOSD in Australia conducted by The Centre for Community Driven Research. A number of themes emerged from this study around the impact of living with NMOSD. In particular, people with NMOSD highlighted feelings of anxiety around disease progression, disease impacts on quality of life and mental health, concerns around caregiver burden, and effects on relationships. The most common response provided by participants was that the goal of treatment is to maintain their condition and prevent worsening or relapses (7/18, 39%).

4.10 Eculizumab is a monoclonal antibody that binds to the C5 terminal complement protein and inhibits it cleavage into pro-inflammatory components (C5a and C5b). It is presumed that the therapeutic effects of eculizumab are due to a reduction in inflammation although the exact mechanism of action in NMOSD is currently unknown.

4.11 The resubmission positioned eculizumab as a second-line preventative therapy in AQP4+ NMOSD patients who experience frequent relapses despite best supportive care or who cannot use best supportive care due to a prior immunosuppressive event

(e.g. malignancies, recurrent infections or hypogammaglobinaemia associated with immunosuppression). Best supportive care generally consists of low dose oral corticosteroids and/or other immunosuppressive agents (rituximab, azathioprine, mycophenolate mofetil, methotrexate or mitoxantrone). Local advice also indicated that some patients may also be managed with recurrent IVIg infusions. The pre-PBAC response positioned eculizumab as a last-line therapy when other treatment options, including rituximab, have failed.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The resubmission maintained that best supportive care, consisting of immunosuppressive therapies including azathioprine, rituximab, mycophenolate mofetil, chronic corticosteroid use and rarely, methotrexate, was the appropriate comparator. The PBAC previously considered that best supportive care may be a reasonable main comparator (paragraph 5.3 eculizumab PSD, November). However, the PBAC also considered that rituximab, which is funded through some public hospitals as a preventative treatment for relapse, is a relevant comparator as (i) due to the incompatibilities between the mechanisms of action, eculizumab and rituximab will not be used in combination; and (ii) eculizumab is likely to replace use of rituximab in clinical practice (paragraph 7.6, eculizumab PSD, November 2020).

5.2 The resubmission reiterated arguments from the initial submission, maintaining that rituximab was not an appropriate comparator because there was no universal access to rituximab in Australia. Additionally, the resubmission stated that as rituximab has not been approved by the TGA or by other regulatory agencies internationally for the treatment of NMOSD, safety and effectiveness have not been established. The PSCR reiterated that rituximab is neither TGA registered nor PBS reimbursed for patients with NMOSD and stated that this posed an equity of access issue. The ESC noted that, although used off-label in NMOSD patients, rituximab is considered to be standard of care in the treatment of this condition. In addition, the ESC noted that biosimilar versions of rituximab were available which at least partly overcome the equity of access issues described. The pre-PBAC response noted that the September 2021 PBAC recommendation that rituximab have an unrestricted listing, meant that rituximab would soon be available on the PBS for patients with NMOSD.

5.3 The resubmission stated that the proposed restriction for eculizumab is in frequently relapsing patients with AQP4+ NMOSD not responding to other immunosuppressive treatments, which included rituximab. Therefore, eculizumab is positioned after rituximab treatment as a last line therapy and will not be used at the same point in the treatment algorithm.

5.4 The ESC considered that if eculizumab was to be used as a last line therapy when all other treatment options, including an adequate trial of rituximab, had failed, then:

- the population of the PREVENT trial was not applicable as the trial population was not representative of patients receiving last line therapy, noting that the inclusion criteria did not require relapses to occur while on treatment and baseline therapies included glucocorticoids alone and no treatment (see Table 3). The pre-PBAC response stated that the majority of patients were pre-treated with a range of immunosuppressive therapies, noting that 93% of patients received supportive immunosuppressive therapies for NMOSD prior to entering the PREVENT trial and more than 75% of patients were receiving immunosuppressive therapies at the time of their historical relapses. The ESC also noted that evidence supporting the likely efficacy of eculizumab when used in the last line population would need to be presented
- the restriction would need to define the proposed patient population more clearly (see paragraphs 3.5 to 3.7).

5.5 If the positioning of eculizumab was as an alternative to immunosuppressive therapies in more severe cases of NMOSD, then the ESC considered that a comparison with rituximab would be valid. The pre-PBAC response stated that the available evidence for rituximab in NMOSD was poor and does not inform the magnitude of effect relative to best supportive care.

Table 3: Prior therapies of patients in the PREVENT trial at baseline

	Eculizumab (N = 96)	Placebo (N = 47)	All patients (N = 143)
None	21 (22%)	13 (28%)	34 (24%)
Glucocorticoids alone	16 (17%)	11 (23%)	27 (19%)
Azathioprine +/- glucocorticoids	37 (39%)	13 (28%)	50 (35%)
Mycophenolate mofetil +/- glucocorticoids	17 (18%)	8 (17%)	25 (17%)
Other drug +/- glucocorticoids	5 (5%)	2 (4%)	7 (5%)
Rituximab	26 (27%)	20 (43%)	46 (32%)

Source: Table 1, p619 of Pittock et al, Eculizumab in AQP4 NMOSD, NEJM, 2019;381(7)

5.6 The resubmission noted that since the initial eculizumab submission in November 2020, satralizumab has been registered on the ARTG for the treatment of adults with NMOSD who have AQP4+ status as monotherapy or in combination with immunosuppressive therapies and is therefore a potential near-market comparator.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, advising that relapses in NMOSD were common and that 50% of patients are wheelchair bound or blind by 5 years. The clinician also discussed the use of rituximab in patients with NMOSD,

advising that some patients were refractory to rituximab.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described the clinical need for new, effective treatments for NMOSD such as eculizumab and noted that eculizumab was associated with fewer side effects than other available treatments. The health care professionals also described the nature of the disease progression and provided case studies as examples.

6.3 The PBAC noted the advice received from MS Australia which highlighted the differences between multiple sclerosis (MS) and NMOSD, including the fact that NMOSD relapses are generally more severe, last longer and occur more often than MS relapses and that most patients do not recover completely from relapses. MS Australia also noted that there was a clinical need for effective NMOSD treatments, particularly in the approximately 25% of patients who continue to relapse on rituximab. Advice was also received from the Centre for Community-Driven Research which was included in the resubmission and is described in paragraph 4.9.

Clinical studies

6.4 The resubmission was based on the following evidence:

- A head-to-head randomised trial comparing eculizumab to placebo in patients with AQP4+ NMOSD (PREVENT), which was presented in the original submission, with additional studies presented as supportive data:
  - an open-label extension study of patients previously enrolled in the PREVENT trial (ECU-NMO-302), with an updated data cut (July 2019) compared with the original submission (October 2018)
  - a combined analysis of the PREVENT trial and the open label extension study (ECU-NMO-302; published in Wingerchuk et al., 2019)
  - a single arm study including NMOSD AQP4+ patients treated with eculizumab at a lower than recommended dose (Pittock et al., 2013)
- A systematic review summarising the results of two RCTs of rituximab for the treatment of NMOSD (Appendix A of the resubmission). During the evaluation, five additional published systematic reviews of rituximab in NMOSD were identified
- A systematic review summarising the results of two RCTs of satralizumab for the treatment of NMOSD, and an indirect comparison of eculizumab versus satralizumab (Appendix B of the resubmission).

6.5 Details of the included studies are provided in the table below.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Eculizumab studies		
PREVENT (ECU-NMO-301)	Alexion (2018). ECU-NMO-301 clinical study report. A randomized, double-blind, placebo controlled, multi-center trial to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica	Internal study report
	Pittock, SJ et al (2019). Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder.	New England Journal of Medicine, 381: 614-625
	A randomised, double-blind, placebo-controlled, multi-center trial to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica	Clinical trial registry; NCT01892345, EUCTR 2013-001150-10
ECU-NMO-302	Alexion (2018). ECU-NMO-302 clinical study report. A phase III, open-label, extension trial of ECU-NMO-301 to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica (NMO). Nov 2018.	Interim internal study report
	Wingerchuk et al (2019). Long-term safety and effectiveness of eculizumab in neuromyelitis optica spectrum disorder.	ECTRIMS 2019 conference abstract (abstract no. 142)
	An Open-Label Extension Trial of Eculizumab in Relapsing NMO Patients.	Clinical trial registry; NCT02003144
Rituximab		
Nikoo (2017)	Nikoo Z, Badihian S, Shaygannejad V, Asgari N, Ashtari F. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: a randomized clinical trial.	Journal of Neurology. 2017; 264(9): 2003-9.
	Comparison of Clinical Effects of Azathioprine and Rituximab NMO-SD Patients.	Clinical trial registry; NCT03002038
RIN-1	Tahara M, Oeda T, Okada K, Kiriyama T, Ochi K, Maruyama H, et al. Safety and efficacy of rituximab in neuromyelitis optica spectrum disorders (RIN-1 study): a multicentre, randomised, double-blind, placebo-controlled trial.	The Lancet Neurology. 2020;19(4):298-306.
Wang (2021)	Wang Y, Chang H, Zhang X, Yin L. Efficacy of rituximab in the treatment of neuromyelitis optica spectrum disorders: An update systematic review and meta -analysis.	Multiple Sclerosis and Related Disorders. 2021; 50:102843.
Mirmosayyeb (2021)	Mirmosayyeb O, Shaygannejad V, Barzegar M, Nehzat N, Ghajarzadeh M. Efficacy and safety of rituximab in treating patients with Neuromyelitis optica spectrum disorder (NMOSD): A systematic review and meta-analysis.	Autoimmunity Reviews. 2021; 20(2):102727.
Damato (2016)	Damato V, Evoli A, Iorio R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis.	JAMA Neurology. 2016; 73(11):1342-1348
Huang (2019)	Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis.	Multiple Sclerosis and Related Disorders. 2019; 35:246-252.
Gao (2019)	Gao F, Chai B, Gu C, Wu R, Dong T, Yao Y, Zhang Y. Effectiveness of rituximab in neuromyelitis optica: a meta-analysis.	BMC Neurology. 2019;19(1):36.
Satralizumab		
SAkuraSky	Yamamura et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder.	New England Journal of Medicine. 2019; 381:2114-24.

Trial ID	Protocol title/ Publication title	Publication citation
	Efficacy and Safety Study of Satralizumab (SA237) as Add-on Therapy to Treat Participants With Neuromyelitis Optica (NMO) and NMO Spectrum Disorder (NMOSD)	Clinical trial registry; NCT02028884
SAkuraStar	Traboulsee et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial.	The Lancet Neurology. 2019; 19: 402–12.
	Efficacy and Safety Study of Satralizumab (SA237) as Monotherapy to Treat Participants With Neuromyelitis Optica (NMO) and Neuromyelitis Optica Spectrum Disorder (NMOSD)	Clinical trial registry; NCT02073279

Source: the resubmission; *additional sources identified during the evaluation*
Note: Abstracts of studies with full publications are not presented

6.6 The key features of the PREVENT trial are summarised in the table below.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Eculizumab vs. placebo						
PREVENT	143	Multicentre, randomised, double-blind. Ecu: 1.8 years; Pbo: 1.1 years	Unclear	NMOSD patients with frequent relapses who are AQP4+	Time to first relapse, relapse rate, disability progression, quality of life	Risk of relapse, treatment efficacy, treatment discontinuation, health state utility values

Source: the resubmission
Abbreviations: AQP4+, aquaporin-4 positive; Ecu, eculizumab; NMOSD, neuromyelitis optica spectrum disorder; Pbo, placebo

6.7 In its consideration of the November 2020 submission, the PBAC noted that the key limitations of the PREVENT trial included the significant number of protocol changes, the higher proportion of patients who discontinued treatment in the eculizumab arm (16.7%) compared to in the placebo arm (6.4%) and the large number of protocol violations (paragraph 7.7, eculizumab PSD, November 2020).

6.8 Patients included in the PREVENT trial were required to have frequent relapses regardless of any prior history of immunosuppressive events. This was inconsistent with the proposed PBS population, which did not specify any relapse criteria for the subgroup of patients with prior immunosuppressive events. If there is a lower absolute risk of relapse in this population, it is likely that the magnitude of benefit associated with eculizumab treatment will be reduced.

6.9 Rituximab was not permitted as a background immunosuppressive therapy in the PREVENT trial due to conflicting mechanisms of action with eculizumab. The resubmission acknowledged that this was not representative of best supportive care in Australia, which can include the use of rituximab treatment. However, the resubmission argued that treatment outcomes in the placebo arm would broadly generalisable to clinical practice as many patients had stopped rituximab treatment prior to enrolment, prior rituximab use was not a treatment effect modifier, and relapse rates while using eculizumab were lower than historical relapse rates that included patients using rituximab. Available published data suggest that rituximab is

an effective treatment for NMOSD and there may be clinically important differences amongst existing immunotherapies (Damato 2016, Huang 2019, Gao 2019, Nikoo 2017, Wang 2021). Additionally, the submission did not address the optimisation of background therapies and it is unclear whether the intensity of background treatment (no therapy, monotherapy, combination therapy) was representative of Australian clinical practice.

Comparative effectiveness

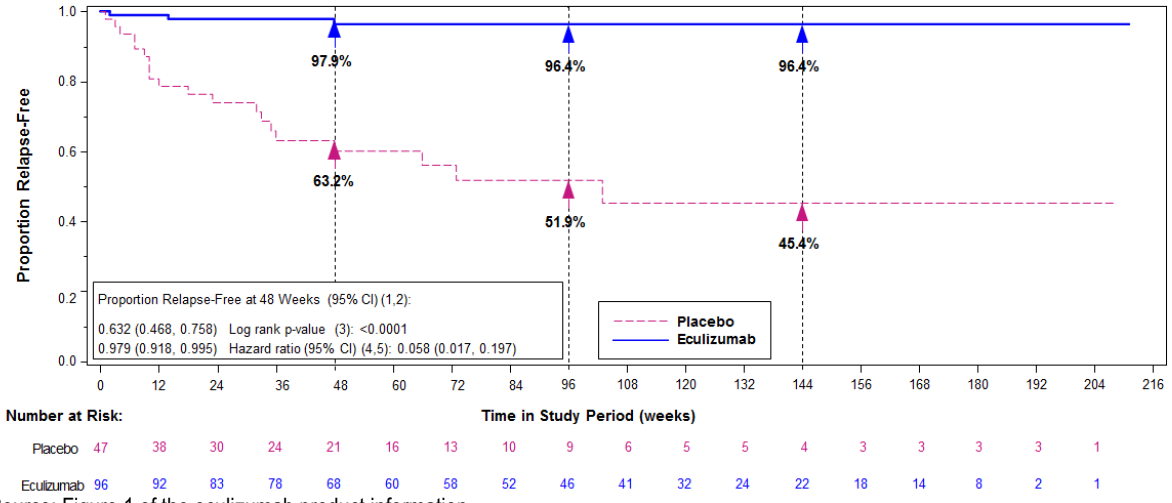
6.10 The key results of the PREVENT trial were unchanged in the resubmission.

6.11 Compared with the November 2020 submission, key changes in the clinical evidence presented included:

- post-hoc subgroup analyses based on the PREVENT trial, that were not available in the original trial report
- a new interim analysis of the ECU-NMO-302 open label extension study (data cut July 2019, as compared to October 2018 in the original submission)
- systematic reviews summarising the evidence for rituximab and satralizumab for the treatment of NMOSD, and an indirect comparison of eculizumab versus satralizumab were included.

6.12 The time to first adjudicated relapse with eculizumab and placebo in the PREVENT trial is presented below.

Figure 1: Kaplan-Meier curve for the time to first adjudicated relapse in the PREVENT trial



Source: Figure 1 of the eculizumab product information
Abbreviations: CI, confidence interval

6.13 Treatment with eculizumab was associated with a statistically significant improvement in the time to first adjudicated relapse compared to placebo (hazard ratio (HR) = 0.058; 95% confidence interval (CI): 0.017, 0.197).

6.14 A comparison of annualised relapse rates between eculizumab and placebo in the PREVENT trial is summarised below.

Table 6: Annualised relapse rates reported in the PREVENT trial

Outcome	Number of relapses	Patient years of follow-up	Annualised relapse rate (95% CI)	Rate ratio (95% CI)	P-value
Adjudicated relapses					
Eculizumab (N = 96)	3	171.32	0.016 (0.005, 0.050)	0.045 (0.013, 0.151)	< 0.0001
Placebo (N = 47)	21[a]	52.41	0.350 (0.199, 0.616)		
On-trial relapses (assessed by treating physician)					
Eculizumab (N = 96)	14	171.32	0.066 (0.036, 0.120)	0.147 (0.078, 0.278)	< 0.0001
Placebo (N = 47)	31[b]	52.41	0.446 (0.272, 0.732)		

Source: Table 2-18 (p 72), Table 2-19 (p 72) of the resubmission; Table 34 (p 119) of the PREVENT trial report
Abbreviations: CI, confidence interval
[a] One patient had two adjudicated on trial relapses.
[b] Two patients each had two adjudicated on-trial relapses

6.15 Treatment with eculizumab was associated with a statistically significant reduction in adjudicated annualised relapse rate compared to placebo (rate ratio (RR) = 0.045; 95% CI: 0.013, 0.151). However, the difference between treatment arms was reduced when on-trial relapses were assessed by the treating physician (RR = 0.147; 95% CI: 0.078, 0.278).

6.16 Interim results of the longer-term extension study ECU-NMO-302 indicated a physician-assessed annualised relapse rate of 0.097 (18 relapses over 185.26 patient-years; Table 2-32 p105 of the resubmission, July 2019 data analysis) in patients treated with eculizumab as compared to a relapse rate of 0.032 (9 relapses over 279.30 years) at the October 2018 data analysis. Further analyses suggested a decrease in the on-trial physician-assessed annualised relapse rate, compared with the historical patient annualised relapse rate, for patients switching from placebo to eculizumab (0.137 vs. 2.164; Table 2-31 p104 of the resubmission, July 2019 data analysis).

6.17 The resubmission included a combined analysis of the PREVENT trial and the longer-term extension study ECU-NMO-302 from the July 2019 data cut. A total of 8/137 (5.8%) patients experienced 9 adjudicated on-trial relapses whilst being treated with eculizumab for over 358.80 patient-years, with an estimated adjudicated on-trial annualised relapse rate of 0.025, and the median change in annualised relapse rate between historical annualised relapse rate and eculizumab annualised relapse rate based on the combined set was -1.923 (range: -6.38 to -0.62).

6.18 There were no results from either the PREVENT study or the longer-term extension study that indicated that eculizumab substantially extends the lifespan of patients with NMOSD.

6.19 The comparison of disability and quality of life measures between eculizumab and placebo in the PREVENT trial was unchanged in the resubmission. The PBAC previously noted that there were no statistically significant differences in disability or quality of life measures, but that the results generally favoured eculizumab. In November 2020, the PBAC agreed with ESC that because patients completed the PREVENT trial six weeks after relapse, it was unclear whether the changes in disability progression

represented temporary differences or permanent effects (paragraph 7.10, eculizumab PSD, November 2020).

6.20 Data from the longer-term extension study suggested no further deterioration in disability or quality of life measures over time which was consistent with the low frequency of relapse.

6.21 The resubmission presented a summary of efficacy and safety data from two trials of rituximab in the treatment of NMOSD (Nikoo 2017 and RIN-1). Data from several systematic reviews of trials and observational studies of rituximab in the treatment of NMOSD identified during the evaluation were also presented. Overall, the results of these studies suggested that the treatment of NMOSD patients with rituximab is associated with a decreased number of relapses and disability improvement. Rituximab was also reasonably well tolerated by patients. Although rituximab appears to be effective for the treatment of NMOSD, the magnitude of the benefit was uncertain.

6.22 The resubmission stated that there were significant differences between the two rituximab trials and the eculizumab trial which limited their exchangeability, such as the included populations and comparator arms and therefore, an indirect comparison was not conducted. The ESC, noting the additional evidence sourced during evaluation, considered that there was an increasing breadth of literature to support the use of rituximab in NMOSD and that a comparison would be beneficial.

Comparative harms

6.23 The resubmission did not present any new safety data.

6.24 In the PREVENT trial, treatment with eculizumab was associated with a lower rate of adverse events compared to the placebo arm. The apparent difference in adverse event rates was primarily driven by the increased incidence of NMOSD-related events in the placebo arm.

6.25 The most frequently reported adverse events (> 20 per 100 patient years) in either treatment arm were NMOSD complications, upper respiratory tract infection, headache, nasopharyngitis, nausea, urinary tract infection, diarrhoea and pain in extremity.

6.26 The adverse event profile reported in the PREVENT trial and extension study was consistent with the known safety profile of eculizumab.

Benefits/harms

6.27 On the basis of direct evidence presented in the submission, for every 100 patients treated with eculizumab in comparison with placebo:

- There would be approximately 38 fewer physician assessed relapses per year (see Table 6).

Clinical claim

6.28 The resubmission described eculizumab as superior in terms of efficacy and non-inferior in terms of safety compared to placebo. The PBAC again considered that eculizumab was more effective than best supportive care in reducing relapses; however, the magnitude of this effect on disability progression and quality of life outcomes was highly uncertain. The PBAC considered that the claim of non-inferior comparative safety was reasonable.

6.29 As no new clinical data were presented for the comparison between eculizumab and best supportive care, the PBAC noted that a number of issues from November 2020 remained unresolved in the resubmission including:

- Whether the results from the placebo arm of the PREVENT trial are representative of best supportive care. The current clinical data suggest that there may be clinically important differences amongst existing immunotherapies and the exclusion of rituximab from the placebo arm may affect the generalisability of results to clinical practice (paragraph 7.6, eculizumab PSD, November 2020). No new arguments relating to this were provided in the resubmission.
- Whether the reduction in relapse frequency associated with eculizumab treatment will lead to a clinically important reduction in disability progression. There was limited follow-up of patients after a relapse during the PREVENT trial and it was unclear whether differences in disability/quality of life measures represent temporary differences (due to relapse) or permanent changes (due to disability progression) (paragraph 7.10, eculizumab PSD, November 2020). No new comparative data was provided to support a reduction in disability progression associated with treatment.
- Whether the reduction in relapse frequency associated with eculizumab treatment will result in a reduction in mortality or extended life for patients with NMOSD (paragraph 7.10, eculizumab PSD, November 2020). No new data was presented to support the assertion that by preventing relapses, eculizumab will reduce NMOSD-related mortality.

6.30 The resubmission made no claim versus rituximab. The current clinical data suggest that there may be clinically important differences amongst existing immunotherapies, which should be considered and the PBAC considered that a formal comparison would be informative.

Economic analysis

6.31 The resubmission presented a stepped economic evaluation of eculizumab with best supportive care compared to best supportive care alone in patients with NMOSD who are AQP4+ with an EDSS score 0-7 and who have frequent relapses. The economic evaluation was based on the PREVENT trial with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.32 The resubmission did not present an economic analysis for the use of eculizumab in patients with a prior immunosuppressive event (estimated to be 8.1% of people with NMOSD in the financial model).

Table 7: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Patients without relapse; average number of relapses; life years; quality adjusted life years
Time horizon	53 years (lifetime), compared to 1-2 years in the PREVENT trial
Methods used to generate results	Markov cohort model (with half-cycle correction)
Treatments	Eculizumab with best supportive care; best supportive care alone
Health states	Twenty health states defined by EDSS score (0-9) and treatment (eculizumab, best supportive care). Two death states defined as relapse-related death or general mortality
Cycle length	Six-monthly
Patient characteristics	Current age (47 years), gender (91% female) and distribution across EDSS health states (0-7) based on those observed in the PREVENT trial, and in a published observational study comparing the characteristics of definitive NMOSD, suspected NMOSD and multiple sclerosis populations attending Australian treatment centres (Bukhari 2020)
Transition probabilities	Transition probabilities for treatment persistence, relapse events and disability progression were derived from PREVENT trial data and the open label extension study. Transition probabilities for relapse-related death were based on published estimates (Kitley 2012). Transition probabilities for general mortality were based on Australian life tables
Extrapolation method	The probability of relapse, treatment efficacy and treatment persistence were assumed to remain constant over time
Utility values	Relapse disutility values were based on a published survey of multiple sclerosis patients in the UK using the EQ-5D-3L utility instrument (Orme 2007) Health state utilities were based on a post-hoc analysis of EQ-5D-3L data (UK weights) from both treatment arms in the PREVENT trial and ECU-NMO-302 extension.
Costs	Relapse costs were based on a poster presentation of US administrative claims data for NMOSD patients (Stafkey-Mailey 2016), and included costs of plasma exchange (both treatment arms), and supplementary dosing of eculizumab (eculizumab treatment arm) based on average use in the PREVENT trial. Health state costs were based on a published observational study of Australian multiple sclerosis patients (Australian MS Longitudinal Study; Palmer 2011) Eculizumab drug costs were based on the proposed effective DPMQ. Treatment administration costs were estimated based on MBS costs for chemotherapy infusions.
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro Healthcare 2020

Source: the resubmission
Abbreviations: DPMQ, dispensed price per maximum quantity; EDSS, Expanded Disability Status Scale; MBS, Medicare Benefits Schedule; NMOSD, neuromyelitis optica spectrum disorder; UK, United Kingdom; US, United States

6.33 The structure of the model is largely unchanged from the previous submission. Patients begin the model in various EDSS health states (0-7) based on the estimated distribution in the Australian NMOSD population. In each cycle, patients can have no event or experience a non-fatal relapse, fatal relapse or death due to general mortality. Patients experiencing a non-fatal relapse may suffer permanent disability progression and transition to a higher EDSS health state. Patients in the eculizumab

treatment arm may discontinue treatment and revert to the same transition probabilities as the best supportive care arm.

6.34 In October 2020, the ESC noted that the economic model was overly complex with 20 health states and two death states and considered it was unclear whether the EDSS health states adequately captured NMOSD-related disability, noting that the probability of disability progression in the model was based on a small number of patients (23 patients; paragraph 6.30, eculizumab PSD, November 2020).

6.35 The ESC noted that the key changes to the economic model included:

- Use of physician assessed relapse rates, as opposed to adjudicated relapse rates used previously.
- The proportion of patients with permanent disability following relapse has decreased (from 0.435 to 0.30), based on a post-hoc four-month follow up after relapse in the open label extension study.
- The risk of fatal relapse has been reduced (from 7% to 2.3% per relapse).
- Cost of plasma exchange and associated supplementary dosing with eculizumab were included.

6.36 The ESC noted that the following changes requested by the PBAC in November 2020 were not made to the economic model:

- Relapse rate over time. Published estimates suggest that the risk of relapse decreases with time since onset (Kunchok 2020, Palace 2019); however, relapse rates in the economic model remained constant over time.
- The economic model assumed constant efficacy over time. In November 2020, the PBAC considered that this assumption could not be validated due to a lack of long-term data (Table 8, eculizumab PSD, November 2020).
- Health state utility values by EDSS stage were retained. In October 2020, the ESC considered that the utilities resulting from regression analyses had better internal consistency.
- Utility estimates based on trial data, which incorporated both relapse and disability progression, double counted the QALY implications of relapse when a disutility impact of relapse was simultaneously modelled. The resubmission argued that this double counting could not be occurring because the two variables are separated in time. Although separated in time in the model, the quality of life impacts as measured in the trial (and which inform QALY estimates in the model) did not separately measure the impacts of relapse and disability progression.

6.37 Key drivers of the economic model are summarised in the table below.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Time horizon	The resubmission again used a 53-year (lifetime) time horizon. In November 2020 the PBAC considered that the time horizon (compared with 1-2 years in the PREVENT trial) increased the uncertainty of the model and noted that the majority of the incremental benefits occurred in the extrapolated period (para 7.15, eculizumab PSD, November 2020). In the current model, 73.8% of incremental costs and 97.0% of incremental QALYs are generated in the extrapolated period beyond two years. The PBAC considered that the difference in life years gained and disability progression were not supported by the clinical evidence.	High, favours eculizumab
Relapse rate	The resubmission estimated the risk of relapse with best supportive care based on the physician assessed relapse rate reported in the placebo arm of the PREVENT trial. It is unclear whether the relapse rate from the PREVENT trial population can be generalised to the PBS population, given that patients were enrolled in the trial during a peak phase in relapse activity with ongoing relapse frequency likely to be substantially lower in most patients. The reported on-trial annualised relapse rates in the PREVENT trial (eculizumab: 0.066; placebo: 0.446) and extension (eculizumab/eculizumab: 0.101; placebo/eculizumab: 0.134) were considerably lower than the historical estimates reported in the two years prior to enrolment in the PREVENT trial (all patients: 1.99). Additionally, historical estimates including all years prior to enrolment also suggested a lower event rate (Listing 16.2.4.4.3.5 of the PREVENT trial report). Although the restriction has been amended to include the same relapse criteria as the PREVENT trial, the PBS population may include lower risk patients who may not achieve the same magnitude of benefit as the trial population. It is unclear whether the relapse rate in the placebo arm of the PREVENT trial is representative of best supportive care in practice due to the exclusion of rituximab as a treatment option. The resubmission assumed that the probability of relapse remained constant over time. This was inconsistent with the published literature, which indicates that the risk of relapse decreases with time since onset (Kunchock 2020, Palace 2019)	High, favours eculizumab
Treatment efficacy	The resubmission estimated the risk of relapse in the eculizumab treatment arm by applying the rate ratio from the time to first physician assessed relapse in the PREVENT trial to the risk of relapse in the best supportive care arm. The resubmission assumed constant treatment efficacy over time. This assumption could not be validated due to a lack of long-term data.	High, favours eculizumab
Relapse mortality	The resubmission assumed that 2.3% of relapses were fatal based on an observational study, which reported 5 NMOSD-related deaths in a Caucasian population who experienced 221 relapses over the same period (Kitley 2012) The resubmission inappropriately assumed all NMOSD deaths reported in Kitley (2012) were associated with relapse. The PBAC noted that information in the publication suggested only one of the five deaths reported was due to relapse (0.45% of all reported relapses), with the majority of deaths being associated with NMOSD disability.	High, favours eculizumab

Description	Method/Value	Impact
Disability progression	The resubmission estimated the probability of disability progression following relapse, based on a post-hoc analysis of EDSS scores at 120 days after relapse from both treatment arms in the PREVENT open label extension study. The mean change in EDSS post-relapse of 0.30 was interpreted in the model as a 30% probability of a one level worsening in EDSS score. This estimate was based on a relatively small number of patients (n=27). There was wide variability in the odds ratio of worsening in terms of EDSS score between relapsing and non-relapsing patients, and the difference between groups was not statistically significant. The PBAC noted that the assumption that an average change of 0.30 is equivalent to 30% of patients worsening a full step each relapse may not be appropriate. The conversion of mean change in EDSS reported in the PREVENT trial extension study into a single full step increment in the model had a major impact on the interpretation of disability progression (as it excluded improvement, half step worsening and multistep worsening) and therefore may not be a reasonable simplifying assumption.	High, favours eculizumab
Health state utility values	In October 2020, the ESC noted that the utility values applied in the model were based on the PREVENT trial which had low sample numbers. This resulted in inconsistencies in the raw utility values between the different EDSS scores and the application of utility values < 0 for EDSS scores ≥ 8. The ESC considered that the utilities resulting from the regression analyses had better internal consistency (Table 8, eculizumab PSD, November 2020). The resubmission argued that the literature consistently shows large quality of life declines at high EDSS health states that are not captured by simple linear regressions. The inclusion of all EDSS observations regardless of relapse status was inappropriate as the EDSS measurements captured during an acute relapse may not be reflective of the underlying EDSS scores for each health state. Additionally, the model separately captures the disutility impact of relapses and therefore the inclusion of utility measurements during relapse in health states estimates will double-count the impact of these events. The resubmission argued that this cannot be occurring because the two variables (EDSS changes and acute QALY loss due to relapse) are separated in time. The resubmission has not appropriately addressed this issue. Although the modelled health state utilities and one-off utility decrement due to relapse are separated in the model, the quality of life measurements made during the PREVENT trial, upon which the utilities are based, included both EDSS changes and relapses. Any differential impacts of EDSS changes and relapse on quality of life can't be separated using the available data.	High, favours eculizumab

Source: Constructed during the evaluation
Abbreviations: EDSS, Expanded Disability Status Scale; NMOSD, neuromyelitis optica spectrum disorder; PBS, Pharmaceutical Benefits Scheme

6.38 The changes to the economic model presented in the resubmission were applied stepwise, starting from the base case of the November 2020 model, summarised in the table below.

Table 9: Stepped changes from model presented in the November 2020 submission to resubmission

Type of resource item	Eculizumab	Best supportive care	Incremental difference
November 2020 submission base case			
Costs ($)	[redacted]	$177,188	[redacted]
QALYs	7.1480	5.2822	1.8658
		Incremental cost per QALY gained	[redacted][1]
Remove patients with EDSS 8 and 9 at model entry			
Costs ($)	[redacted]	$169,632	[redacted]
QALYs	7.5696	5.5976	1.9720
		Incremental cost per QALY gained	[redacted][1]
Physician determined relapses (original submission based on adjudicated relapses)			
Costs ($)	[redacted]	$176,521	[redacted]
QALYs	6.8836	4.9370	1.9466
		Incremental cost per QALY gained	[redacted][1]
Reduce disability progression per relapse (0.3 compared with 0.435 in original submission)			
Costs ($)	[redacted]	$161,327	[redacted]
QALYs	7.3082	5.5599	1.7483
		Cost per QALY gained	[redacted][1]
Reduce mortality associated with relapse (2.3% compared with 7% in original submission)			
Costs ($)	[redacted]	$211,192	[redacted]
QALYs	7.9746	6.5315	1.4431
		Cost per QALY gained	[redacted][1]
Costs of supplementary dosing included (cost of plasma exchange and supplementary dosing with eculizumab added to the proportion of patients with relapse who required plasma exchange, based on use in PREVENT)			
Costs ($)	[redacted]	$301,893	[redacted]
QALYs	7.9746	6.5315	1.4431
		Cost per QALY gained	[redacted][1]
Update cost of administration (MBS item 13950; $111.40)			
Costs ($)	[redacted]	$301,893	[redacted]
QALYs	7.9746	6.5315	1.4431
		Cost per QALY gained	[redacted][1]
Eculizumab effective price ([redacted]% reduction compared with November 2020 submission; from $5,640.63 AEMP to $[redacted] AEMP)			
Costs ($)	[redacted]	$301,893	[redacted]
QALYs	7.9746	6.5315	1.4431
		Cost per QALY gained	[redacted][1]

Source: compiled during the evaluation
Abbreviations: AEMP, approved ex-manufacturer price; QALY, quality adjusted life year
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.39 The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation.

6.40 Based on the economic model, treatment with eculizumab was associated with a cost per QALY gained of > $1,055,000 compared to best supportive care for the treatment of NMOSD. The incremental cost per QALY gained in the November 2020 submission was > $1,055,000. The changes with the most significant impact on the ICER included reducing disability progression per relapse, reducing mortality associated with relapse, and the reduction in the price of eculizumab.

6.41 The PBAC has previously considered ICERs of approximately $100,000 to $300,000 per QALY gained for other rare diseases (paragraph 6.94, ravulizumab PSD, July 2020). During the evaluation, threshold analyses were conducted to determine the price reduction required for eculizumab to achieve an ICER of $100,000 (93.7% reduction), $200,000 (88.8% reduction) or $300,000 (84.0% reduction) per QALY gained.

6.42 The results of the sensitivity analyses reported in the resubmission are summarised in the table below.

Table 10: Results of sensitivity analyses

Analysis	Incremental cost ($)	Incremental QALY	ICER
Base case	[redacted]	1.4431	[redacted]1
Discount rate (base case: 5% for benefits and costs)			
3.5% discount rate	[redacted]	1.8311	[redacted]1
0% discount rate	[redacted]	3.5502	[redacted]1
Time horizon (base case: 53 years)			
10 years	[redacted]	0.4813	[redacted]1
20 years	[redacted]	1.0020	[redacted]1
30 years	[redacted]	1.2984	[redacted]1
Population characteristics (base case: EDSS distribution based on Bukhari 2020)			
EDSS 0	[redacted]	1.0688	[redacted]1
EDSS 1	[redacted]	1.2994	[redacted]1
EDSS 2	[redacted]	1.2163	[redacted]1
EDSS 3	[redacted]	1.5728	[redacted]1
EDSS 4	[redacted]	1.6455	[redacted]1
EDSS 5	[redacted]	1.2824	[redacted]1
EDSS 6	[redacted]	1.6425	[redacted]1
EDSS 7	[redacted]	0.8064	[redacted]1
Annualised relapse rate in best supportive care arm (base case: 0.446 based on physician assessed relapses in the placebo arm of the PREVENT trial)			
ARR based on adjudicated relapses (0.350)	[redacted]	1.3978	[redacted]1
ARR based on physician assessed upper 95% CI (0.732)	[redacted]	1.8770	[redacted]1
ARR based on physician assessed lower 95% CI (0.272)	[redacted]	1.0269	[redacted]1
Treatment effect of eculizumab (base case: RR from time to physician assessed relapse in the PREVENT trial = 0.147)			
RR based on on-trial relapses upper 95% CI (0.278)	[redacted]	1.1964	[redacted]1
RR based on on-trial relapses lower 95% CI (0.078)	[redacted]	1.5777	[redacted]1
Weighted decline in risk based on Palace (2019)	[redacted]	1.3723	[redacted]1
Probability of disability progression (base case: 0.30 based on a post-hoc analysis of the PREVENT trial, assumed single step EDSS progression)			
Decreased by 50% (0.150)	[redacted]	1.0151	[redacted]1
Increased by 50% (0.450)	[redacted]	1.7772	[redacted]1
Original submission value (0.435)	[redacted]	1.7480	[redacted]1
Probability of fatal relapse (base case: 0.023 based on Kitley 2012 publication)			
No risk of fatal relapse	[redacted]	1.2483	[redacted]1
Original submission value (0.07; Mealy 2018)	[redacted]	1.7483	[redacted]1
Probability of treatment discontinuation (base case: 0.0465 per cycle based on the PREVENT trial)			
Increase probability by 50% (0.0698)	[redacted]	1.1205	[redacted]1
Decrease probability by 50% (0.0233)	[redacted]	2.0011	[redacted]1
No treatment discontinuations	[redacted]	3.1134	[redacted]1
Disability health state utility values (base case: based on raw scores with UK weights from a post-hoc analysis of the PREVENT trial)			
Utilities based on raw scores with French weights from the PREVENT trial	[redacted]	1.4571	[redacted]1
Utilities based on Kobelt 2006a (European MS patients)	[redacted]	1.2982	[redacted]1
Utilities based on Kobelt 2006b (UK MS patients)	[redacted]	1.5301	[redacted]1
Utilities based on Orme 2007 (UK MS patients)	[redacted]	1.4437	[redacted]1
QALY loss due to relapse (base case: 0.01775)			
Removed (0)	[redacted]	1.4066	[redacted]1
Doubled (0.3550)	[redacted]	1.4797	[redacted]1

Source: the resubmission
Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; pa, per annum; QALY, quality-adjusted life year; RR, rate ratio
The redacted values correspond to the following ranges:
[1] > $1,055,000

6.43 The results of the sensitivity analyses indicated that the model was most sensitive to time horizon, discount rate, annualised relapse rate in the best supportive care arm, eculizumab treatment effects, population EDSS state at initiation, risk of fatal relapse, risk of disability progression and utility values for severe disability health states. Changes to cost inputs (such as health state costs) did not significantly affect the ICER, due to the significant cost of eculizumab.

6.44 Overall, the model in the resubmission, which partly addressed some of the concerns raised in response to the original submission, provides additional certainty that the ICER is approximately > $1,055,000 per QALY gained. The PSCR stated that the revised economic model has completely addressed the most important variables (e.g. EDSS decline per relapse, aligning the modelled population with the trial) and partially addressed other variables where the evidence better supports the approach taken by the original submission (e.g. constant efficacy over time, constant relapse rates over time, health state utility values). The PSCR considers that the ICER is as certain as can be expected in a rare condition, and whilst the ICER is high, the clinical evidence and economic model form a reliable basis for decision making. The ESC considered that although some changes could be made, including a more conservative duration of effect, at the current price, the ICER was likely no less than > $1,055,000 per QALY gained.

Drug cost/patient/year

6.45 The estimated drug cost for eculizumab in the initial month of treatment was $[redacted] (based on 3 x 300 mg vials x 4 weeks using a weighted public/private DPMQ of $[redacted]). The estimated drug cost per patient per year for eculizumab in the continuation phase was $[redacted] (based on 4 x 300 mg vials x 26 fortnights using a weighted public/private DPMQ of $[redacted]; 100% persistence). This is reduced compared with the November 2020 submission due to the proposed special pricing arrangement.

6.46 The estimated drug costs (based on vial price, dosing regimen and adherence) were consistent across all sections of the resubmission. However, the economic model assumed an annual discontinuation rate of 9.3% whereas the budget impact model assumed 100% persistence.

6.47 The resubmission also estimated the drug costs associated with supplemental dosing of eculizumab during plasma exchange, based on average use by the proportion of patients requiring plasma exchange in the PREVENT trial. The estimated drug cost for supplemental dosing of eculizumab per patient was $[redacted] per relapse, based on

the average use of 9.6 x 300 mg vials using a weighted public/private DPMQ of $[redacted]. In the trial, 4/14 patients (28.6%) received supplementary dosing with eculizumab during a relapse. The use of supplementary eculizumab during plasma exchange may vary significantly in practice and as advised by the ESC in October 2020, would likely occur in admitted patients in public hospitals (paragraph 3.4, eculizumab PSD, November 2020).

6.48 The resubmission did not estimate the drug costs associated with best supportive care.

Estimated PBS usage & financial implications

6.49 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial implications of listing eculizumab on the PBS/RPBS for NMOSD.

6.50 Key differences compared to the previous November 2020 submission included a major change in methodology (prevalence-based approach rather than mixed incidence/prevalence approach) as well as changes to the majority of inputs used in the analysis (prevalence, eligibility criteria, uptake rates, compliance, price).

6.51 Key inputs are summarised in the table below.

Table 11: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalence of NMOSD	Based on a median prevalence estimate (0.00104%) from six studies conducted in primarily white populations with adequate sample sizes that were identified in published systematic reviews of the epidemiology of NMOSD. The November 2020 submission estimated a prevalence of between 0.0007% (Bukhari 2017) and 0.001% (expert opinion). Some studies only reported AQP4+ NMOSD and therefore the resubmission inflated these prevalence estimates assuming 90% of NMOSD cases are AQP4+ Bukhari 2017 (Australia) 0.00070% Aboul-Enein 2018 (Austria) 0.00078% Sepulveda 2018 (Spain) 0.00099% Papp 2018 (Denmark) 0.00109% Jonsson 2019 (Sweden) 0.00116% Papp 2020 (Hungary) 0.00191%	This estimate was broadly consistent with the results of two published systematic reviews of NMOSD prevalence which suggested a prevalence of approximately 1:100,000 individuals in white populations (Hor 2020; Papp 2021). However, these systematic reviews noted that there were substantial differences in prevalence across different racial groups with much higher prevalence in Asian (3.5:100,000) and Black (up to 10:100,000) populations. Additionally, the systematic reviews acknowledged substantial uncertainty surrounding published prevalence estimates due to varying methodological approaches and incomplete data capture.

Parameter	Value applied and source	Comment
Proportion with AQP4+	90.1%, based on an NMOSD epidemiological study in Australia and New Zealand (Bukhari 2017). This was unchanged from November 2020 submission. Estimate was calculated based on the proportion of diagnosed NMOSD cases that were seropositive (73 of 81 cases, 90.1%).	Plausible estimates of AQP4+ range from 70-90% (Hor 2020).
Proportion with EDSS < 7	Based on an NMOSD epidemiological study in Australia and New Zealand (Bukhari 2020). These criteria were not included in the proposed restriction or applied to the financial analysis in the November 2020 submission. Estimate based of histogram of EDSS distribution at last assessment in NMOSD cases (94.7% with EDSS 0-7)	-
Patients with frequent relapses	NMOSD outcomes prediction model (Palace 2019). Estimate calculated based on the assumption that all patients with 3 relapses in the past 2 years (6.6%) and 50% of patients with 2 relapses in the past 2 years (5.5%) while receiving immunosuppressive therapy (IST) would meet the proposed PBS relapse criterion (total 12.1%). Estimates in November 2020 derived from Palace 2019 ranged from 17.6% to 57.1%. Based on 17.6% of patients having at least 2 attacks in the preceding 2 years, inflated to include patients who may experience 2 relapses in the future.	This estimate was inherently uncertain due to the lack of detailed data on relapse timing and background therapies, but the approach used in the resubmission appeared reasonable for the base case analysis.

Parameter	Value applied and source	Comment
Patients with prior immunosuppressive event	Based on a non-randomised retrospective comparison of treatment outcomes associated with ISTs in France (Poupart 2020) Estimate calculated based on individual patient data on number of patients who discontinued IST due to adverse events (11/136; 8.1%). The November 2020 submission used 11.8% (Poupart 2020; proportion of patients with a documented serious infectious event).	Patients in the study received ISTs (rituximab, azathioprine, mycophenolate mofetil, cyclophosphamide, mitoxantrone) and did not receive corticosteroids as first-line therapy. Data from the study suggest differential discontinuation rates between ISTs. The study authors noted potential limitations with the safety and treatment discontinuation data that are likely to be incomplete due to the retrospective design of the study. The availability of new therapies for NMOSD may result in reduced tolerance for IST-related adverse events and therefore the proportion of patients with a prior immunosuppressive event may be underestimated. Additionally, concerns regarding the impact of long-term immunosuppression may also increase utilisation of newer therapies.
Uptake rate	Assumed 85-95% uptake over six years. The November 2020 submission assumed uptake of 50% to 65%.	No data were provided in support of the assumption.
Treatment compliance	Assumed perfect compliance (100%). The November 2020 submission assumed 89.7% treatment persistence.	No data were provided in support of the assumption. The economic model assumed an annual discontinuation rate of 9.3%.

Source: the resubmission

Abbreviations: AQP4+, aquaporin-4 positive; DPMQ, dispensed price per maximum quantity; IST, immunosuppressive therapy; MBS, Medicare Benefits Schedule; NMOSD, neuromyelitis optica spectrum disorder; PBS, Pharmaceutical Benefits Scheme

6.52 The table below presents the estimated use and financial implications of eculizumab over 6 years of listing.

Table 12: Estimated utilisation and cost of eculizumab

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Australian population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients with NMOSD (0.00104%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Proportion meeting eligibility criteria ([redacted]%)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Uptake rates	85.0%	92.5%	95.0%	95.0%	95.0%	95.0%
Treated patients	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total eculizumab vials[a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]
Net cost to PBS/RPBS	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Cost of administration[b]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to Government	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Eculizumab November 2020 submission						
Total treated patients	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Total eculizumab vials	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to PBS/RPBS	[redacted][5]	[redacted][6]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][10]

Source: the resubmission

Abbreviations: NMOSD, neuromyelitis optica spectrum disorder

[a] 1 initiation script and 12 continuation scripts assumed in year 1 (108 vials); 0.25 initiation and 12.75 continuation scripts assumed in subsequent years (105 vials), based on assumption that 25% of patients are initiating therapy (1 initiation script, 12 continuation scripts) and 75% are continuing therapy (13 continuation scripts).

[b] $94.70 per administration based on MBS item 13950 (parenteral administration of an antineoplastic agent)

The redacted values correspond to the following ranges:

[1] > 10,000,000

[2] < 500

[3] 500 to < 5,000

[4] 5,000 to < 10,000

[5] $10 million to < $20 million

[6] $20 million to < $30 million

[7] $0 to < $10 million

[8] $30 million to < $40 million

[9] $40 million to < $50 million

[10] $50 million to < $60 million

6.53 The net cost of listing eculizumab on the PBS/RPBS for the treatment of NMOSD was estimated to be up to $20 million to < $30 million in the sixth year of listing, with a cumulative total cost of $100 million to < $200 million over six years. For comparison, the November 2020 submission estimated a cumulative total cost of $200 million to < $300 million over six years. This difference was primarily due to the reduction in the estimated utilisation of eculizumab as well as a reduction in the price of eculizumab ([redacted]% reduction).

6.54 The proportion of NMOSD patients meeting the proposed eligibility requirements in the current resubmission ([redacted]%) was lower than previous estimates ([redacted]% over 6 years). This difference was primarily due to the switch to a prevalence-based approach which corrected logical inconsistences associated with the mixed incidence/ prevalence approach used in the previous submission. The tightening of the requested restriction (a new EDSS criterion and a narrower definition of frequent relapses) and a lower estimate of patients with prior immunosuppressive events also contributed to

the smaller patient numbers. As acknowledged by the sponsor, the simplified prevalence approach used in the current resubmission may underestimate the eligible population size as patients meeting the clinical criteria retain their eligibility for life if they receive any treatment with eculizumab (patients who do not receive treatment within the eligibility window would need to re-qualify for treatment).

6.55 The estimated utilisation of eculizumab decreased in the current resubmission (cumulative total of 20,000 to < 30,000 vials over six years) compared to the November 2020 submission (cumulative total of 30,000 to < 40,000 vials over six years). This reduction was not proportional to the reduction in the eligible population size as it was also affected by revised assumptions regarding uptake rates and treatment compliance.

6.56 The previous submission estimated initial uptake rates in newly eligible patients (50% in Year 1 increasing to 65% in Year 6) but also included additional uptake in subsequent years (50% in Year 1 increasing to 65% in Year 6) in patients who do not initiate treatment when first eligible. The DUSC advice previously noted the uptake rates in the newly eligible patients were possibly underestimated given the unmet clinical need for new treatments in NMOSD. In contrast, the current resubmission assumed uptake rates of 85% in Year 1 increasing to 95% in Year 6 with no distinction between newly eligible and previously eligible patients. Overall, the uptake assumptions underlying the current estimate were consistent with those in the previous submission but the switch to a prevalence-based approach essentially brings forward the estimates of additional uptake in subsequent years.

6.57 The resubmission assumed perfect compliance (adherence and persistence) to therapy while the previous submission assumed an annual discontinuation rate of approximately 10% per year. The perfect compliance assumption is unlikely to reflect clinical practice particularly for patients who have not experienced a recent relapse given the treatment burden associated with eculizumab treatment (fortnightly IV infusions).

Financial Management – Risk Sharing Arrangements

6.58 The resubmission proposed an expenditure cap risk sharing arrangement based on the estimated PBS/RPBS budget impact of eculizumab for NMOSD. The resubmission stated that the sponsor would rebate any expenditure [redacted].

Table 13: Risk sharing arrangement expenditure caps

	Year 1 (2022)	Year 2 (2023)	Year 3 (2024)	Year 4 (2025)	Year 5 (2026)	Year 6 (2027)
Government expenditure on PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: the resubmission

6.59 The nominated expenditure thresholds are uncertain as they were based on eligible patient numbers which are likely to have been underestimated and utilisation values

which may have been overestimated. While an expenditure cap may address the risk of underestimation of the eligible population, it may be appropriate to consider the inclusion of a compliance adjustment factor to reduce the risk associated with assuming perfect compliance in the treated population.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of eculizumab for the treatment of patients with neuromyelitis optica spectrum disorder (NMOSD) who are aquaporin-4 positive (AQP4+). Although the PBAC considered that eculizumab was more effective than best supportive care in reducing relapses, the magnitude of this effect on disability progression and quality of life remained highly uncertain. The PBAC noted that although the resubmission partly addressed some of the concerns with the economic model, the incremental cost effectiveness ratio (ICER) remained excessively high (> $1,055,000 per quality adjusted life year (QALY)) and advised that a further substantial price reduction would be required to achieve an acceptable ICER. The PBAC noted that although the number of eligible patients had been reduced compared to the November 2020 submission, as eculizumab was proposed as a lifelong prophylactic treatment, at the proposed price, the cost of listing remained high.

7.2 The PBAC welcomed the input from the health professional and organisations via the Consumer Comments facility which outlined the disease progression of NMOSD and the effects of NMOSD on quality of life, as well as the use of current treatments, including rituximab.

7.3 The PBAC noted that the proposed restriction was updated in the resubmission to align with the inclusion criteria of the PREVENT trial in terms of Expanded Disability Status Scale (EDSS) score and frequency and number of prior relapses. The PBAC noted that although further updates to the proposed restriction in the pre-PBAC response better defined a 'prior immunosuppressive event', there was no evidence presented of the cost-effectiveness of eculizumab in this population.

7.4 The PBAC noted that the resubmission again nominated best supportive care as the primary comparator, reiterating arguments from the initial submission as to why rituximab was not a suitable comparator, despite prior advice in November 2020 that rituximab would be a relevant comparator. The PBAC also noted that the PSCR and pre-PBAC response repositioned eculizumab as a last line treatment (i.e. after rituximab). The pre-PBAC response updated the proposed restriction, requiring patients to have relapsed 'despite an adequate trial of other accessible preventive treatments for NMOSD including rituximab, azathioprine and mycophenolate'. The PBAC noted that the updated restriction did not define 'adequate trial', nor did it consider that the wording limited use of eculizumab to the last-line setting.

7.5 In addition, the PBAC noted that only 32% of patients included in the PREVENT trial

had received prior rituximab. The PBAC considered the PREVENT trial population was therefore not representative of patients receiving last line therapy.

7.6 The PBAC noted that the resubmission presented a summary of two trials of rituximab in NMOSD which suggested that rituximab was associated with a decrease in relapse rates and an improvement in disability. The PBAC noted that data from several other systematic reviews and studies were available. The PBAC reiterated that rituximab is used for the treatment of NMOSD in Australian clinical practice and is a relevant comparator. The PBAC considered that a formal comparison with rituximab was required, noting its September 2021 recommendation for an unrestricted listing for rituximab.

7.7 In terms of clinical data, the PBAC recalled that the results from the PREVENT trial demonstrated that eculizumab was associated with:

(i) a statistically significant improvement in the time to first adjudicated relapse compared to placebo (HR = 0.058; 95% CI: 0.017, 0.197); and
(ii) a statistically significant reduction in adjudicated annualised relapse rate compared to placebo (HR = 0.045; 95% CI: 0.013, 0.151; when on-trial relapses were assessed by the treating physician HR = 0.147; 95%: 0.078, 0.278).

7.8 The PBAC noted that the resubmission presented additional post-hoc subgroup analyses based on the PREVENT trial and an updated interim analysis from the ECU-NMO-302 open label extension study (July 2019 data cut as compared to October 2018 in the November 2020 submission). The resubmission also presented a combined analysis of the PREVENT trial and the July 2019 data analysis of the ECU-NMO-302 open-label extension study.

7.9 Based on the results of the PREVENT trial, the PBAC again considered that eculizumab was superior to best supportive care in reducing relapses. The PBAC considered that the additional data presented in the resubmission did not address the issues raised in November 2020 relating to whether:

(i) a reduction in relapse frequency associated with eculizumab treatment led to a clinically important reduction in disability progression and quality of life outcomes or an extended life expectancy for patients with NMOSD
(ii) the results from the placebo arm were representative of best supportive care.

7.10 The PBAC again considered that eculizumab was non-inferior to best supportive care in terms of comparative safety.

7.11 The PBAC noted that the resubmission presented a revised stepped cost-utility analysis comparing eculizumab plus best supportive care to best supportive care alone for patients with AQP4+ NMOSD and who have frequent relapses. The PBAC noted that although the structure of the economic model was unchanged and remained complex, and again applied a 53-year time horizon, the resubmission made some revisions, including the use of physician assess relapse rates (as opposed to

adjudicated relapse rates), decreasing the proportion of patients with permanent disability following relapse from 0.435 to 0.30, reducing the risk of fatal relapse from 7% to 2.3% and including the cost of plasma exchange, which were recommended following the November 2020 consideration.

7.12 However, the PBAC noted that a number of changes requested in November 2020 and outlined in paragraph 6.36 were not implemented in the revised economic model. The PBAC also recalled that it had stated that a substantial price reduction would be required to achieve an acceptable ICER.

7.13 The PBAC noted that the changes applied (as outlined in paragraph 7.11) and the application of a [redacted]% price reduction resulted in an ICER of > $1,055,000 per QALY. Overall, the PBAC considered that the resubmission partly addressed some of the issues raised in response to the original submission, and that the economic analysis as presented provided additional certainty that the ICER exceeded > $1,055,000 per QALY gained. The PBAC considered that this remained unacceptably high, again noting that it has previously considered ICERs in the range of $100,000 to $300,000 per QALY acceptable for rare diseases.

7.14 As noted in paragraph 7.3, the resubmission did not present an economic analysis for the use of eculizumab in patients who have had a prior immunosuppressive event, therefore the cost effectiveness of eculizumab in this population could not be assessed.

7.15 The PBAC noted that the resubmission provided revised utilisation and financial estimates which resulted in an estimated cost over the first six years of listing of $100 million to < $200 million (compared to $200 million to < $300 million in the November 2020 submission).

7.16 The PBAC considered that the use of a prevalence-based approach, rather than a mixed incidence/prevalence approach, was appropriate.

7.17 The PBAC noted that the resubmission had also made changes to a number of inputs including prevalence, eligibility criteria, uptake rates compliance and price. The PBAC noted that although the uptake rate of eculizumab had been increased from 50%-65% in the previous submission to 85%-95% in the resubmission no data were provided to support the change. In addition, the PBAC noted that compliance in the resubmission was 100%, as compared to 89.7% in the previous submission. The PBAC considered that this was inappropriate. Overall, the PBAC considered that although the estimates were more closely aligned with the proposed restriction, they remained overestimated.

7.18 Noting that the estimated cost per patient per year was approximately $[redacted], and that treatment is proposed as a lifelong prophylaxis, the PBAC considered that at the proposed price, the cost of listing remained high.

7.19 The PBAC noted that the resubmission proposed a Risk Sharing Arrangement (RSA)

based on the estimated PBS/RPBS expenditure.

7.20 The PBAC considered that a resubmission for eculizumab should address the clinical, economic and financial issues raised above. The PBAC advised that a formal comparison between eculizumab and rituximab would be informative and reiterated that a substantial price reduction would be required to achieve an acceptable ICER. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

7.21 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

There are no TGA approved therapies reimbursed for neuromyelitis optica spectrum disorder (NMOSD) in Australia and given the severity and rare nature of this disease, Alexion is committed to continue to work with the Government to reach an agreement that ensures equitable access for people living with this devastating disease.