6.04 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 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 (AQP4) positive and who have either frequent relapses or a prior immunosuppressive event.

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 submission

Component	Description
Population	Patients with neuromyelitis optica spectrum disorder who are AQP4 positive 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 submission
AQP4 = aquaporin-4

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.

2.3 The submission 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 myelin oligodendrocyte glycoprotein (MOG) testing is currently being considered by MSAC as

the existing item subsidises AQP4/MOG testing at a lower level than charged by providers (MSAC Application 1582).

2.4 Eculizumab for NMOSD was recently considered by the Canadian Agency for Drugs and Technologies in Health (CADTH). The ESC noted that eculizumab was recommended for the treatment of NMOSD if a number of conditions were met, including a 96% price reduction.

Previous PBAC considerations

2.5 Eculizumab is currently subsidised through 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 (PNH). The PBAC has not previously considered eculizumab for this indication.

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

3 Requested listing

Medicinal Product Pack	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Available brands
Initial treatment					
Eculizumab, 300 mg/30 mL injection, 30 mL vial	1	1	0	Public: $[redacted] Private: $[redacted]	Soliris
Continuing treatment					
Eculizumab, 300 mg/30 mL injection, 30 mL vial	1	1	5	Public: $[redacted] Private: $[redacted]	Soliris

Episodicity:	Relapsing
Condition:	Neuromyelitis optica spectrum disorder (NMOSD)
PBS Indication:	Patients with NMOSD
Treatment phase:	Initial
Restriction type:	☒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 Patient must have had at least one relapse in the last 12 months with at least two relapses in the last 24 months; or 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

3.1 Eculizumab is only being considered for outpatient use. The PBAC advised that treatment of admitted patients (public and private) in public hospitals remains the responsibility of the states.

3.2 The proposed price per vial is consistent with its other PBS subsidised indications.

3.3 Based on the recommended dosing regimen the initial treatment script should include 12 vials (3 x 300 mg vial per week for 4 weeks) and the continuing script should include 8 vials (4 x 300 mg vials per fortnight) with up to 5 repeats.

3.4 The submission did not propose a separate listing to facilitate supplemental dosing of eculizumab in patients undergoing plasma exchange (which is used as an acute treatment for relapse in NMOSD). The ESC considered that the absence of a separate, supplemental dosing listing from the proposed PBS-listing was reasonable, noting that such use would likely occur in admitted patients in public hospitals and thus not be subsidised by the PBS.

3.5 The requested restriction did not include any age limit while the TGA indication is limited to adult patients as there are no clinical data on the efficacy and safety of eculizumab in paediatric patients. There is currently an ongoing study of weight-based eculizumab dosing in paediatric patients with NMOSD due for completion in November 2021 (ECU-NMO-303).

3.6 The current TGA indication covers a broad population of adult patients with AQP4 positive NMOSD while the requested restriction narrows eligibility to two subgroups:

- Patients with frequent relapses: defined as 2 relapses in the previous 2 years with at least one relapse in the last 12 months. This is a broader inclusion criterion than used in the key clinical trial, which included patients with 2 relapses in the previous year or 3 relapses in the previous 2 years with at least one relapse in the last 12 months. However, the submission reasoned that the trial population was comparable to the proposed PBS population based on the reported historical annualised relapse rate of 1.99 in the previous 24 months. This reasoning appeared to be based on a misinterpretation of annualised relapse rates with trial participants averaging approximately 2 relapses per year, not 2 relapses over 2 years. As a consequence, the PBS population is likely to include lower risk patients who may not achieve the same magnitude of benefit as the trial population; or
- Patients with a prior immunosuppressive event: defined as a serious adverse event that requires cessation of immunosuppressive treatment. Patients in this subgroup did not need to meet any relapse criteria. This was inconsistent with the clinical trial inclusion criteria which required all patients to have frequent relapses regardless of prior treatment history. Additionally, the submission did not present an economic analysis of the cost-effectiveness of eculizumab in this population (estimated in the submission as approximately 10% of the Australian NMOSD population).

3.7 The requested restriction did not stipulate failure with at least one prior therapy which is inconsistent with the proposed place in therapy as a second-line treatment. The PBAC considered that it may be appropriate to include a criterion limiting treatment to patients who have failed first-line agents, particularly given the substantial price differential between first-line therapies and eculizumab.

3.8 The requested restriction did not include any criteria regarding disability impairment. This was inconsistent with the available clinical evidence which was limited to patients with an Expanded Disability Status Scale (EDSS) score < 7 (covering patients from fully ambulatory to wheelchair bound). The risk benefit profile of treating patients with more advanced disease is currently unknown.

The sponsor in its Pre-Sub-Committee Response (PSCR) agreed that the clinical criteria in the proposed PBS listing were broader than the inclusion criteria of the PREVENT trial, but considered that there is a high unmet need for an effective and safe relapse prevention treatment option as, unlike MS, progression does not occur without relapse. Given the high requested price of eculizumab and the uncertain magnitude of benefit in terms of disability progression, the PBAC considered that the proposed restriction should align with the inclusion criteria of the PREVENT trial in terms of number of prior relapses and EDSS score. The sponsor in its pre-PBAC response stated that the eligibility criteria of the key PREVENT trial were narrower than the current treatment guidelines and that preventative treatment should be administered, even in the setting of prolonged clinical remission. Further, the sponsor contended that strictly aligning the PBS restriction with the inclusion criteria of the PREVENT trial would result in very few patients gaining access to eculizumab. In order to reduce negative financial impacts of using eculizumab outside of circumstances considered cost-effective, the sponsor proposed a risk-sharing arrangement (RSA) in its pre-PBAC response (see paragraph 6.59).

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

4 Population and disease

4.1 NMOSDs 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. 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 (higher in African and Asian populations) and evolving diagnostic criteria.

4.2 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).

4.3 Patients with NMOSD who are AQP4 positive 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.

4.4 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. Monophasic disease (single event) and progressive disease courses have been also been observed in some patients but these forms of the disease appear to be less common. 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.

4.5 Relapses may be managed in the community setting or require hospitalisation depending on the severity of relapse (approximately 50% of relapses required hospitalisation in the key clinical trial). 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.

4.6 The mortality associated with NMOSD has substantially decreased over time with the inclusion of less severe patients under the diagnostic umbrella of NMOSD and the use of immunosuppressive therapy and plasma exchange. The current mortality associated with NMOSD is unclear but appears to be low.

4.7 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.

4.8 The submission positioned eculizumab as a second-line preventative therapy in AQP4-positive 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.

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

5 Comparator

5.1 The submission nominated best supportive care as the main comparator. The main arguments provided in support of this nomination were that there are no other treatments with specific indications for NMOSD and access to off-label therapy is not universal in Australia.

5.2 The majority of NMOSD therapies are available and subsidised under unrestricted listings on the PBS (corticosteroids, azathioprine, mycophenolate mofetil, methotrexate). Therefore, there should be no major limitations to the use of these drugs by specialists familiar with NMOSD. Rituximab does not have an unrestricted PBS listing but the submission noted that it is funded through some hospitals. Additionally, ongoing treatment with IVIg is also subsidised in Australia for the treatment of NMOSD under the National Blood Authority but the level of utilisation is currently unclear.

5.3 Overall, the arguments presented in the submission were not well supported. Nevertheless, best supportive care may be a reasonable main comparator as eculizumab is primarily intended to be used in addition to existing immunosuppressive therapy, which potentially represents a new place in therapy.

5.4 However, specific immunosuppressive agents (such as azathioprine, mycophenolate mofetil and rituximab) may also be considered relevant comparators given the potential for eculizumab to displace these therapies over time due to concerns with long-term immunosuppression. Additionally, the submission argued that eculizumab would not be used in combination with rituximab due to reduced efficacy as a result of conflicting mechanisms of action. Therefore, eculizumab is likely to replace use of rituximab in clinical practice.

5.5 The PSCR reiterated that rituximab was prohibited in the PREVENT trial due to the incompatibility between the mechanisms of action of eculizumab and rituximab. In addition, the PSCR stated that as rituximab is not TGA registered or PBS listed for the treatment of NMOSD, equity of access to rituximab is a key consideration. The ESC noted that the majority of NMOSD patients would be treated at specialist centres, reducing the risk of access inequity. The pre-PBAC response disagreed, stating that patients are treated both in specialist centres and general and private neurology practices and therefore, the risks of inequitable access to rituximab remain.

5.6 During the evaluation, it was noted that two other therapies (satralizumab, inebilizumab) had recently received international approvals for the treatment of NMOSD.

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 discussed the progressive nature of NMOSD (including that many patients do not recover from their first relapse) and the unpredictability of further attacks which means that patients remain on preventative therapies long-term and are at risk of long-term immunosuppression with existing therapies. He also outlined the high unmet need for effective subsidised therapies, and emphasised that relapse prevention is the main goal of therapy.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (3) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from MS Neurology, Australian and New Zealand Association of Neurologists, and a joint submission from MS Australia and MS Research Australia, the Centre for Community-Driven Research clarifying the likely use of eculizumab in clinical practice. The PBAC specifically noted the advice that the use of eculizumab may reduce the risk of relapse and that it has minimal side effects. The comments outlined the experience and expectations of individuals in the NMOSD community, including the hope that an effective treatment might prevent relapses and improve patients' ability to walk, stamina, bladder function, ability to move without pain and help with the fatigue and sight.

Clinical studies

6.3 The submission was based on one head-to-head randomised trial comparing eculizumab to placebo in patients with AQP4-positive NMOSD (PREVENT). The submission also presented an interim analysis from an open-label extension study of patients previously enrolled in the PREVENT trial as supportive data (ECU-NMO-302).

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
PREVENT (ECU-NMO-301)	Alexion (2018). ECU-NMO-301 clinical study report. A randomized, double-blind, placebo controlled, multi-centre 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-centre 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

Source: Table 2-3 (p 30-31), Table 2-4 (p 32) of the submission; p 30 text of the submission
Note: Abstracts of studies with full publications are not presented

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

Table 3: 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 who are AQP4+	Time to first relapse, relapse rate, disability progression, quality of life	Risk of relapse, treatment efficacy, treatment discontinuation, risk of disability progression, health state utility values

Source: Table 2-5 (p 34-35), Table 2-18 (p 65-66), Section 2.4 (p 39-53) of the submission
AQP4+ = aquaporin-4 positive; Ecu = eculizumab; NMOSD = neuromyelitis optica spectrum disorder' Pbo = placebo

6.6 The ESC considered that the risk of bias in the PREVENT trial was unclear due to a number of significant protocol changes, differential discontinuations between treatments arms (16.7% in the eculizumab arm versus 6.4% in the placebo arm) and a substantial number of major protocol violations (approximately 40% of patients had a major violation).

6.7 A key consideration in the interpretation of outcomes from the PREVENT trial was the limited follow-up of patients experiencing an on-trial relapse (patients completed the PREVENT study 6 weeks after relapse). This timeframe appeared insufficient to adequately capture post-relapse recovery or adequately assess the treatment effect of eculizumab in patients experiencing multiple relapse events.

6.8 The interim analysis from the ongoing extension study (ECU-NMO-302) was considered to be at high risk of bias given the observational study design and incomplete follow-up. The submission provided the results of an interim April 2018 report which included 39 patients experiencing an on-trial relapse during the PREVENT

trial (average additional follow-up of approximately 1.6 years). The sponsor also provided some additional results from a later October 2018 cut-off which included 119 relapsing and non-relapsing patients (median additional follow-up of approximately 0.4 years).

6.9 The PBAC noted the key applicability issues with the PREVENT trial which are summarised below.

Table 4: Key applicability issues with the PREVENT trial

Issue	Discussion
Relapse frequency	The relapse eligibility criteria in the PREVENT trial (3 relapses in previous 2 years or 2 relapses in previous year) were stricter than those proposed for the requested PBS population, which required patients with frequent relapses to have had at least one relapse in the last 12 months, with at least two relapses in the last 24 months. However, the submission argued that the trial population was comparable to the proposed PBS population based on the reported historical annualised relapse rate of 1.99 in the previous 24 months. This argument appeared to be based on a misinterpretation of annualised relapse rates, with trial participants averaging approximately 2 relapses per year, not 2 relapses over 2 years. It is likely that the PBS population will include patients with lower risk of relapse. In general, a smaller absolute risk of relapse will reduce the magnitude of benefit associated with eculizumab treatment. The PSCR agreed that the clinical criteria in the proposed restriction were broader than the eligibility criteria of the PREVENT trial in terms of relapse frequency. The PSCR referenced data from the Palace 2019[1] study (see table below) which the PSCR claimed showed that relapse activity in the prior 2 years has only a modest effect on the proportion of patients relapsing in the next 2 years. The PSCR suggested that the number of prior relapses is not necessarily synonymous with future risk of relapse or severity of disease and stated that as NMOSD progression and disability does not occur without a relapse, a reduction in relapses results in a reduction of disability. Thus, the aim of the restriction was to target patients who will benefit the most from eculizumab. The ESC noted that the Palace 2019 study did not apply the same definitions of prior relapse as were used in the clinical trial or adjust for the clustering nature of relapses which has been reported in a number of longitudinal studies and discussed in regulatory documents (EMA workshop on NMOSD 2015; TGAs delegate's recommendation for eculizumab). Further, the relapse categories used in the Palace 2019 study were not mutually exclusive and therefore higher risk patients were also included in lower risk categories. The ESC noted that the Palace 2019 data indicated that relaxing the restriction criteria around the number of prior relapses would result in a population who have a lower absolute risk of further relapses (e.g. with no relapse criterion, 54% of patients would be likely to relapse within 2 years, versus 68% in a group of patients with ≥ 3 relapses in the previous 2 years, based on the data presented). The pre-PBAC response acknowledged that the Palace 2019 analysis did not apply the same definitions of prior relapse as per the PREVENT trial, but stated that the results did not demonstrate a clear trend for an increasing proportion of patients with relapses in those who had experienced more relapses in the past 2 years. However, the PBAC considered there were a number of issues with the Palace 2019 analysis (as identified by ESC above) and agreed with evaluation and the ESC that the proposed PBS population would include patients with a lower risk of relapse than those enrolled in the trial. **Risk of relapse based on prior relapse criteria**

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

<table>
<tr><th>Issue</th><th>Discussion</th></tr>
<tr><td></td><td>
<table>
<tr><th>Number of relapses in previous 2 years</th><th>Disease duration</th><th>Relapsing in 1 year</th><th>Relapsing in 2 years</th><th>Average % of patients fulfilling criteria over time</th></tr>
<tr><td>≥ 3 relapses</td><td>Any</td><td>46.6%</td><td>67.9%</td><td>6.6%</td></tr>
<tr><td>≥ 2 relapses</td><td>Any</td><td>42.6%</td><td>63.7%</td><td>17.6%</td></tr>
<tr><td>≥ 1 relapses</td><td>Any</td><td>38.7%</td><td>59.2%</td><td>40.7%</td></tr>
<tr><td>No relapse criterion</td><td>Any</td><td>34.5%</td><td>54.2%</td><td>100%</td></tr>
</table>
Source: Adapted from Table 7, p1320 of Palace 2019.

The main outcomes of the PREVENT trial were based on adjudicated relapses as determined by a central independent committee rather than being assessed by the treating physician. However, the submission argued that results were broadly consistent between relapse assessment methods and adjudicated relapses represent a more robust outcome. The sensitivity analyses suggested that there may be differences in both the absolute risk of relapses and the estimated treatment effect of eculizumab depending on relapse definition. Both definitions appear relevant to the consideration of efficacy outcomes but on-trial relapses may be more applicable to the proposed PBS population</td></tr>
<tr><td>History of immunosuppressive events</td><td>The submission noted that all 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. However, the submission argued that the relative treatment effect of eculizumab was likely to be generalisable to the proposed immunosuppressed subgroup on the basis that results were consistent across subgroups including patients with and without background immunosuppressive therapy. This claim appeared reasonable, but the lower absolute risk of relapse in this population is likely to reduce the magnitude of benefit associated with eculizumab treatment. The PSCR noted that patients who have experienced an immunosuppressive event with prior treatment have no alternate treatment options and therefore have a high need for relapse prevention treatments.</td></tr>
<tr><td>Best supportive care</td><td>The submission noted that rituximab was not permitted as a background immunosuppressive therapy in the PREVENT trial due to conflicting mechanisms of action with eculizumab. The submission acknowledged that this was not representative of best supportive care in Australia, which can include the use of rituximab treatment. However, the submission argued that treatment outcomes in the placebo arm were 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, Tahara 2020). 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. The PSCR reiterated that rituximab use was prohibited in the PREVENT trial due to the incompatibility between the mechanisms of action of eculizumab and rituximab. In addition, the PSCR stated that as rituximab is not TGA registered or PBS listed for use in NMOSD, the effectiveness, safety and dose determination has not been established. In addition, the PSCR stated that given the lack of registration in Australia, access to rituximab is dependent on where the patient in treated, resulting in equity issues. The ESC considered that the majority of NMOSD patients would be treated in specialist centres reducing the risk of access inequity for rituximab treatment.</td></tr>
<tr><td>Baseline disability</td><td>The trial evidence was limited to patients with an EDSS score ≤ 7 (covering patients from fully ambulatory to wheelchair bound). The risk benefit profile of treating patients with more advanced disease is currently unknown.</td></tr>
<tr><td>Patient age</td><td>The trial evidence was limited to adult patients. The efficacy and safety of weight-based eculizumab dosing in paediatric patients is currently unknown.</td></tr>
</table>

Source: Table 2-32 (p 91-93) of the submission

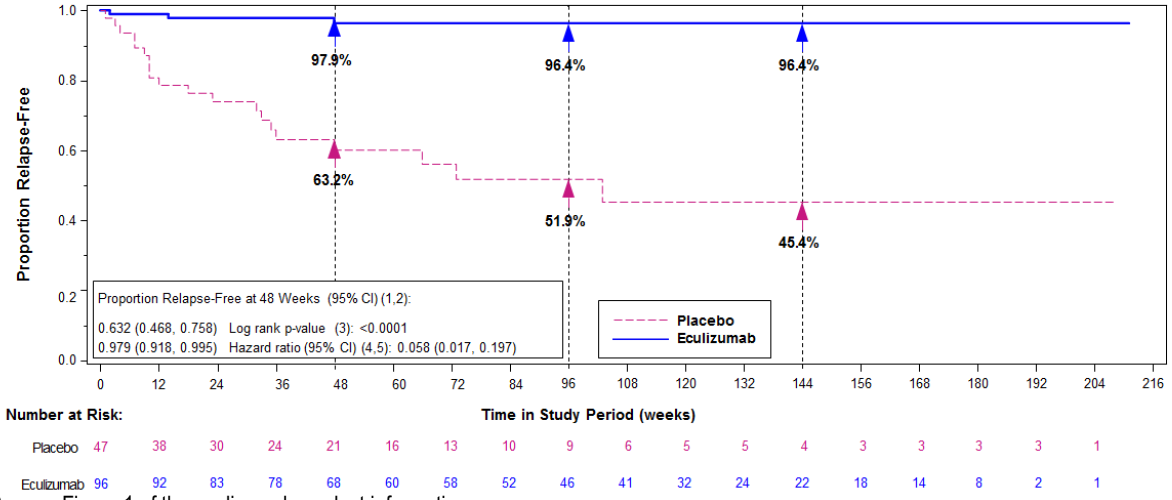
EDSS = Expanded Disability Status Scale; EMA = European Medicines Agency; ESC = Economic Sub-Committee; NMOSD = neuromyelitis optica spectrum disorder; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response; TGA = Therapeutic Goods

Administration

Comparative effectiveness

6.10 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
CI = confidence interval

6.11 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).

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

Table 5: 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)		
On-trial relapses requiring hospitalisation					
Eculizumab (N = 96)	6	171.32	0.04 (0.02, 0.08)	NR	< 0.0001
Placebo (N = 47)	15	52.41	0.31 (0.19, 0.50)		
On-trial relapses requiring acute treatment with high dose oral corticosteroids					
Eculizumab (N = 96)	7	171.32	0.04 (0.02, 0.09)	NR	0.0733
Placebo (N = 47)	6	52.41	0.11 (0.05, 0.25)		
On-trial relapses requiring acute treatment with intravenous corticosteroids					
Eculizumab (N = 96)	12	171.32	0.07 (0.04, 0.12)	NR	< 0.0001
Placebo (N = 47)	22	52.41	0.42 (0.28, 0.64)		
On-trial relapses requiring acute treatment with plasma exchange					
Eculizumab (N = 96)	4	171.32	0.02 (0.01, 0.06)	NR	0.0001
Placebo (N = 47)	10	52.41	0.19 (0.10, 0.35)		

Source: Table 2-15 (p 58), Table 2-16 (p 58) of the submission; Table 34 (p 119) of the PREVENT trial report
CI = confidence interval; NR = not reported
[a] one patient had two adjudicated on trial relapses.
[b] two patients each had two adjudicated on-trial relapses

6.13 The ESC noted that 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). Treatment with eculizumab appeared to be associated with a reduction in relapses across all severity levels.

6.14 Interim results of the longer term extension study indicated an adjudicated annualised relapse rate of 0.032 (9 relapses over 279.30 years; October 2018 data analysis) in patients treated with eculizumab. Further analyses suggested a decrease in the on-trial annualised relapse rate for patients switching from placebo to eculizumab (0.446 vs. 0.134; October 2018 data analysis) while the annualised relapse rate remained relatively constant in patients continuing with eculizumab treatment (0.066 vs. 0.101; October 2018 data analysis).

6.15 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.

6.16 A comparison of disability and quality of life measures between eculizumab and placebo in the PREVENT trial is summarised below.

Table 6: Disability and quality of life measures reported in the PREVENT trial

Outcome	Baseline, mean (SD)	Change from baseline, median (range)	Change from baseline, mean (SD)	Difference in change from baseline, mean (95% CI)	P-value[a]
EDSS (0-10 scale, with higher scores indicating increased disability)					
Eculizumab (N = 96)	4.15 (1.65)	0.00 (-3.5, 1.5)	-0.18 (0.81)	-0.29 (-0.59, 0.01)	0.0597
Placebo (N = 47)	4.26 (1.51)	0.00 (-2.0, 2.5)	0.12 (0.95)		
Hauser Ambulation Index (0-9 scale, with higher scores indicating increased walking impairment)					
Eculizumab (N = 96)	2.4 (2.17)	0.0 (-5, 3)	-0.4 (1.08)	-0.87 (-1.32, -0.42)	NS
Placebo (N = 47)	2.1 (1.40)	0.0 (-2, 8)	0.5 (1.61)		
Modified Rankin Scale (0-6 scale, with higher scores indicating increased dependence)					
Eculizumab (N = 96)	2.1 (1.14)	0.0 (-4, 2)	-0.2 (0.72)	-0.32 (-0.57, -0.06)	NS
Placebo (N = 47)	2.1 (0.98)	0.0 (-2, 3)	0.1 (0.75)		
Kurtzke functional system score – visual (0-6 scale, with higher scores indicating lower visual acuity)					
Eculizumab (N = 96)	3.2 (2.15)	-1.0 (-4, 3)	-0.7 (1.15)	-0.27 (-0.58, 0.04)	NS
Placebo (N = 47)	2.7 (2.32)	0.0 (-2, 2)	-0.3 (0.93)		
EQ-5D-3L Visual analogue score (0-100 scale, with higher scores indicating increased quality of life)					
Eculizumab (N = 96)	63.6 (20.00)	0.0 (-30.0, 60.0)	5.4 (18.53)	6.43 (0.63, 12.23)	NS
Placebo (N = 47)	59.1 (20.39)	0.0 (-28.0, 40.0)	0.6 (16.39)		
EQ-5D-3L Index score (0-1 scale, with higher scores indicating increased quality of life)					
Eculizumab (N = 96)	0.68 (0.196)	0.03 (-0.57, 0.56)	0.05 (0.18)	0.09 (0.02, 0.15)	NS
Placebo (N = 47)	0.68 (0.196)	0.00 (-0.67, 0.41)	-0.04 (0.21)		
SF-36 Physical component score (0-100 scale, with higher scores indicating increased physical quality of life)					
Eculizumab (N = 96)	38.6 (9.83)	2.6 (-19.8, 34.1)	3.4 (7.7)	3.10 (0.49, 5.71)	NS
Placebo (N = 47)	36.9 (10.85)	0.4 (-19.9, 22.6)	0.7 (8.3)		
SF-36 Mental component score (0-100 scale, with higher scores indicating increased mental quality of life)					
Eculizumab (N = 96)	47.0 (12.55)	-0.1 (-27.8, 28.6)	0.5 (10.6)	1.84 (-1.61, 5.29)	NS
Placebo (N = 47)	44.0 (11.40)	0.4 (-29.1, 20.6)	-0.1 (11.8)		

Source: Table 2-17 (p 59) of the submission; Table 31 (p 115), Table 32 (p 116), Table 14.2.3.2.1.1 (p 744), Table 14.2.3.2.2.1 (p 745), Table 14.2.3.3.42.1 (p 871); 14.2.3.3.47.1(p 884) of the PREVENT trial report

CI = confidence interval; EDSS = Expanded Disability Status Scale; NS = not significant; SD = standard deviation

[a] The PREVENT trial used a hierarchical testing order for outcomes to account for multiplicity of testing (with EDSS assessed before other disability or quality of life outcomes). As the difference between arms was non-significant for EDSS, no further inferences can be made for other disability or quality of life outcomes

6.17 There were no statistically significant differences in disability or quality of life measures between treatments, but results generally favoured the eculizumab arm. The numerical differences in disability and quality of life measures between treatment arms were consistent with the higher incidence of relapse in the placebo arm. However, it is unclear whether these changes represent temporary differences or permanent effects as patients completed the PREVENT study 6 weeks after relapse. The PSCR stated that the average recovery occurs over three months, with the majority of recovery from most relapses occurring within the first 30 days post relapse. As such, the PSCR argued that the follow-up of 6 weeks after a single relapse adequately captured the disability following a relapse as the majority of the recovery would have occurred. In addition, the PSCR stated that as the majority of relapses in NMOSD result in disability with permanent change (the PSCR cited an Australian

collaborative study (Khalilidehkordi, 2020[2]) which found that disability was permanent in 71% of patients irrespective of whether there was partial or no recovery following a relapse), the disability and quality of life measures do not represent temporary differences. However, the ESC considered that the magnitude of the effect on disability progression remained unclear.

6.18 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.

Comparative harms

6.19 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.

6.20 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.

6.21 The adverse event profile reported in the PREVENT trial and extension was consistent with the known safety profile of eculizumab. The PSCR noted that eculizumab has been used for over 10 years in the treatment of PNH, myasthenia gravis and aHUS with no new safety signals. The PSCR considered that the long-term safety observed across these indications could be extrapolated to NMOSD patients.

Benefits/harms

6.22 The PBAC considered that the magnitude of the effect of eculizumab on disability progression and quality of life outcomes was highly uncertain.

Clinical claim

6.23 The submission described eculizumab as superior in terms of efficacy and non-inferior in terms of safety compared to placebo. The ESC considered that these claims were reasonable.

6.24 However, the ESC noted that the following issues should be considered:

- Whether the results of the PREVENT trial can be generalised to the proposed lower risk PBS population. The relapse eligibility criteria in the PREVENT trial (2 relapses in the previous year or 3 relapses in the previous 2 years) were stricter than those

[2] Khalilidehkordi E, et al. Relapse patters in NMOSD: evidence for earlier occurrence of optic neuritis and possible seasonal variation. Frontiers in Neurology. 2020;11:537. doi: 10.3389/fneur.2020.00537

proposed for the requested PBS population (2 relapses in the previous 2 years; or an immunosuppressive event with prior treatment) and it is likely that the PBS population will include patients with a lower risk of relapse. A smaller absolute risk of relapse will reduce the magnitude of benefit associated with eculizumab treatment. Although the PSCR presented data from Palace 2019 which suggested that the number of prior relapses is not necessarily synonymous with future risk of relapse or severity of disease, the ESC noted that this study did not apply the same definitions of prior relapse as used in the PREVENT trial or adjust for the clustering nature of relapses. The ESC noted that the Palace 2019 data indicated that relaxing the restriction criteria around the number of prior relapses would result in a population who have a lower absolute risk of further relapses.

- 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. The PSCR stated that rituximab use was prohibited in the PREVENT trial due to the incompatibility between the mechanisms of action of eculizumab and rituximab. In addition, the PSCR noted that rituximab is not TGA registered for use in NMOSD in Australia and that access to rituximab is therefore dependent on where the patient is treated, resulting in equity issues. The ESC noted that the majority of NMOSD patients would be treated in specialist centres, where rituximab would be available, reducing the risk of access inequity.
- While eculizumab had a significant impact on reducing relapses in the trial, the magnitude of the effect on disability progression is unclear. There was limited follow-up of patients after a relapse during the PREVENT trial and it was unclear whether differences in disability and quality of life measures represent temporary differences (due to relapse) or permanent changes (due to disability progression). The PSCR stated that the average recovery occurs over three months, with the majority of recovery from most relapses occurring within the first 30 days post relapse. As such, the PSCR stated that follow-up of 6 weeks after a single relapse would adequately capture disability following a relapse as the majority of the recovery would have occurred. In addition, the PSCR stated that as the majority of relapses in NMOSD result in disability with permanent change (the PSCR cited an Australian collaborative study (Khalilidehkordi, 2020[3]) which found that disability was permanent in 71% of patients irrespective of whether there was partial or no recovery following a relapse), the disability and quality of life measures do not represent temporary differences. The ESC considered that although there were data that suggested increasing relapses are associated with increasing disability

[3] Khalilidehkordi E, et al. Relapse patters in NMOSD: evidence for earlier occurrence of optic neuritis and possible seasonal variation. Frontiers in Neurology. 2020;11:537. doi: 10.3389/fneur.2020.00537

and, therefore, reducing relapses should be associated with reduced disability, the magnitude of this effect was unclear.

6.25 The PBAC considered that the claim of superior comparative effectiveness was reasonable in terms of extending the time to relapse for the population presented in the trial, but considered that efficacy in the proposed PBS population was uncertain as the eligibility of the PREVENT trial differed from the proposed PBS restriction.

6.26 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

6.27 The submission presented a stepped economic evaluation of eculizumab with best supportive care compared to best supportive care alone in patients with NMOSDs who are AQP4 positive 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.

6.28 The submission did not present an economic analysis for the use of eculizumab in patients with a prior immunosuppressive event who do not otherwise meet the relapse criteria (estimated in the submission as approximately 10% of the Australian NMOSD population).

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. The ESC considered that the long time horizon added to the uncertainty in the model as the majority of the incremental benefits occurred in the extrapolated period.
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. The ESC considered that the model structure was overly complex and, noting the small patient numbers in each EDSS state and the non-significant difference in overall EDSS score between treatment groups in the PREVENT trial, were unclear as to how well the EDSS states captured NMOSD related disability. The ESC noted the model submitted to CADTH appeared to have a simpler structure with four health states that aligned with key NMOSD disabilities (relapse free, relapse, long-term disability and death). The pre-PBAC response clarified that the CADTH model was not necessarily simpler as the four health states were further divided into a series of tunnel health states. The pre-PBAC response also stated that a simpler "relapse free" health state (as used in the model submitted to CADTH) inappropriately combines all patients of varying disabilities in a single health state with a single utility value and a single estimate of resource utilisation.
Cycle length	Six-monthly
Patient characteristics	Current age (47 years), gender (91% female) and distribution across EDSS health states based on a published observational study comparing the characteristics of definitive NMOSD, suspected NMOSD and multiple sclerosis populations attending Australian treatment centres (Bukhari 2020)
Transition probability	Transition probabilities for treatment persistence, relapse events and disability progression were derived from PREVENT trial data. Transition probabilities for relapse-related death were based on published estimates (Mealy 2018). 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 (Orne 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). 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 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: Table 3-1 (p 110-111) of the submission

CADTH = Canadian Agency for Drugs and Technologies in Health; DPMQ = dispensed price per maximum quantity; EDSS = Expanded Disability Status Scale; ESC = Economic Sub-Committee; MBS = Medicare Benefits Schedule; NMOSD = neuromyelitis optica spectrum disorder; UK = United Kingdom; US = United States

6.29 Patients begin the model in various EDSS health states based on the estimated distribution in the Australian NMOSD population (Bukhari 2020). 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.

6.30 The ESC noted that the economic model was overly complex with 20 health states and two death states. The ESC considered it was unclear whether the EDSS health states adequately capture NMOSD-related disability, and also noted the probability of disability progression in the model was based on a small number of patients (23 patients) from a post-hoc analysis of EDSS scores in the PREVENT trial at four to six weeks after relapse. The ESC noted the model submitted to CADTH appeared to have a simpler structure with four health states that aligned with key NMOSD disabilities (relapse free, relapse, long-term disability and death). The pre-PBAC response clarified that the CADTH model was not necessarily simpler as the four health states were further divided into a series of tunnel health states. The pre-PBAC response also stated that a simpler "relapse free" health state (as used in the model submitted to CADTH) inappropriately combines all patients of varying disabilities in a single health state with a single utility value and a single estimate of resource utilisation.

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

Table 8: Key drivers of the model

Description	Method/Value	Impact
Relapse rate	The submission estimated the risk of relapse with best supportive care based on the adjudicated annualised 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 requested PBS population given the differences in eligibility criteria between the two populations. Overall, the PBS population is likely to include lower risk patients who may not achieve the same magnitude of benefit as the trial population. It is unclear whether 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 modelling of relapses based on adjudicated events may underestimate the frequency of relapses in clinical practice which would typically be assessed by the treating physician. The PSCR noted that the incremental effect of eculizumab relative to best supportive care observed in the trial when relapse rates were based on adjudicated events or treating physician assessment were similar (adjudicated rates: eculizumab = 0.350 versus placebo = 0.016; difference = 0.334; physician rates: eculizumab = 0.446 versus placebo = 0.066; difference = 0.380) and stated that the submission applied adjudicated rates were more conservative. However, the ESC noted that adjudicated rates were not more conservative if both the underlying relapse rate and treatment efficacy estimates were applied. Overall, the ESC considered that the use of the adjudicated event relapse definition may not reflect how eculizumab would be administered in clinical practice, but noted this only had a minor impact on the ICER. The submission 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 submission estimated the risk of relapse in the eculizumab treatment arm by applying the hazard ratio from the time to first adjudicated relapse in the PREVENT trial to the risk of relapse in the best supportive care arm. Treatment efficacy estimates based on relapses assessed by the treating physician may be more applicable to clinical practice (as outlined above). The submission assumed constant treatment efficacy over time. This assumption could not be validated due to a lack of long-term data.	High, favours eculizumab

Description	Method/Value	Impact
Relapse mortality	The submission assumed that 7% of relapses were fatal based on an observational study reporting a 7% all-cause mortality incidence in an NMOSD population (Mealy 2018). The ESC noted that some of the health gain produced by the model was associated with increased survival for those treated with eculizumab, and this seemed unsupported by the evidence presented. The pre-PBAC response stated that the assumption of a survival benefit with eculizumab treatment due to a reduction in fatal relapses was reasonable as relapses are associated with a risk of mortality. The submission inappropriately based the mortality assumption on all-cause mortality (7.0%) rather than NMOSD specific mortality (5.2%). The publication by Mealy noted that there were substantial differences in mortality outcomes between racial groups (African: 19/175, 10.9%; non-African: 3/252, 1.2%). In general, the non-African estimates are likely to be more relevant to the Australian population with NMOSD (primarily Asian or Caucasian; Bukhari et al 2017). The mortality estimate reported in the Mealy publication was not based on relapse events but deaths reported in a population with an average follow-up duration of approximately 10 years (in which patients may have experienced multiple relapse events). Therefore applying the risk estimate to each relapse will substantially overestimate the cumulative mortality risk. To derive a mortality risk per relapse would require the mortality estimate to be distributed across the relapse events that occurred during the observation period. The PSCR stated that the PREVENT trial was not powered to demonstrate a reduction in mortality. The PSCR also stated that the mean age of death in Mealy 2018 was 52 years, which revealed a substantial premature mortality in the NMOSD cohort. Removing mortality from the economic model resulted in a 27% increase in the ICER (see 'No risk of fatal relapse' sensitivity analysis in Table 10).	High, favours eculizumab
Disability progression	The submission estimated the probability of disability progression following relapse, based on a post-hoc analysis of EDSS scores at 4-6 weeks after relapse from both treatment arms in the PREVENT trial. It was unclear whether the estimates from the PREVENT trial adequately reflect the risk of permanent disability progression given they were based on the first assessment 30 days after relapse while the trial data, published reviews and treatment guidelines all suggest the potential for further recovery beyond this time point (UptoDate 2019; Kessler 2016). The PSCR stated that although the 30 day follow up did not capture all potential recovery, post hoc analysis of the PREVENT trial and the open-label extension study found that the EDSS scores 30 days post relapse were the same as those at 120 days, with peak disability reached at 90 days (Berthele, 2020). Thus, the PSCR stated that the 30 day follow-up adequately captured the level of recovery and disability progression was not overestimated in the model. The post hoc data also indicated a mean EDSS score increase of approximately 0.3 points across all patients at 120 days post an adjudicated relapse and that 30% of EDSS changes were clinically meaningful at 120 days. However, the ESC noted that the economic model estimated a mean EDSS score increase of 0.435 points across all patients, with 43.5% of patients having a clinically important change in EDSS score. The ESC noted that the model overestimates the risk of disability progression, and the model estimates would need a relative reduction of approximately 30% to align with the new post hoc data. The submission noted that the economic model did not attempt to capture visual disability associated with NMOSD. The submission claimed that this approach may underestimate the benefits of delaying disability progression.	High, favours eculizumab

Description	Method/Value	Impact
Health state utility values	The submission stated that health state utility values were based on a post-hoc, random effects regression of EQ-5D-3L utility scores reported in the PREVENT trial and the ECU-NMO-302 extension study. This was incorrect, as the presented values were based on the raw utility scores. There was a limited number of observations informing higher EDSS scores (> 7) which was consistent with the inclusion criteria of the PREVENT trial (patients with EDSS scores 0-7). The inclusion of all EDSS observations regardless of relapse status was inappropriate as measurements captured during an acute relapse may not be reflective of the underlying 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 submission acknowledged some inconsistencies in utility values between different EDSS scores (i.e. utility values did not consistently correlate with disability level). To address this issue, the submission merged the utility values from some EDSS steps in order to get a consistent decline with increasing disability. The utility adjustments applied in the submission were poorly justified (e.g. EDSS 0 is primarily informed by EDSS 1.5) and do not adequately address the internal consistency issues associated with using the raw values. 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.	High, favours eculizumab

Source: Constructed during the evaluation
EDSS = Expanded Disability Status Scale; ESC = Economic Sub-Committee; ICER = incremental cost-effectiveness ratio; NMOSD = neuromyelitis optica spectrum disorder; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response

6.32 The submission estimated the probability of treatment discontinuation in the eculizumab arm based on the discontinuation rate reported in the PREVENT trial (9.3 per 100 patient-years of follow-up). The main cause of discontinuation in the trial was due to personal reasons (e.g. relocation, change of employment etc.). It was unclear whether discontinuation rates from the PREVENT trial (observed in a tightly regulated study setting) would be representative of clinical practice and it was unclear whether they would remain constant over the longer term time horizon of the model.

6.33 The results of the stepped economic evaluation are summarised below. During the evaluation, the time horizon of the first modelled step (i.e. Step 2a) was changed from 18 months to 36 months in order to coincide with the last trial based step. Additionally, Step 3 of the modelled analysis was divided into two sub-steps (introduction of fatal relapses; lifetime time horizon). Finally, Step 4 was also divided into two sub-steps (include utilities; introduction of disability progression).

Table 9: Stepped economic evaluation of eculizumab compared to best supportive care

Type of resource item	Eculizumab	Best supportive care	Incremental difference
Step 1a: Trial based efficacy - 48 week results (approximately 1 year), drug and administration costs only			
Costs	[redacted]	$0	[redacted]
Patients without relapse	0.979	0.632	0.347
Incremental cost per additional patient free from relapse			[redacted][1]
Step 1b: Trial based efficacy - 96 week results (approximately 2 years), drug and administration costs only			
Costs	[redacted]	$0	[redacted]
Patients without relapse	0.964	0.519	0.445
Incremental cost per additional patient free from relapse			[redacted][1]
Step 1c: Trial based efficacy - 144 week results (approximately 3 years), drug and administration costs only			
Costs	[redacted]	$0	[redacted]
Patients without relapse	0.964	0.454	0.510
Incremental cost per additional patient free from relapse			[redacted][1]
Step 2a: Modelled efficacy – 36 month time horizon, drug and administration costs only			
Costs	[redacted]	$0	[redacted]
Average number of relapses	0.0557	0.9610	-0.9053
Incremental cost per relapse avoided			[redacted][1]
Step 2b: Modelled efficacy – 36 month time horizon, drug and administration costs only, allow eculizumab discontinuations			
Costs	[redacted]	$0	[redacted]
Average number of relapses	0.1546	0.9610	-0.8064
Incremental cost per relapse avoided			[redacted][1]
Step 2c: Modelled efficacy – 36 month time horizon, drug, administration and relapse costs, allow eculizumab discontinuations			
Costs	[redacted]	$8,874	[redacted]
Average number of relapses	0.1546	0.9610	-0.8064
Incremental cost per relapse avoided			[redacted][1]
Step 3a: Modelled efficacy – 36 month time horizon, drug, administration and relapse costs, allow eculizumab discontinuations, include fatal relapse events			
Costs	[redacted]	$8,636	[redacted]
LYs	2.7745	2.6956	0.0789
Cost per LY gained			[redacted][1]
Step 3b: Modelled efficacy – lifetime time horizon, drug, administration and relapse costs, allow eculizumab discontinuations, include fatal relapse events			
Costs	[redacted]	$40,996	[redacted]
LYs	8.4077	7.3796	1.0280
Cost per LY gained			[redacted][1]
Step 4a: Modelled efficacy – lifetime time horizon, drug, administration and relapse costs, allow eculizumab discontinuations, include fatal relapse events; apply utility estimates for relapses and EDSS health states			
Costs	[redacted]	$40,996	[redacted]
QALYs	8.3615	7.3063	1.0552
Cost per QALY gained			[redacted][1]
Step 4b: Modelled efficacy – lifetime time horizon, drug, administration and relapse costs, allow eculizumab discontinuations, include fatal relapse events; include risk of disability progression with relapse; apply utility estimates for relapses and EDSS health states			
Costs	[redacted]	$40,996	[redacted]
QALYs	7.1480	5.2822	1.8658
Cost per QALY gained			[redacted][1]
Step 5: Modelled efficacy – lifetime time horizon, drug, administration, relapse and EDSS health state costs, allow eculizumab discontinuations, include fatal relapse events; include risk of disability progression with relapse;			

apply utility estimates for relapses and EDSS health states			
Costs	[redacted]	$177,188	[redacted]
QALYs	7.1480	5.2822	1.8658
		Cost per QALY gained	[redacted][1]

Source: Table 3-21 (p 154) of the submission
EDSS = Expanded Disability Status Scale; LY = life year; QALY = quality-adjusted life year

The redacted values correspond to the following ranges:
[1] > $1,055,000

6.34 The extrapolation of treatment benefits beyond the clinical trial data had the largest impact on the stepped economic evaluation. The introduction of fatal relapse events and disability progression with relapse also had substantial impacts on the economic evaluation.

6.35 Based on the economic model, treatment with eculizumab was associated with a cost per quality adjusted life year (QALY) gained of > $1,055,000 compared to best supportive care for the treatment of NMOSD patients with frequent relapses. The cost effectiveness of eculizumab for the treatment of NMOSD patients with a prior immunosuppressive event is unknown.

6.36 The PBAC has previously considered incremental cost effectiveness ratios (ICERs) of approximately $100,000 to $300,000 per QALY gained for other rare diseases (paragraph 6.94 ravulizumab July 2020 PBAC Public Summary Document (PSD)). The ESC noted that during the evaluation, threshold analyses were conducted to determine the price reduction required for eculizumab to achieve an ICER of $100,000 (95.1% reduction), $200,000 (90.4% reduction) or $300,000 (85.7% reduction) per QALY gained.

6.37 The ESC noted the disaggregated health outcomes which estimated that patients treated with eculizumab had, on average, 1.612 fewer relapses than patients treated with best supportive care over the 53 year time horizon of the model (with an average of 6.6 relapses per patient in the eculizumab arm, and 8.2 in the best supportive care arm). The ESC considered that these modelled clinical gains were small considering the cost of the medication and the long-term nature of treatment (the model estimated that the average eculizumab drug costs were $[redacted] per patient, for an average time on treatment (undiscounted) of 9.9 years).

6.38 The ESC also noted that the model estimated an average of 4.6 life years gained (undiscounted) in the eculizumab arm compared to best supportive care (with an average of 30.0 life years per patient in the eculizumab arm, and 25.4 in the best supportive care arm), which the ESC considered was uncertain given the lack of evidence of a survival benefit.

6.39 The ESC considered that the highly complex structure of the model, long time horizon in which the majority of incremental benefits occurred in the extrapolated period and the use of non-trial based inputs, such as for NMOSD mortality, meant the outcomes were highly uncertain in terms of estimating the cost-effectiveness of eculizumab.

Noting the recommendation by the CADTH, the ESC considered that a similar substantial price reduction would be required to mitigate the uncertainties in the model to achieve an ICER approaching a more acceptable value.

6.40 The submission presented the results of a validation exercise comparing modelled severe disability or death in the best supportive care arm with estimates from an NMOSD risk prediction tool (Palace 2019). During the evaluation an alternative validation cohort was specified based on alternative assumptions around patient ethnicity, gender and age of onset. The results of the evaluation's validation exercise suggest that the base case analysis substantially overestimated the risk of severe disability or death compared to values derived from an external risk prediction model with Australian NMOSD patient characteristics. The results of the model can be calibrated to the match the risk of the alternative validation cohort by removing relapse mortality and reducing disability progression by 35% (tested in sensitivity analyses below).

6.41 The results of key sensitivity analyses are summarised below.

Table 10: Results of sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER
Base case	[redacted]	1.8658	[redacted][1]
Time horizon (base case: 53 years)			
30 years	[redacted]	1.7226	[redacted][1]
20 years	[redacted]	1.3753	[redacted][1]
10 years	[redacted]	0.6836	[redacted][1]
Annualised relapse rate in best supportive care arm (base case: 0.350 based on adjudicated relapses in the placebo arm of the PREVENT trial)			
ARR based on adjudicated relapses upper 95% CI (0.616)	[redacted]	2.3749	[redacted][1]
ARR based on adjudicated relapses lower 95% CI (0.199)	[redacted]	1.3221	[redacted][1]
ARR based on on-trial relapses (0.446)	[redacted]	2.0966	[redacted][1]
Decreasing risk of relapses over time (-1.76% per cycle)	[redacted]	1.8152	[redacted][1]
Treatment effect of eculizumab (base case: 0.058 based on HR from time to adjudicated relapse in the PREVENT trial)			
RR based on adjudicated relapses (0.045)	[redacted]	1.8984	[redacted][1]
RR based on on-trial relapses (0.147)	[redacted]	1.6491	[redacted][1]
Probability of disability progression (base case: 0.435 based on a post-hoc analysis of the PREVENT trial, assumed single step EDSS progression, patients cannot progress from EDSS 9 to EDSS 10 - death)			
Decrease probability by 20% (0.3480)	[redacted]	1.7278	[redacted][1]
Decrease probability by 35% (0.2828) [consistent with external validation]	[redacted]	1.6160	[redacted][1]
Probability of fatal relapse (base case: 0.070 based on Mealy 2018 publication)			
No risk of fatal relapse	[redacted]	1.4699	[redacted][1]
Probability of treatment discontinuation (base case: 0.0465 based on the PREVENT trial)			
Increase probability by 50% (0.0698)	[redacted]	1.4416	[redacted][1]
Decrease probability by 50% (0.0233)	[redacted]	2.6078	[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 linear regression with UK weights from the PREVENT trial	[redacted]	1.4578	[redacted][1]
Utilities based on linear regression with UK weights from the PREVENT trial but with utility of 0 for EDSS levels of 8+	[redacted]	1.7405	[redacted][1]
Utilities based on linear regression with UK weights from the PREVENT trial but with utility of 0.1 for EDSS levels of 8+	[redacted]	1.6581	[redacted][1]
Relapse costs (base case: $9,926.65 per event based on Stafkey-Mailey 2016; no supplementary eculizumab dosing)			
Include supplementary eculizumab dosing	[redacted]	1.8658	[redacted][1]

Source: 3-28 (p 160-162) of the submission

ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; HR = hazard ratio; ICER = incremental cost effectiveness ratio; MS = multiple sclerosis; QALY = quality adjusted life year; RR = rate ratio; UK = United Kingdom

The redacted values correspond to the following ranges:

[1] > $1,055,000

6.42 The results of the sensitivity analyses indicated that the model was most sensitive to time horizon, annualised relapse rate in the best supportive care arm, eculizumab treatment effects, risk of fatal relapse, risk of disability progression and utility values for severe disability health states.

6.43 A multivariate sensitivity analysis was conducted during the evaluation including the use of on-trial relapse rate and treatment effect, decreasing relapse rate over time (-1.76% per cycle), no relapse mortality, 35% reduced disability progression

(consistent with external validation data) and supplementary eculizumab dosing. The results of this analysis are summarised below.

Table 11: Results of multivariate sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER
On-trial relapse rate (0.446) and treatment effect (0.147), decreasing relapse rate over time (-1.76% per cycle), no relapse mortality, 35% reduced disability progression and supplementary eculizumab dosing	[redacted]	1.0065	[redacted][1]

Source: Constructed during the evaluation based on the ECU_Section3_CUA TreeAge model
ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year
The redacted values correspond to the following ranges:
[1] *> $1,055,000*

6.44 Treatment with eculizumab was associated with a cost per QALY gained of > $1,055,000 compared to best supportive care under the multivariate analysis.

6.45 Based on this multivariate sensitivity analysis, threshold analyses were conducted during the evaluation to determine the price reduction required for eculizumab to achieve an ICER of $100,000 (96.9% reduction), $200,000 (94.4% reduction) or $300,000 (91.9% reduction) per QALY gained in the multivariate analysis.

Drug cost/patient/year

6.46 The estimated drug cost for eculizumab in the initial month of treatment was $[redacted] (based on 3 vials x 4 weeks using a weighted public/private dispensed price per maximum quantity (DPMQ) of $[redacted]). The estimated drug cost per patient per year for eculizumab in the continuation phase was $[redacted] (based on 4 vials x 26 fortnights using a weighted public/private DPMQ of $[redacted]). The estimated drug costs (based on vial price, dosing regimen and duration of use) were consistent across all sections of the submission. The vial price for eculizumab is consistent with its other PBS subsidised indications.

6.47 The submission did not estimate the drug costs associated with best supportive care.

Estimated PBS usage & financial implications

6.48 This submission was considered by DUSC.

6.49 The submission used an epidemiological approach to estimate the utilisation and financial impact of eculizumab. The incident cohort-based approach used to estimate the size of the treated population was difficult to interpret alongside the approach used to estimate the size of the eligible population (based on prevalence). In particular, it was difficult to reconcile eligibility assumptions in the estimates of use (ongoing eligibility in the mixed incident cohort) with eligibility patterns in the prevalent pool of patients (increasing pool of frequently relapsing patients, constant proportion of patients with prior immunosuppressive event).

6.50 The PSCR proposed altering the estimates to include a prevalence approach to estimate the eligible and treated patients. The PSCR stated that the incident-cohort

approach was taken because the source (Palace 2019) only provided information on the proportion of the AQP4 positive NMOSD population who would be eligible for treatment at a single point in time, that those patients who did not qualify at that single point in time remained 'at risk' of becoming eligible and the incident cohort approach reflected this, and that, for simplicity, the response provided a prevalence only approach to estimating the patient population size and expected financial impact. The DUSC noted that the updated estimates of use included with the PSCR applied a constant proportion to estimate the number of patients who are AQP4 positive and frequently relapsing. However, the updated estimates continued to use the incident cohort-based approach to estimate the size of the treated population, although the number of patients treated in Year 1 was higher, and the number of newly eligible patients in later years was lower, than in the submission. The pre-PBAC response clarified that for the estimates provided in the PSCR, the prevalence of NMOSD was applied to the Australian Bureau of Statistics population projection to calculate the size of the treated population. The PBAC considered the prevalence estimate applied in the PSCR revised estimates (0.001%) and the submission (0.0007%) were unreliable and likely underestimated (see paragraphs 6.55 and 6.57).

6.51 Key inputs are summarised in the table below.

Table 12: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Prevalence of NMOSD	0.0007% (revised to 0.001% in PSCR)	Bukhari (2017). Based on data across the Australian and New Zealand network of 23 specialist clinics for demyelinating diseases collected over 3 years from 2011 to 2013. Data were based on patients who fulfilled the Wingerchuk 2015 NMOSD diagnostic criteria. To facilitate a capture-recapture methodology, four laboratories in Australia that offer routine AQP4-antibody testing provided details of positive cases detected in their laboratories for the same time period. Crude point prevalence rates were calculated for the prevalence date of 1 July 2013 based on 147 cases: 0.53 (95% CI 0.45 to 0.62) per 100,000. After adjustments using capture-recapture analysis, the estimated total number of NMOSD cases was 193 which results in a prevalence estimate for NMOSD of 0.70 (95% CI 0.61 to 0.78) per 100 000. PSCR estimate was based on the opinion of 6 experts.	The authors of the study acknowledged that the prevalence rate may be an underestimate as cases were only based on currently or recently active cases who were either seen in the specialist clinics or had undergone AQP4 antibody testing within the 3-year study period. Results from the study suggest approximately half of the cases comprised of positive laboratory-based tests that were not captured in the clinical records of the specialist clinics. This suggests a potential prevalent pool of patients with historical diagnosis that may not be captured in this study. The authors of the study also acknowledged they may have underestimated cases, and that their results were lower than other published estimates. The worldwide prevalence estimates range from approximately 0.5 to 4 patients per 100,000 population. However, these estimates are highly variable given observed racial associations (higher in African and Asian, particularly Japanese, populations) and evolving diagnostic criteria. There is a current application for MBS listing of a new test to detect AQP4 antibodies for diagnosis of NMO (MSAC application 1582). The PICO

Data	Value	Source	Comment
			Advisory Sub-committee advised that a survey of laboratories be conducted to determine how many tests are currently being done. Data sourced from Queensland Health (public sector) suggest 235 positive tests over a 5-year period (2015-2019). The estimated number of prevalent patients in Australia is relatively low compared to estimates from Queensland Health alone. The PSCR acknowledged that the prevalence rate from Bukhari (2017) was likely an underestimate and provided updated financial estimates in which the prevalence was 0.001%, which was based on the opinion of 6 experts. DUSC noted that the PSCR did not provide details about the 6 clinical experts, the questions they were asked, or the method of collecting the data. DUSC noted that the number of test samples processed in Queensland includes test samples from Victoria, but NSW, WA, and SA have separate laboratories, and that separate laboratories exist for private testing in Queensland, and commented the prevalence could be up to five times higher than that the prevalence proposed by the PSCR. DUSC noted the claim in the PSCR that diagnosed patients may be tested up to four times a year, as the test may act as a biomarker for disease severity, and commented that a prevalence of 0.005% would depend on no duplication of testing for patients. DUSC also noted that it had been established that 'reverse seroconversion' was not thought to be a useful marker of disease prognosis, and therefore repeated testing appeared unlikely to be widespread. DUSC commented that prevalence usually accounts for all patients affected by a disease; however, DUSC agreed with the commentary that in this case there may be historical diagnosed asymptomatic patients not included in the prevalence estimate, due to the relapsing nature of NMOSD. Additionally, DUSC considered that NMOSD is a relatively newly recognised disease and diagnosis rates may increase in future years, particularly once treatments are PBS listed.

Data	Value	Source	Comment
Proportion of patients who are AQP4 antibody positive	90.1%	Bukhari (2017). Based on the proportion of diagnosed NMOSD cases that were seropositive (73 of 81 cases, 90.1%).	DUSC considered that the estimate appeared reasonable. Other studies cited in the submission suggest that AQP4 antibodies are present in approximately 73 to 90% of cases (Jarius 2012, Kessler 2016, Wingerchuk 2015, Papp 2018).
Proportion with AQP4+ and frequent relapses	Submission: Yr 1: 17.6% Yr 2: 27.7% Yr 3: 36.6% Yr 4: 44.3% Yr 5: 51.1% Yr 6: 57.1% PSCR: 40.7%	Palace (2019). NMOSD outcomes prediction model based on 441 patients from five NMO specialist centres in the UK, USA, Japan and Martinique, who collectively experienced 1,976 attacks. The model predicts an average of 17.6% of patients will have at least 2 attacks in the preceding 2 years at any given time point. The submission claimed that applying the 17.6% estimate to the prevalent pool will underestimate the number of eligible patients as it does not account for patients who might have 2 relapses in the future. The submission attempted to calculate a 2-year relapse rate using the adjudicated annualised relapse rate in the placebo arm of the PREVENT trial (calculated as 0.35 x 0.35 = 0.1225). This estimate was applied each year to the remaining cohort who were ineligible each year as an inflation factor. The PSCR instead applied 40.7% as a 'steady state estimate' for the prevalence of frequently relapsing patients, based on the risk of at least one relapse in 2 years in Palace (2019)	The submission did not adequately justify the need for adjustments to the average estimate from the Palace study that is intended to represent the average proportion of patients fulfilling eligibility criteria over time. It may be more appropriate to apply the unadjusted estimate to the prevalent pool of patients in each year. The adjusted estimates used in the submission did not meet face validity, with a majority of prevalent patients qualifying for disease in Year 6, which will continue to grow over time. The PBAC considered the restriction should align with the eligibility criteria of the trial in terms of frequency and number of prior relapses, and thus considered the change applied in the PSCR likely overestimated the eligible population.

Data	Value	Source	Comment
Proportion with AQP4+ and prior IST event	11.8%	Poupart (2020). Retrospective cohort study involving 10 French university hospitals in the multiple sclerosis and NMOSD network. Medical records from 1993 to 2017 were retrieved for patients who were diagnosed with NMOSD based on Wingerchuk 2015 criteria, positive for AQP4 or anti-MOG antibodies, initiated IST treatment as first-line therapy within 3 years of disease onset and had at least 1 year of follow-up. The estimate was based on a subset of patients who received first-line therapy with rituximab, azathioprine or mycophenolate mofetil. The submission assumed the proportion of patients with a documented serious infectious event (15/127, 11.8%) is representative of the proportion who experienced a prior IST event.	There were significant concerns with the applicability of the estimated prevalence of patients with a prior immunosuppressive event including: - inadequately justified use of a selected retrospective analysis that may not reflect the broader literature; - potential incompleteness of safety data from the study; - unclear applicability of the study population who received other immunosuppressive therapies only (rituximab, mycophenolate mofetil, azathioprine); and - data from the Poupart study suggest a higher number of patients may also discontinue immunosuppressive therapy due to adverse events not directly related to infections. In practice, there may be potential for broader interpretation of the restriction due to concerns with long-term use of immunosuppressants. DUSC noted that this subgroup is a small contributor to the estimates and considered that the reasonableness of this estimate would depend on the final PBS restriction.
Estimated population initiating treatment with eculizumab			
Total newly eligible patients (incident cohort)	Yr 1: < 500 Yr 2: < 500 Yr 3: < 500 Yr 4: < 500 Yr 5: < 500 Yr 6: < 500	Based on estimated number of patients in each qualifying subgroup (AQP4+ and frequently relapsing; AQP4+ and prior IST event). The submission assumed 100% are newly qualifying patients in Year 1. In subsequent years, the incident cohort was estimated by subtracting patients from the previous year from patients in the following year.	See comments above.
Uptake rates in newly eligible patients	Yr 1: 50% Yr 2: 55% Yr 3: 60% Yr 4: 65% Yr 5: 65% Yr 6: 65%	Assumed	There were no data provided in support of the assumption. DUSC considered that these uptake rates were possibly underestimated as there is an unmet clinical need for NMOSD treatments.
Patients eligible in previous years who did not initiate treatment (incomplete uptake)	Yr 1: < 500 Yr 2: < 500 Yr 3: < 500 Yr 4: < 500 Yr 5: < 500 Yr 6: < 500	The submission assumed that patients who were previously eligible and did not initiate treatment (due to incomplete uptake) could initiate treatment in subsequent years.	This subgroup of patients was poorly defined in the submission. The reasons for incomplete uptake in the first year and subsequent years was not described in the submission. While patients with a prior IST event never lose eligibility, patients qualifying as frequently relapsing may lose eligibility over time. Ongoing eligibility should be estimated separately for these subgroups.

Data	Value	Source	Comment
Uptake rates in previously eligible patients who did not initiate treatment	Yr 1: 50% Yr 2: 55% Yr 3: 60% Yr 4: 65% Yr 5: 65% Yr 6: 65%	Assumed. Same as uptake rates in newly eligible patients.	There were no data provided in support of the assumption. DUSC considered that the application of uptake rates to patients who were eligible in previous years but did not initiate to initiate eventually, which may not align with the restriction. DUSC considered that it may have been more reasonable to assume a higher proportion of eligible patients would initiate in the year that they are diagnosed.
Estimated population continuing treatment with eculizumab			
Treatment persistence	89.7%	Based on the discontinuation rate from the PREVENT trial (9.3 per 100 patient-years of follow-up). The submission assumed the rate of discontinuation remained constant over time.	It was unclear whether discontinuation rates from the PREVENT trial (observed in a tightly regulated setting) would be representative of clinical practice. There are insufficient long-term data available to validate the assumption of a constant discontinuation rate over time. Using the incident cohort approach, patients who discontinued were assumed to cease treatment permanently. In practice, some of these patients may reinitiate treatment following a future relapse. DUSC noted that without treatment NMOSD patients acquire increasing disability but are expected to have normal lifespans, especially in patients of non-African ethnicity (Mealy et al).[4] DUSC commented that given the lack of other therapeutic options patients are likely to continue if possible, however the addition of the continuation criteria to limit initial and continuing treatment in patients who have progressed disease may help limit treatment in patients with increasing disability.

Source: compiled during the evaluation

AQP4+ = aquaporin-4 antibody positive; CI = confidence interval; DUSC = Drug Utilisation Sub-Committee; IST = immunosuppressive therapy; MBS = Medical Benefits Schedule; MOG = myelin oligodendrocyte glycoprotein; MSAC = Medical Services Advisory Committee; NMO = neuromyelitis optica; NMOSD = neuromyelitis optica spectrum disorder; PBS = Pharmaceutical Benefits Scheme; PICO = population – intervention – comparator – outcome; PSCR = pre-Sub-Committee response; UK = United Kingdom; USA = United States of America ; Yr = year

6.52 The tables below present the estimated use and financial implications of eculizumab over the first 6 years of listing (Table 13 – from the submission; Table 14 - updated estimates from the PSCR).

[4] Mealy MA, Kessler RA, Rimler Z, et al. Mortality in neuromyelitis optica is strongly associated with African ancestry. Neurol Neuroimmunol Neuroinflamm. 2018;5:e468.doi:10.1212/NXL0000000000000468

Table 13: Estimated use and financial implications presented in the submission

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients initiating treatment	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Patients continuing treatment	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications						
Initial year vials of eculizumab[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Continuing year vials of eculizumab[a]	0	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Total cost of eculizumab	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][8]
Patient co-pay	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net cost to PBS	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][8]
Cost to MBS	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net cost to Government	[redacted][4]	[redacted][5]	[redacted][6]	[redacted][7]	[redacted][7]	[redacted][8]

Source: Table 4-3 (p 166), Table 4-4 (p 168), Table 4-5 (p 168), Table 4-8 (p 171), Table 4-9 (p 173) of the submission; 'ECU_Section4_BIM' Excel workbook of the submission

MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

[a] Based on 108 vials per patient during the initial year and 104 vials per patient in continuing years

The redacted values correspond to the following ranges:

[1] < 500
[2] 500 to < 5,000
[3] 5,000 to < 10,000
[4] $10 million to < $20 million
[5] $20 million to < $30 million
[6] $30 million to < $40 million
[7] $40 million to < $50 million
[8] $50 million to < $60 million
[9] $0 to < $10 million

Table 14: Updated estimated use and financial implications presented in the PSCR

		Source	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
A	Patients with NMOSD	0.00001 x ABS pop. estimates	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
B	AQP4 positive	90% x A	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
C	AQP4 positive and frequently relapsing	40.7% x B	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
D	AQP4 positive and SAEs	11.8% x B	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
E	Total eligible patients	C + D	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
F	Expected uptake	Assumption	50%	55%	60%	65%	65%	65%
G	**Total treated patients**	**E x F**	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
H	Total number of vials*	Year 1: 108xG Year 2-6: 105xG	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
I	Cost to PBS/RPBS	$5,646.22 x H	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
J	Patient co-pay	$27.70 x 13 x G	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
K	**Net cost to PBS/PRBS**	**I – J**	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]

Source: Table 1, p6 of the PSCR

ABS = Australian Bureau of Statistics; AQP4 = aquaporin-4; NMOSD = neuromyelitis optica spectrum disorder; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response; RPBS = Repatriation Pharmaceutical Benefits Scheme; SAE = serious adverse event

* 108 vials for all patients in the first year, as per the PREVENT trial. Assumption that 25% of patients are initiating in subsequent years; 25% x 108 vials + 75% x 104 vials = 105 vials in Years 2-6

The redacted values correspond to the following ranges:
[1] < 500
[2] 5,000 to < 10,000
[3] $30 million to < $40 million
[4] $40 million to < $50 million
[5] $50 million to < $60 million
[6] $0 to < $10 million

6.53 The estimated net cost of listing eculizumab on the PBS in the submission was $10 million to < $20 million in Year 1 of listing, increasing to $50 million to < $60 million in Year 6, a cumulative total of $200 million to < $300 million over 6 years. The total cost to Government (including MBS administration costs) was $10 million to < $20 million in Year 1, increasing to $50 million to < $60 million in Year 6, a cumulative total of $200 million to < $300 million over 6 years.

6.54 The revised estimates in the PSCR estimated a net cost of listing eculizumab on the PBS of $30 million to < $40 million in Year 1, $50 million to < $60 million in Year 6 and a cumulative total of $200 million to < $300 million over the first 6 years.

6.55 DUSC considered that the estimates presented were underestimated. The main issues identified were that the:

- updated estimates of use included with the PSCR applied a constant proportion to estimate the number of patients who are AQP4 positive and frequently relapsing. However, the updated estimates continued to use the incident cohort-based approach to estimate the size of the treated population. Given the absence of time limitation following relapse in the new restriction, a prevalent approach would have better estimated utilisation. The pre-PBAC response clarified that a prevalence approach was used to estimate the size of the treated population.
- prevalence of NMOSD was increased to 0.001% in the PSCR, from 0.0007% in the submission. The prevalence may still be underestimated as:
  - there is likely to be a potential pool of patients with historical diagnosis that were not captured in the study sample; and
  - the rates of AQP4-antibody testing in Queensland suggests the prevalence of NMOSD is higher than 0.001%, although the Queensland figures do not identify if, and how many, patients are tested multiple times in a year.
- uptake rates applied to newly eligible patients were possibly underestimated as there is an unmet clinical need for treatments for NMOSD. It may have been more reasonable to assume that a higher proportion of eligible patients would initiate in the year they are diagnosed.

6.56 Overall DUSC commented that eculizumab is proposed as a lifelong prophylaxis treatment for a non-life-limiting disease, and that at the current price the estimated cost was approximately $50 million to < $60 million per year to treat less than < 500 patients per year.

6.57 The submission applied a prevalence estimate of 0.7 per 100,000 (0.0007%) based on Bukhari 2017 which used data collected from 1 January 2011 to 31 December 2013. The authors of the study acknowledged they may have underestimated cases, and that their results were lower than other published estimates. The worldwide prevalence estimates range from approximately 0.5 to 4 patients per 100,000 population (noting these estimates are highly variable given observed racial associations and evolving diagnostic criteria). Further, the PBAC noted that the prevalence estimate applied in the PSCR (0.001%) was based on the opinions from six clinicians who treat patients with NMOSD and the PSCR did not provide any further details regarding the clinicians, the questions they were asked, or the method of collecting their opinions. The PBAC agreed with DUSC that there may be a considerable risk of bias associated with this expert opinion. Overall the PBAC considered the prevalence estimates applied in the PSCR and the submission were unreliable and likely underestimated.

6.58 The submission did not address the financial implications associated with the need for supplemental eculizumab dosing for patients undergoing plasma exchange (which is used as an acute treatment for relapse in NMOSD). However, the ESC noted that most use in this setting would likely occur in admitted patients in public hospitals and, thus, will not be subsidised by the PBS.

Financial Management – Risk Sharing Arrangement

6.59 No RSA was proposed in the submission. However, the pre-PBAC response acknowledged the uncertainty in the eligible patient population and proposed a RSA. The pre-PBAC response proposed a [redacted] cap (based on a prevalence of [redacted] per [redacted] = < 500 patients in Year 1, increasing to < 500 patients in Year 6).

Quality use of Medicines

6.60 There were no issues identified in the submission. DUSC noted that the listing of eculizumab for NMOSD would be a substantial change to the treatment algorithm for a rare disease and considered that clinicians would require appropriate educational support. DUSC considered that the restriction should require the patient to be vaccinated against meningococcal infection.

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 NMOSD. 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 outcomes was highly uncertain. The PBAC noted that the incremental cost effectiveness ratio (ICER) was > $1,055,000 per quality adjusted life year (QALY) and advised that a significant price reduction would aid in achieving

an acceptable ICER. The PBAC, noting that eculizumab was proposed as a lifelong prophylactic treatment, considered that, at the proposed price, the cost of listing eculizumab on the PBS was high for the number of patients expected to be treated.

7.2 The PBAC welcomed the input from the three organisations via the Consumer Comments facility which noted that the use of eculizumab may reduce the risk of relapse.

7.3 The PBAC noted that NMOSD is characterised by acute clinical attacks (relapses) which predominantly target the optic nerves and spinal cord, 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 PBAC noted that mortality associated with NMOSD is unclear, but appeared to be low (i.e. NMOSD is unlikely to substantially reduce a patient's life expectancy).

7.4 The PBAC noted that the proposed PBS restriction was broader than the inclusion criteria of the key trial (PREVENT) in terms of patient age, background immunosuppressive therapies, level of disability (EDSS score), frequency of relapses, the number of prior relapses and history of prior immunosuppressive events. 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.

7.5 The PBAC considered that any future restriction should state 'This drug is not PBS-subsidised if it is prescribed to a public hospital in-patient' given the high potential for this to occur relative to other PBS listed drugs.

7.6 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 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. The PBAC considered exclusion of rituximab from the trial population may affect the generalisability of the results to clinical practice.

7.7 The PBAC noted that the clinical evidence was based on the results of one multicentre, double-blind RCT, PREVENT (N = 143), which compared eculizumab to placebo and an open-label, one-armed, ongoing extension study (ECU-NMO-302). The PBAC noted that the key limitations of the PREVENT trials 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.

7.8 The PBAC noted that the primary outcome of the PREVENT trial was time-to-first adjudicated on-trial relapse, and that patients completed the trial six weeks after relapse. The PBAC considered this was insufficient to assess the treatment effect of

eculizumab in patients experiencing multiple relapse events and to assess post-relapse recovery.

7.9 The PBAC noted that eculizumab demonstrated a statistically significant improvement in the time to first adjudicated relapse compared to placebo (HR = 0.058; 95% CI: 0.017, 0.197). The PBAC also noted that treatment with eculizumab was associated with a statistically significant reduction in adjudicated annualised relapse rate compared to placebo (HR = 0.045; 95% CI: 0.013, 0.151), which was slightly reduced when on-trial relapses were assessed by the treating physician (HR = 0.147; 95%: 0.078, 0.278).

7.10 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. The PBAC also noted that the submission presented no evidence that eculizumab reduced mortality or extended life for patients with NMOSD.

7.11 The PBAC considered that eculizumab was superior to placebo in terms of extending the time to relapse, but considered that efficacy in the proposed PBS population was unclear as the eligibility criteria of the PREVENT trial did not match the proposed PBS restriction. 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.

7.12 In terms of safety, the PBAC noted that the eculizumab arm of the PREVENT trial was associated with fewer adverse events than the placebo arm, which was primarily driven by the increased incidence of NMOSD-related events in the placebo arm. The PBAC noted that the adverse event profile of eculizumab in the PREVENT trial was consistent with the known safety profile of eculizumab. Overall, the PBAC considered that eculizumab was non-inferior compared to placebo in terms of safety.

7.13 The PBAC noted that the submission presented a stepped cost-utility analysis which compared eculizumab plus best supportive care to best supportive care alone in patients with AQP4 positive NMOSD and who have frequent relapses. 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.

7.14 The PBAC noted that the economic analysis resulted in a base case ICER for eculizumab of > $1,055,000 per QALY gained compared to standard of care.

7.15 The PBAC noted that the ICER was > $1,055,000 per QALY and considered that model submitted was not a reliable basis for estimating the cost-effectiveness of eculizumab because the:

- generalisability of the comparative clinical evidence from the PREVENT trial to the proposed PBS population was uncertain due to differences between the eligibility criteria of the PREVENT trial and the proposed PBS restriction;
- 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;
- 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. The PBAC considered that a difference in life years gained was not supported by the evidence and that the modelled reduction in relapses was small considering the cost of eculizumab and the long-term nature of the treatment;
- 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;
- submission estimated the probability of disability progression following relapse based on a post-hoc analysis of EDSS scores at 4-6 weeks after relapse. The PBAC noted that the PREVENT trial did not demonstrate a statistically significant difference in EDSS scores and the PBAC considered the estimates were uncertain in terms of whether they reflected permanent disability progression; and
- utility values were based on a limited number of observations from the PREVENT trial.

7.16 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.

7.17 The PBAC, noting the DUSCs comments that eculizumab is proposed as a lifelong prophylaxis treatment for a non-life-limiting disease, considered that, at the proposed price, the cost of eculizumab to the PBS/RPBS of approximately $200 million to < $300 million over the first six years (updated PSCR estimates) for less than < 500 patients was very high. In addition, the PBAC agreed with DUSC that the financial estimates were uncertain for the reasons outlines in paragraph 6.55. While DUSC considered the financial estimates were underestimated, the PBAC noted the estimates were based on a relatively broad restriction. The PBAC considered that the restriction should more closely align with the inclusion criteria of the trial (per paragraph 7.4), which would reduce some of the parameters (e.g. it would reduce the proportion of patients with

AQP4+ and frequent relapses compared with the value in the PSCR, and remove the proportion of patients with a prior IST event).

7.18 The sponsor in its pre-PBAC response proposed a RSA to help mitigate any uncertainties relating to the financial estimates (eligible patient population) and the proposed restriction not aligning with the inclusion criteria of the trial. The proposed RSA consisted of a [redacted] cap based on the [redacted] estimated in the PSCR (i.e. before applying the uptake assumptions). 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.

7.19 The PBAC advised that any future resubmission should be a major resubmission and address the clinical, economic and financial issues raised above. The PBAC reiterated that a substantial price reduction would aid in achieving an acceptable ICER and reduce the cost associated with eculizumab. In addition, the PBAC considered that a RSA outlining the proposed subsidisation caps and rebates would be highly informative to its deliberations.

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

Outcome:
Rejected

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

Alexion is disappointed with the PBAC's decision not to recommend eculizumab, the first approved treatment for NMOSD. We appreciate there is a high threshold of evidence required to establish the value of a new treatment, which can be even more challenging in rare diseases, however, given the severity of the disease and the substantial unmet need, adult patients with NMOSD in Australia will greatly benefit from access to eculizumab. It is pertinent to note that therapies currently used to treat

NMOSD in Australia are not approved by the TGA. As such, we will continue to work with the PBAC and the Department of Health to reach an agreement that ensures long term, sustainable access for people living with this devastating disease.

In relation to paragraph 2.4, in Canada, there is no specific Health Technology Assessment (HTA) pathway for rare disease. Eculizumab for NMOSD was assessed under the CADTH Common Drug Review, which uses an ICER threshold of approximately $50K/QALY for most treatments. The 96% price reduction referenced in the CADTH recommendation is based on this $50K/QALY threshold.