6.09 RAVULIZUMAB, Solution concentrate for I.V. infusion 300 mg in 3 mL, Solution concentrate for I.V. infusion 1,100 mg in 11 mL, Ultomiris®, Alexion Pharmaceuticals Australasia Pty Ltd

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of adult patients with neuromyelitis optica spectrum disorders (NMOSD). The submission requested listing for patients who are aquaporin-4 (AQP4) positive who have experienced a recent relapse event, despite prior treatment with rituximab or who cannot tolerate rituximab.

1.2 Listing was requested on the basis of a cost effectiveness analysis versus best supportive care (placebo)

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

Component	Description
Population	Adult patients with neuromyelitis optica spectrum disorders who are aquaporin-4 (AQP4) positive who have experienced a recent relapse event, despite prior treatment with rituximab or who cannot tolerate rituximab.
Intervention	Ravulizumab intravenous infusion on Day 1 (weight-based dosing 2,400-3,000 mg) followed by a second dose on Day 15 and then every 8 weeks (weight-based dosing 3,000-3,600 mg). As monotherapy or in combination with best supportive care (including corticosteroids and other immunosuppressive agents such as azathioprine and mycophenolate mofetil).
Comparator	Best supportive care alone (placebo)
Outcomes	Reduction in relapse frequency leading to reductions in disability progression, quality of life impairments and mortality
Clinical claim	Ravulizumab is superior in terms of efficacy and non-inferior in terms of safety compared to best supportive care

Source: Table 1-1, p27 of the submission

2 Background

Registration status

2.1 Ravulizumab was approved by the TGA on 22 January 2024 for 'the treatment of adult patients with Neuromyelitis Optica Spectrum Disorder (NMOSD) who are anti-aquaporin 4 (AQP4) antibody positive. Ravulizumab is not intended for the acute treatment of a NMOSD relapse.'

2.2 Ravulizumab is also TGA approved for the treatment of paroxysmal nocturnal haemoglobinuria, atypical haemolytic uraemic syndrome and generalised myasthenia gravis.

Previous PBAC consideration

2.3 The sponsor has previously prepared two PBAC submissions requesting PBS listing of eculizumab for NMOSD (November 2020 and November 2021 PBAC meetings). Neither of these submissions were recommended by the PBAC, who noted issues with the choice of comparator, uncertain downstream impacts of relapse reduction on disability and quality of life outcomes, the high and uncertain cost effectiveness estimates and the substantial budget impact associated with lifelong prophylactic treatment for a rare disease (as outlined in Table 2). The current submission stated that the sponsor does not intend to continue to seek reimbursement of eculizumab for this indication.

Table 2: Comparison of key components from the ravulizumab and eculizumab PBAC submissions

Component	Eculizumab November 2020 PBAC submission	Eculizumab November 2021 PBAC submission	Ravulizumab November 2024 PBAC submission
Place in therapy	Second-line treatment in patients who experience frequent relapses despite best supportive care or who cannot use best supportive care due to a prior immunosuppressive event.	Second-line treatment in patients who experience frequent relapses despite best supportive care or who cannot use best supportive care due to a prior immunosuppressive event. Revised in the PSCR/pre-PBAC response to last-line treatment when other treatment options (including rituximab) have failed.	Second-line treatment in patients with a recent relapse, despite prior rituximab treatment, who are contraindicated to rituximab or who have experienced a serious adverse event while using rituximab that required treatment discontinuation.
Restriction – number of prior relapses	≥ 1 relapse in the last 12 months with ≥ 2 relapses in the last 24 months	≥ 2 relapses in the last 12 months or ≥ 3 relapses in the last 24 months with ≥ 1 relapse in the previous 12 months despite treatment with immunosuppressive therapy	At least one relapse in the last 12 months despite treatment with rituximab
Modelled outcomes	Eculizumab LYs: 14.60 Eculizumab QALYs: 7.15 Eculizumab total cost: $[redacted] Placebo LYs: 12.81 Placebo QALYs: 5.28 Placebo total cost: $177,188 ICER per QALY gained: $[redacted][1]	Eculizumab LYs: 15.81 Eculizumab QALYs: 7.97 Eculizumab total cost: $[redacted] Placebo LYs: 15.04 Placebo QALYs: 6.53 Placebo total cost: $301,893 ICER per QALY gained: $[redacted][1]	Ravulizumab LYs: 15.33 Ravulizumab QALYs: 8.98 Ravulizumab total cost: $[redacted] Placebo LYs: 12.27 Placebo QALYs: 2.92 Placebo total cost: $284,705 ICER per QALY gained: $[redacted][2]
Annual cost per patient	$[redacted] per year.	$[redacted] per year.	$[redacted] per year.
Estimated treated population over first 6 years [a]	[redacted][3] to [redacted][3] patients	[redacted][3] to [redacted][3] patients	[redacted][3] to [redacted][3] patients
Cost to PBS over 6 years	$[redacted][4] million over 6 years	$[redacted][5] million over 6 years	$[redacted][5] million over 6 years

Source: Constructed during the evaluation

[a] Table 12, ravulizumab Minutes, November 2021 PBAC meeting.

Abbreviations: LYs, life years; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; QALYs, quality adjusted life years.

The redacted values correspond to the following ranges:

1 > $1,055,000

2 $455,000 to < $555,000

3 < 500

4 $200 million to < $300 million

5 $100 million to < $200 million

2.4 Ravulizumab is currently listed on the PBS for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed price for maximum quantity Published	Effective	Max. qty packs	Max. qty units	№.of Rpts	Available brands
RAVULIZUMAB						
INITIAL TREATMENT						
Ravulizumab, 300 mg/3 mL IV infusion	$6,574.12 (Public hospital) $6,622.79 (Private hospital)	$ (Public hospital) $ (Private hospital)	1	1	3	Ultomiris
Ravulizumab, 1,100 mg/11 mL IV infusion	$24,105.11 (Public hospital) $24,153.78 (Private hospital)	$ (Public hospital) $ (Private hospital)	1	1	3	
CONTINUING TREATMENT						
Ravulizumab, 300 mg/3 mL IV infusion	$6,574.12 (Public hospital) $6,622.79 (Private hospital)	$ (Public hospital) $ (Private hospital)	1	1	2	Ultomiris
Ravulizumab, 1,100 mg/11 mL IV infusion	$24,105.11 (Public hospital) $24,153.78 (Private hospital)	$ (Public hospital) $ (Private hospital)	1	1	2	
Category / Program: Section 100 – Highly Specialised Drugs Program						
Prescriber type: Medical Practitioners						
Restriction type: Authority Required (in writing only via post/HPOS upload)						
Indication: Neuromyelitis optica spectrum disorder (NMOSD)						
Treatment Phase: Initial treatment – loading dose						
Clinical criteria:						
Patient must have a confirmed diagnosis of NMOSD with AQP4-IgG						
AND						
Clinical criteria:						
Patient must have an Expanded Disability Status Scale (EDSS) score of less than or equal to 7						
AND						
Clinical criteria:						
Patient must have had at least one relapse in the last 12 months						
AND						
Clinical criteria:						
Patient must have received treatment with rituximab prior to the most recent relapse OR Patient must be contraindicated for treatment with rituximab including: hypersensitivity to rituximab, excipients or murine proteins, hypogammaglobinaemia, low CD4 or CD8 counts OR Patient must have experienced a serious adverse event to rituximab that requires treatment discontinuation, including: progressive multifocal leukoencephalopathy (PML), severe pulmonary event, serious cardiac arrhythmia, toxic epidermal necrolysis or Stevens-Johnson syndrome, hypogammaglobinaemia						
Treatment criteria:						
Must be treated by a neurologist, or must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.						
Patient must not receive more than 2 weeks of treatment under this restriction						
Population criteria:						
Patient must be aged 18 years or older.						
Prescribing Instructions:						

At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for 2 weeks of treatment, according to the specified dosage in the approved Product Information (PI). Refer to the approved PI for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested. Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.
Two authority prescription forms will be required to cover for the 26 weeks of initial therapy with ravulizumab, one for the loading dose and one for the 24 week balance which can be sought under the Balance of Supply.
The authority application must be in writing and must include all of the following: (1) A completed authority prescription form(s); (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
This drug is not PBS subsidised if it is prescribed to a public hospital inpatient
This drug is not intended for the acute treatment of a NMOSD relapse
The terms attack, relapse and event are considered synonymous in NMOSD
Administrative Advice:
The Expanded Disability Status Scale (EDSS) may be calculated here [Kurtze 1983; https://www.neurology.org/doi/10.1212/wnl.33.11.1444]. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments, used to quantify physical disability and monitor changes in the level of disability over time. The scale ranges from 0 (normal neurologic examination) to 10 (death) in 0.5-unit increments.
No increase in the maximum number of repeats may be authorised.
Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Caution:
WARNING: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Indication: Neuromyelitis optica spectrum disorder (NMOSD)
Treatment Phase: Balance of Supply – maintenance doses
Clinical criteria:
Patient must have received PBS-subsidised loading dose of ravulizumab for this condition
AND
Clinical criteria:
The treatment must provide no more than the balance of supply of up to 24 weeks treatment under this restriction
Treatment criteria:
Must be treated by a neurologist, or must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.

Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
At the time of authority application, medical practitioners must request the appropriate number of vials to cover 3 maintenance doses based on the patient's weight and as per the approved Product Information (PI). Refer to the approved PI for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved. An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
This drug is not PBS subsidised if it is prescribed to a public hospital inpatient
Administrative Advice:
No increase in the maximum number of repeats may be authorised.
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Caution:
WARNING: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Indication: Neuromyelitis optica spectrum disorder (NMOSD)
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS subsidised treatment with this drug for this condition
Treatment criteria:
Must be treated by a neurologist, or must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.
Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
At the time of authority application, medical practitioners must request the appropriate number of vials to cover 3 maintenance doses based on the patient's weight and as per the approved Product Information (PI). Refer to the approved PI for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved. An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
The authority application must be in writing and must include all of the following: (1) A completed authority prescription form(s); (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
This drug is not PBS subsidised if it is prescribed to a public hospital inpatient
Administrative Advice:
No increase in the maximum number of repeats may be authorised.

Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Caution:
WARNING: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Category / Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Indication: Neuromyelitis optica spectrum disorder (NMOSD)
Treatment Phase: Transition from non-PBS subsidised to PBS subsidised treatment (grandfather)
Clinical criteria:
Patient must have a confirmed diagnosis of NMOSD with AQP4-IgG
AND
Clinical criteria:
Patient must have recorded baseline Expanded Disability Status Scale (EDSS) score of 0–7 prior to initiation of ravulizumab
AND
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of PBS listing]
Treatment criteria:
Must be treated by a neurologist, or must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.
Population criteria:
Patient must be aged 18 years or older.
Prescribing Instructions:
At the time of authority application, medical practitioners must request the appropriate number of vials to cover 3 maintenance doses based on the patient's weight and as per the approved Product Information (PI). Refer to the approved PI for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved. An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
The authority application must be in writing and must include all of the following: (1) A completed authority prescription form(s); (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
This drug is not PBS subsidised if it is prescribed to a public hospital inpatient
Administrative Advice:

The Expanded Disability Status Scale (EDSS) may be calculated here [Kurtze 1983; https://www.neurology.org/doi/10.1212/wnl.33.11.1444]. The EDSS is an ordinal clinical rating scale that ranges from 0 (normal neurologic examination) to 10 (death) in half-point increments, used to quantify physical disability and monitor changes in the level of disability over time. The scale ranges from 0 (normal neurologic examination) to 10 (death) in 0.5-unit increments.
No increase in the maximum number of repeats may be authorised.
Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Caution:
WARNING: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.

3.1 The submission proposed a special pricing arrangement for ravulizumab consisting of a % rebate on the published AEMP per vial.

3.2 The submission did not provide any clinical data or economic analysis directly related to ravulizumab use in patients who cannot tolerate rituximab due to contraindications or previous serious adverse events.

3.3 The ESC considered that the clinical criterion requiring patients to have had a recent relapse event despite prior treatment with rituximab was ambiguous and should be more clearly defined e.g. in line with current clinical guidelines, which define treatment failure as a 'severe attack during therapy despite sufficient dosing and sufficient time to expect full action' (Kumpfel 2024). The evaluation also considered that it may be appropriate for the restriction to define what constitutes an adequate trial of rituximab therapy, the severity of the relapse event and the relative timing between the last dose of rituximab therapy and the relapse event. Clinical guidelines state that full onset of action with rituximab treatment occurs after 8–12 weeks (Kumpfel 2024). Overall, the PBAC considered the restriction should clearly state that patients must have had a recent relapse event in the previous 12 months while receiving treatment with rituximab (unless intolerant or contraindicated to rituximab).

3.4 The ESC advised that a stopping criterion should be included in the restriction to ensure ravulizumab is used to prevent accumulation of disability, i.e., to prevent use when disability is worsening. The ESC advised that this criterion should specify that ravulizumab treatment should be discontinued if the patient's Expanded Disability Status Scale (EDSS) score worsens.

3.5 The proposed grandfathering restriction does not require any prior use of rituximab. This was not consistent with the proposed place in therapy.

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

4 Population and disease

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

4.2 The worldwide prevalence of NMOSD ranges from approximately 0.07 to 10 patients per 100,000 population, with an overall pooled prevalence of 1.51 per 100,000 using the 2015 NMOSD diagnostic criteria (Bagherieh 2023). However, these estimates are highly variable given observed racial associations with NMOSD (higher in African and Asian populations) and evolving diagnostic criteria.

4.3 The majority of NMOSD patients (> 80% of cases) have AQP4 positive disease in which the immune system develops autoantibodies for the AQP4 water channel protein that is expressed on the surface of astrocytes in the central nervous system. Binding of these antibodies to the target protein triggers a complement-mediated cascade resulting in astrocyte damage, axonal degeneration and neural cell death.

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. The Pre-Sub-Committee Response (PSCR) highlighted that NMOSD patients may develop severe and irreversible disability and that 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, blind spots in vision, bilateral motor weakness, numbness or tingling sensations, tonic spasms, neuropathic pain, bladder/bowel dysfunction, nausea, vomiting, vertigo, respiratory failure and prolonged hiccoughs.

4.5 The ESC considered that there is a high clinical need for effective therapies to treat NMOSD. The ESC considered that the submission and the commentary had clearly outlined the severity of NMOSD, the impact of relapses, and the clinical need to prevent relapses and thereby reduce both the temporary and permanent disability associated with NMOSD.

4.6 Patient perspectives included in the submission indicated that many patients expressed a high degree of anxiety regarding the risk of disability progression, with their main treatment goal being to maintain their current condition and avoid relapses. Patients noted that disability progression can have major impacts on physical activity and mental/emotional health as well as having substantial negative impacts to quality of life, relationships, social interactions and workforce participation. Patients indicated that the highest priority symptoms were limb weakness or paralysis, loss of clear vision and loss of bowel or bladder control. Patients also indicated that the most important factor in their decision-making regarding treatments was the safety/side effect profile of the medication. Most patients indicated that they would

continue to use a therapy long term (10 years or longer) if it was able to maintain a good quality of life. Patients indicated they wanted additional disease-specific treatment options to manage this condition which were more accessible and had fewer or less intense side effects.

4.7 The PSCR also highlighted the impact of NMOSD on caregivers, including that it can be challenging for carers to balance employment and caregiving duties. The PSCR noted that a scenario analysis demonstrated that the ICER reduced by 20% (from $455,000 to < $555,000/QALY to $355,000 to < $455,000/QALY, as presented in Table 13) when the societal perspective was used, rather than the health system perspective.

4.8 Historically, NMOSD has been associated with increased mortality compared to the general population; however, recent studies have indicated that the excess mortality associated with these conditions (due to relapses, complications of severe disability or long-term immunosuppression) appears to be declining over time, potentially due to differences in diagnostic criteria, use of preventative treatment for relapses and improved acute management of relapses (Mealy 2018). The submission provided data from a recent sponsor-commissioned mortality study indicating that between 2014 and 2020, the mortality rate in NMOSD patients from the UK was 3 times higher than the general population (Francis 2024).

4.9 Depending on the severity of the relapse, relapses may be managed in the community setting or require hospitalisation. 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.

4.10 Relapse prevention for NMOSD has traditionally been based on the use of immunosuppressive therapies such as corticosteroids, azathioprine and mycophenolate mofetil. However, based on recent clinical trials, treatment guidelines have switched towards using antibody therapies (with or without other immunosuppressive therapies) such as rituximab, eculizumab, ravulizumab, satralizumab and inebilizumab as the preferred agents for relapse prevention. The submission claimed that rituximab has become established as the first-line treatment for relapse prevention in Australian clinical practice.

4.11 Treatment guidelines indicate no clear preference between antibody therapies, with the choice of therapy depending on several factors such as disease activity and severity, mode and onset of action, potential combination with immunosuppressive therapies, effect on autoimmune and other comorbidities, family planning, frequency and route of drug administration, safety profile, as well as drug availability and regulatory approval status. Patients who experience treatment failure with an antibody therapy should be switched to an alternative antibody therapy. If no other antibody therapies are available, the guidelines recommend the use of antibody therapy in combination with immunosuppressive therapies or the use of intermittent

plasma exchange (PLEX)/immunoadsorption (IA) or haematopoietic stem cell transplantation (HSCT). The guidelines also note that intravenous immunoglobulin (IVIg), methotrexate and tacrolimus may be considered treatment options in some limited circumstances.

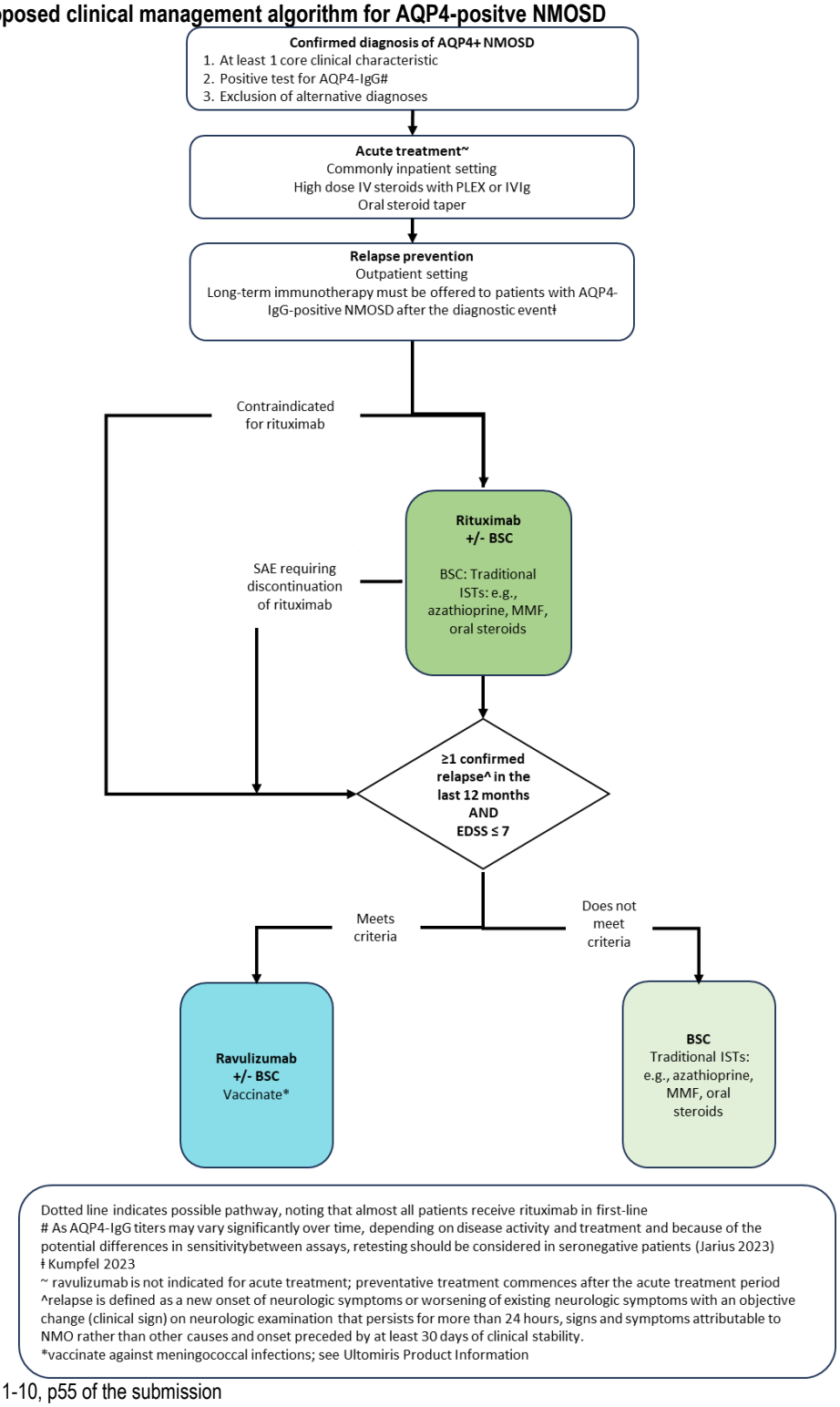
4.12 The PSCR stated 'it is not possible to predict the severity of a NMOSD relapse meaning any relapse can cause severe and irreversible disability, hence key international guidelines recommend prompt initiation of relapse preventative treatment, preferably with targeted monoclonal antibodies, upon diagnosis (Kumpfel et al. 2023).'

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

4.14 Ravulizumab is intended to be used as a chronic treatment for NMOSD and patients who discontinue therapy may restart treatment if a disease relapse occurs.

4.15 The clinical management algorithm positions ravulizumab with or without concomitant immunosuppressive therapy (e.g. corticosteroids, azathioprine, mycophenolate mofetil) as an alternative to immunosuppressive therapies alone (best supportive care) as a second-line treatment option in patients with a recent relapse, despite prior rituximab treatment, who are contraindicated to rituximab or who have experienced a serious adverse event while using rituximab that required treatment discontinuation.

Figure 1: Proposed clinical management algorithm for AQP4-positve NMOSD



Source: Figure 1-10, p55 of the submission

Abbreviations: AQP4, aquaporin-4; BSC, best supportive care; IST, immunosuppressive therapy; IV, intravenous; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorders; PLEX; plasma exchange

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

5 Comparator

5.1 The submission nominated best supportive care (e.g. corticosteroids, azathioprine, mycophenolate mofetil and some limited use of IVIg/PLEX) as the main comparator. The main arguments provided in support of this nomination were that there are no other subsidised antibody treatment options available after rituximab treatment failure and ravulizumab can be used in combination with most other treatment options rather than replacing these therapies.

5.2 The submission assumed that rituximab would not be used in the second-line treatment setting. The evaluation and the ESC considered that this was inconsistent with current treatment guidelines which indicate that rituximab may be continued after a disease relapse event (potentially with escalation of concomitant immunosuppressive therapy) given the lack of other available antibody therapies (Kumpfel 2024). The PSCR highlighted that the guidelines recommend that in the event of treatment failure with a monoclonal antibody, therapy should be switched to another monoclonal antibody, preferably with a different mode of action. Following treatment failure with rituximab, ravulizumab was one of the recommended subsequent treatment choices. The PSCR acknowledged that, 'for patients who relapse on first-line rituximab, the dearth of treatment options in Australia can result in some patients continuing rituximab' which it stated was suboptimal compared with other targeted therapies that are not subsidised in Australia.

5.3 In consideration of both the November 2020 and November 2021 eculizumab submissions, the PBAC noted that rituximab was a relevant comparator to the newer antibody therapies (paragraph 7.6 eculizumab Public Summary Document (PSD), November 2020 PBAC meeting; paragraph 7.4 and 7.20 eculizumab PSD, November 2021 PBAC meeting).

5.4 The ESC considered that it was likely that in clinical practice rituximab would be continued after a relapse as part of best supportive care and that, if PBS-listed for NMOSD, ravulizumab would replace some use of rituximab. Therefore, the ESC considered that rituximab would represent a substantial part of best supportive care in clinical practice and was a relevant comparator for patients who do not have a contraindication to rituximab or intolerance requiring rituximab cessation.

5.5 The ESC considered that satralizumab (TGA, FDA and EMA approved), inebilizumab (FDA and EMA approved, under TGA review) and eculizumab (biosimilars have been approved by both the FDA in May 2024 and EMA in February/March 2023 for other indications) were all potentially relevant near-market comparators as these therapies are included as alternative treatment options to ravulizumab and rituximab in current treatment guidelines.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented two case studies, one of a patient (diagnosed in 1998) who experienced only minimal recovery from relapses and whose condition deteriorated to irreversible disability and the requirement for palliative care. The other, more recent case study was of a patient who relapsed on rituximab and has been relapse-free since commencing ravulizumab through the clinical trial. The clinician outlined that the pathology of NMOSD is different to multiple sclerosis (MS) as NMOSD targets astrocytes, and the relapses are substantially more severe (for example, the clinician stated that 40% of patients with NMOSD are blind within five years, and 25% are wheelchair-bound within six years of diagnosis). In NMOSD disability is driven by relapses, compared to MS where deterioration is more gradual. The clinician explained that a single relapse can cause permanent disability. He further outlined that, while he would like complement inhibitors to be available for all patients with NMOSD, there is a critical need for this option in patients who experience relapses despite rituximab or who are unable to tolerate rituximab.

6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon condition.

Consumer comments

6.3 The PBAC noted and welcomed the input from individuals (3), health care professionals (4) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the debilitating nature of NMOSD, including the substantial impact on quality of life including through reduced mobility, decreased ability to participate in the activities of daily life, pain, vision loss, fear of relapse, and the impact on families and carers. The comments outlined that each relapse leads to a worsening of disability and potential loss of vision. Organisations and health professionals outlined that NMOSD relapses are generally more severe, prolonged and frequent compared to relapses in MS. Unlike in MS, most people do not recover completely from NMOSD relapses and are potentially more likely to be left with permanent disability, and at an earlier stage. The comments stated that therefore, preventing relapses in people living with NMOSD is crucial.

6.4 The comments also described a range of benefits associated with ravulizumab treatment including the efficacy demonstrated in the clinical trial, the manageable safety profile and the potential to cease or reduce doses of corticosteroids.

Clinical studies

6.5 The submission was based on a comparison of ravulizumab treatment from a single-arm interventional study (CHAMPION-NMOSD) with a historical placebo arm from the pivotal randomised controlled trial for eculizumab (PREVENT). The submission also

presented an interim analysis (June 2022 cut-off) from an ongoing extension study of patients previously enrolled in the CHAMPION-NMOSD study as supportive data. The PBAC has previously considered the PREVENT trial as part of the November 2020 and November 2021 eculizumab submissions.

6.6 Details of the included studies are provided in Table 3.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ALXN1210-NMO-307 (CHAMPION-NMOSD)	Alexion (2022). A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD).	Internal study report
	Pittock et al (2023). Ravulizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder.	Annals of Neurology 93:1053-1068.
	Ortiz et al (2024). Immediate and sustained terminal complement inhibition with ravulizumab in patients with anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder.	Frontiers in Neurology 15.
ALXN1210-NMO-307 Extension study	Alexion (2022). Addendum to A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD).	Internal study report.
ALXN1210-NMO-301 (PREVENT)	Alexion (2018). A randomized, double-blind, placebo controlled, multi-center trial to evaluate the safety and efficacy of eculizumab in patients with relapsing neuromyelitis optica.	Internal study report.
	Pittock et al (2019). Eculizumab in Aquaporin-4–Positive Neuromyelitis Optica Spectrum Disorder.	New England Journal of Medicine;381:614-625.

Source: Table 2-3, pp75-76 of the submission
Note: Abstracts of studies with full publications are not presented

6.7 The key features of the CHAMPION-NMOSD study and PREVENT trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ravulizumab versus placebo						
CHAMPION-NMOSD	58	Single arm study with a comparison to the historical control arm from the PREVENT trial (average follow-up: 1.4 years in the ravulizumab arm)	High	Adult patients with a diagnosis of NMOSD (2015 criteria) with minimal to severe disability (EDSS score 0-7) and a history of relapse (≥ 1 relapse in last 12 months) who were AQP4+	Primary: Time to first adjudicated relapse Other outcomes: change in functional measures (EDSS, HAI) and change in quality of life (EQ-5D-3L VAS, EQ-5D-3L Index, SF-36)	Baseline characteristics, treatment effects, adverse events, relapse utility values, relapse costs.
Eculizumab versus placebo						
PREVENT	143	Randomised, double-blind, placebo-controlled trial (average follow-up: 1.8 years in eculizumab arm)	Unclear	Adult patients with a diagnosis of NMOSD (2006 criteria) with minimal to severe disability (EDSS score 0-7) and a history of relapse (≥ 2 relapses in previous year or ≥ 3 relapses in previous 2 years with one relapse in last 12 months) who were AQP4+	Primary: Time to first adjudicated relapse Other outcomes: change in functional measures (EDSS, HAI) and change in quality of life (EQ-5D-3L VAS, EQ-5D-3L Index, SF-36)	Relapse risk, disability progression, relapse utility values, relapse costs

Source: Section 2.3.1, pp78-87; Section 2.4, pp88-105 of the submission
Abbreviations: AQP4; aquaporin-4; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index; NMOSD, neuromyelitis optica spectrum disorders

6.8 The CHAMPION-NMOSD study was designed as single-arm study with a historical external control arm. The submission stated that this design was developed in conjunction with regulators as it would have been unethical to randomise patients to a placebo group given the availability of antibody therapy for NMOSD (particularly given the similarity between ravulizumab and eculizumab). The submission also stated that an active control trial was not considered feasible for a rare disease given the large patient numbers that would be required to demonstrate non-inferiority to existing therapies.

6.9 The submission noted that the primary analysis was based on adjudicated relapses (assessed using an external committee) to ensure consistency in definition and to address the tendency for physicians to over-report relapses due to increased vigilance in the trial setting. The submission noted that there was a greater incentive to report relapses in the PREVENT trial compared to the CHAMPION-NMOSD study as patients in the PREVENT trial who experienced a relapse were eligible for open-label eculizumab treatment in the extension study. These arguments appear reasonable, and use of adjudicated relapses may be necessary due to the limitations of available clinical data.

6.10 There were substantial differences in baseline disease characteristics between studies such as the mean number of prior relapses (CHAMPION-NMOSD ravulizumab 3.6 versus PREVENT placebo 6.3), proportion of patients with transverse myelitis symptoms (ravulizumab 58.6% versus placebo 89.4%), mean EDSS score (ravulizumab

3.30 versus placebo 4.26), mean HAI score (ravulizumab 1.2 versus placebo 2.1), mean EQ-5D-3L index score (ravulizumab 0.77 versus placebo 0.68), mean EQ-5D-3L visual analogue score (ravulizumab 73.6 versus placebo 59.1) and the proportion with no baseline immunosuppressive therapy (ravulizumab 51.7% versus placebo 27.7%). Overall, the PREVENT trial appeared to have enrolled a more severely affected patient population compared to the CHAMPION-NMOSD study. To address these differences, the CHAMPION-NMOSD study report also compared groups using propensity stratification, PREVENT trial stratification and stabilised inverse probability of treatment weightings. However, there was only limited reporting of patient characteristics using these approaches and residual differences remained between study groups.

6.11 Overall, despite the measures taken to minimise bias, the evaluation and the ESC considered that there remained a high risk of bias associated with the CHAMPION-NMOSD study design.

6.12 The interim analysis from the ongoing extension study, in which all patients received ravulizumab treatment, was considered to be at high risk of bias given the observational study design and incomplete follow-up.

6.13 The PREVENT trial had an unclear risk of bias 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).

6.14 The submission acknowledged that the requirement for prior rituximab use in the requested restriction was not consistent with the CHAMPION-NMOSD study which did not require any specific therapies (36.2% had any prior use of rituximab and 20.7% were using rituximab prior to their last relapse). However, the submission argued that prior rituximab use was unlikely to be a treatment effect modifier based on a post hoc subgroup analysis. While prior rituximab use may not be treatment effect modifier, it is likely that requiring prior use of rituximab in the proposed restriction would result in more advanced disease with higher baseline disability in the PBS population compared to the overall CHAMPION-NMOSD population. The ESC considered that this limited the representativeness of the CHAMPION-NMOSD study to the proposed Australian population.

6.15 The submission did not consider the applicability of the PREVENT trial to the Australian clinical setting. The requested restriction (like the CHAMPION-NMOSD trial) only requires patients to have a single recent relapse in the previous 12 months, while patients enrolled in the PREVENT trial were required to have multiple recent relapses. Additionally, the requested restriction includes a requirement for prior rituximab use which was not consistent with the PREVENT trial which did not require any specific therapies (42.6% had any prior use of rituximab with the same proportion using rituximab prior to their last relapse).

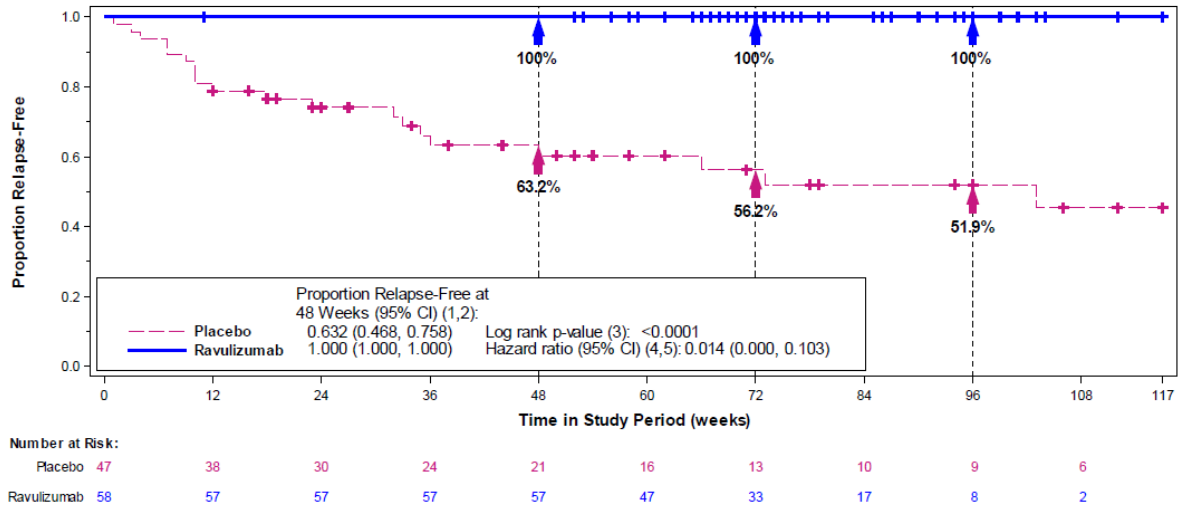
6.16 The PBAC previously noted that the PREVENT trial was not representative of patients receiving treatment in the last-line setting (i.e. after rituximab) with only a limited number of patients with prior rituximab exposure (paragraph 7.5 eculizumab PSD, November 2021 PBAC meeting).

6.17 Additionally, the evaluation and the ESC considered that the concomitant therapies used in the historical placebo arm of the PREVENT trial (including 27.7% no therapy; 23.4% corticosteroid monotherapy; 23.4% immunosuppressant monotherapy; 25.5% corticosteroids with immunosuppressants; 0% rituximab) were not representative of best supportive care in current treatment guidelines, particularly in the second-line setting, which is likely to include rituximab and escalated immunosuppressive therapies. As a consequence, the risk of relapse in the historical placebo arm was likely overestimated.

Comparative effectiveness

6.18 The time to first adjudicated relapse in the ravulizumab arm of the CHAMPION-NMOSD study and the historical placebo arm of the PREVENT trial is presented in Figure 2.

Figure 2: Kaplan-Meier survival curve for the time to first adjudicated relapse with ravulizumab and historical placebo (full analysis set)



Source: Figure 2-4, p107 of the submission

6.19 Treatment with ravulizumab was associated with a statistically significant improvement in the time to first adjudicated relapse compared to the historical placebo (HR = 0.014; 95% CI: 0.000, 0.103). There were no adjudicated relapses associated with ravulizumab treatment compared to 37% of placebo patients who had relapsed by 48 weeks, 44% by 72 weeks and 48% by 96 weeks. Additionally, there were no adjudicated relapses associated with ravulizumab treatment during the longer-term extension study (median follow-up 138.4 weeks).

6.20 Additional sensitivity analyses using different patient populations (per-protocol), censoring (for COVID-19 related adverse events and missed/delayed doses) and

adjustment methods (propensity score stratification, PREVENT trial stratification; sIPTW weighting, time since most recent relapse) were broadly consistent with the main analysis given that there were no adjudicated relapses associated with ravulizumab treatment during the CHAMPION-NMOSD study.

6.21 A tipping point analysis indicated that only an unmeasured confounder that is associated with an 8.33 times greater risk of an adjudicated relapse and that occurs 8.33 times more in patients in the placebo group would result in a non-significant treatment effect. The submission therefore claimed that any unmeasured confounder is unlikely to have a large enough impact on the results of the primary analysis to account for the observed treatment effect.

6.22 The submission noted that the efficacy of ravulizumab (based on time to first adjudicated relapse) was consistent across prespecified subgroups defined by geographic region, sex, race, baseline age, baseline immunosuppressive treatment and prior use of rituximab in the previous year. The submission also presented a post hoc subgroup analysis of patients with multiple historical relapses and rituximab use prior to their last relapse (target PBS population). Similar to the overall population, treatment with ravulizumab in the post hoc subgroup was associated with a statistically significant reduction in relapse risk compared to the historical placebo arm (HR = 0.085; 95% CI: 0.001, 0.708).

Table 5: Results for the post hoc subgroup analysis of time to first adjudicated relapse in patients with multiple historical relapses and rituximab use prior to their last relapse (HR used in the economic model)

	Overall		Multiple relapses and rituximab prior to last relapse	
	Ravulizumab N = 58	Placebo N = 47	Ravulizumab N = 12	Placebo N = 20
Proportion of patients with relapse	0 (0.0%)	20 (42.6%)	0 (0.0%)	7 (35.0%)
Median follow-up time, weeks	73.50	36.00	84.79	35.57
HR (95% CI)	0.014 (0.000, 0.103)		0.085 (0.001, 0.708)	

Source: Table 2-19, p108; Table 2-35, p129; Table 2-36, p130 of the submission; Table AUS.1.2.1, pp6-8; Table AUS.1.2.2, pp9-13 of Attachment 4 of the submission
Abbreviations: CI, confidence interval; HR, hazard ratio

6.23 Both the EMA evaluation report and TGA Delegate's overview noted that the absence of adjudicated relapses with ravulizumab in the CHAMPION-NMOSD study compared favourably to the historical placebo arm from the PREVENT trial and was sufficient to demonstrate that ravulizumab was associated with a clinically relevant reduction in relapse risk (pp21-23 of the ravulizumab AUSPAR; pp87-91 of the ravulizumab EPAR). However, the regulators noted that despite the measures taken by the sponsor to reduce the risk of bias associated with using a historical control design there remained a risk that treatment benefits may have been overestimated (pp68-69 of the ravulizumab EPAR).

6.24 The proportion of patients experiencing clinically important worsening in functional measures (Expanded Disability Status Scale and Hauser Ambulation index) in the ravulizumab arm of the CHAMPION-NMOSD study and the historical placebo arm of the PREVENT trial is summarised in Table 6.

6.25 The Expanded Disability Status Scale (EDSS) is a widely used instrument to assess disability in NMOSD clinical trials. The score ranges from 0 (normal neurologic function) to 10 (death) in half-point increments. EDSS scores of 4.5 or less are determined by the degree of impairment to various functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral or mental, other) in fully ambulatory patients. EDSS scores of 5.0 or higher are determined by the degree of ambulatory impairment.

6.26 The Hauser Ambulation Index (HAI) was used in the CHAMPION-NMOSD study and PREVENT trial to assess mobility-related disability. The score ranges from 0 (asymptomatic) to 9 (wheelchair-bound, unable to transfer independently) in full-point increments.

Table 6: Proportion of patients with clinically important worsening in functional measures with ravulizumab and placebo (full analysis set, based on median follow-up of 73.5 weeks for ravulizumab, 36 weeks for placebo)

Outcome	Ravulizumab n/N (%)	Historical placebo n/N (%)	Odds ratio (95% CI)	p-value
Clinically important worsening in HAI score[a]	2/58 (3.4%)	11/47 (23.4%)	0.155 (0.031, 0.771)	0.0228
Clinically important worsening in EDSS score[b]	6/58 (10.3%)	11/47 (23.4%)	0.332 (0.106, 1.042)	0.0588

Source: Table 2-24, p115; Table 2-25, p116 of the submission

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HAI, Hauser Ambulation Index

[a] Clinically important worsening in HAI score was evaluated as a change from baseline (first day of treatment) to either the end of the primary treatment period, or, for patients with a physician-determined relapse, the week 6 follow-up visit. Clinically important worsening was conditional on the baseline value and was defined as a baseline HAI score of 0 with a subsequent increase of ≥2 points or a baseline HAI score > 0 with a subsequent increase of ≥1 point. The analysis was performed using logistic regression, adjusting for baseline HAI.

[b] Clinically important worsening in EDSS score was evaluated as a change from baseline (first day of treatment) to either the end of the primary treatment period or, for patients with a physician-determined relapse, the week 6 follow-up visit. Clinically important worsening was conditional on the baseline value and was defined as a baseline EDSS score of 0 with a subsequent increase of ≥2 points, a baseline EDSS score between 1 and 5 with a subsequent increase of ≥1 point, or a baseline EDSS score > 5 with a subsequent increase of ≥0.5 points. The analysis was performed using logistic regression, adjusting for baseline EDSS

6.27 Treatment with ravulizumab was associated with a statistically significant reduction in the proportion of patients experiencing a clinically important worsening using the HAI measure compared to the historical placebo. The statistical significance of this result was sensitive to different methods of adjusting for differences between the study populations but consistently favoured ravulizumab. There was no statistically significant difference between treatments for the proportion of patients experiencing a clinically important worsening using the EDSS measure although results generally favoured ravulizumab.

6.28 The effect of relapses on EDSS and HAI in the ravulizumab arm of the CHAMPION-NMOSD study and the historical placebo arm of the PREVENT trial are summarised in Table 7.

6.29 Patients completed the PREVENT trial 6 weeks after their first relapse and a matching assessment timepoint was also used for the CHAMPION-NMOSD study. This timeframe may be insufficient to fully capture the impact of post-relapse recovery.

Table 7: Effect of relapse on functional measures (full analysis set)

Outcome	Ravulizumab			Historical placebo		
	N	Mean (SD)	Median (IQR)	N	Mean (SD)	Median (IQR)
Effect of adjudicated relapses on Hauser Ambulation Index (0-9 scale, with higher scores indicating increased walking impairment)						
Last assessment prior to relapse	0	NA	-	20	2.3 (2.10)	-
Change 24-48 hours after relapse	0	NA	NA	19	+1.1 (1.47)	0.0 (0, 2)
Change at Week 1 after relapse	0	NA	NA	20	+1.3 (2.24)	0.0 (0, 3)
Change at Week 4 after relapse	0	NA	NA	19	+0.2 (1.40)	0.0 (0, 1)
Change at Week 6 after relapse	0	NA	NA	18	+0.2 (1.62)	0.0 (0, 0)
Effect of adjudicated relapses on Expanded Disability Status Scale (0-10 scale, with higher scores indicating increased disability)						
Last assessment prior to relapse	0	NA	-	20	3.88 (1.70)	-
Change 24-48 hours after relapse	0	NA	NA	19	+0.97 (1.10)	+1.0 (0.0, 2.0)
Change at Week 1 after relapse	0	NA	NA	20	+0.83 (1.16)	+0.5 (0.0, 1.0)
Change at Week 4 after relapse	0	NA	NA	19	+0.37 (0.91)	+0.5 (0.0, 1.0)
Change at Week 6 after relapse	0	NA	NA	18	+0.08 (1.07)	0.0 (0.0, 0.5)

Source: Table 14.2.4.1.1.1, pp569-570; Table 14.2.4.1.3.1, pp581-582; Table 14.2.4.2.1.1, pp593-594; Table 14.2.4.2.3.1, pp611-612 of the CHAMPION-NMOSD study report

Abbreviations: IQR, interquartile range; NA, not applicable; SD, standard deviation

6.30 The results indicate that patients experiencing a relapse had a substantial worsening of functional measures at the time of relapse, with many patients then experiencing a gradual recovery over the next 6 weeks.

6.31 There were no statistically significant differences in quality of life outcomes (EQ-5D-3L index score; EQ-5D-3L visual analogue score; SF-36 mental and physical component scores) between treatment arms, although results numerically favoured ravulizumab.

Comparative harms

6.32 An overall summary of the adverse events reported in ravulizumab arm of the CHAMPION-NMOSD study and the historical placebo arm of the PREVENT trial is presented in Table 8. There were substantial differences in baseline characteristics between the CHAMPION-NMOSD study and the PREVENT trial which may indicate underlying differences in patient populations. Additionally, these comparisons are associated with a high risk of bias given the open-label nature of the CHAMPION-NMOSD study.

Table 8: Summary of key adverse events with ravulizumab and historical placebo (safety set)

Adverse event	Events per 100 patient years [number of events]	
	Ravulizumab (N = 58) 84.1 patient years	Placebo (N = 47) 47.7 patient years
Any adverse event	390.2 [328 events]	1160.0 [553 events]
Treatment-related adverse event	45.2 [38 events]	165.7 [79 events]
Serious adverse event	9.5 [8 events]	92.3 [44 events]
Adverse events leading to treatment discontinuation	3.6 [3 events]	6.3 [3 events]
Deaths	0	0
Adverse events of special interest		
Meningococcal infection	2.4 [2 events]	-

Source: Table 2-26, p119 of the submission

6.33 Treatment with ravulizumab was associated with a lower rate of adverse events compared to the historical placebo arm.

6.34 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.

6.35 In regard to adverse events of special interest, treatment with ravulizumab was associated with two serious meningococcal infections, despite all patients being vaccinated before commencing study drug treatment.

6.36 The interim analysis of the CHAMPION-NMOSD extension study (July 2022 cut-off; 102.9 patient years of therapy) did not identify any additional safety concerns with ravulizumab treatment.

6.37 The adverse event profile reported in the CHAMPION-NMOSD study and extension was consistent with the known safety profile of ravulizumab.

Benefits/harms

6.38 On the basis of the evidence presented in the submission, for every 100 patients treated with ravulizumab in comparison with placebo:

- There would be approximately 48 fewer patients with an adjudicated relapse at 96 weeks.

Clinical claim

6.39 The submission described ravulizumab as superior in terms of efficacy and non-inferior in terms of safety compared to best supportive care. The ESC considered that the clinical claim was supported. However, the ESC considered the magnitude of benefit was potentially overestimated due to limitations associated with the study design (non-randomised comparison with a historical control). The ESC also noted that the following issues should be considered:

- Whether the relapse risk in the historical placebo is representative of best supportive care in the second-line treatment setting, given the lack of patients using rituximab and the substantial proportion of patients using no therapy or corticosteroids only.
- While it was reasonable to assume that a reduction in relapse frequency would be associated with a reduction in disability progression and quality of life impairments (due to the underlying disease process for NMOSD), the evaluation and the ESC considered that quantification of these benefits was difficult to estimate due to the limited follow-up of patients after a relapse in the clinical studies, and it was unclear whether differences in disability/quality of life measures represent temporary differences (due to relapse) or permanent changes (due to disability progression). The PSCR and pre-PBAC response argued

that relapses incur both acute and ongoing impacts on quality of life, with the latter arising from 'permanent impairment due to astrocyte cell death leading to neurodegeneration and disability.'

- The established risk of serious infection (particularly meningococcal infections) associated with the ongoing use of complement inhibitors.

6.40 The PBAC considered that the claim of superior comparative effectiveness versus best supportive care was reasonable.

6.41 The PBAC considered that the claim of non-inferior safety versus best supportive care was reasonable.

Economic analysis

6.42 The submission presented a stepped economic evaluation of ravulizumab compared to placebo as monotherapy or in combination with best supportive care for the treatment of patients with NMOSD who are AQP4 positive and who have had a recent relapse despite prior use of rituximab. The economic evaluation was based on data from the CHAMPION-NMOSD study (ravulizumab single arm study), the PREVENT trial (eculizumab versus placebo RCT) and additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.43 Key components of the economic evaluation are summarised in Table 9.

Table 9: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Relapses avoided; life years; quality adjusted life years
Time horizon	30 years
Methods used to generate results	Markov cohort model
Treatments	Ravulizumab and placebo as monotherapy or in combination with best supportive care (consisting of immunosuppressive therapies such as corticosteroids, azathioprine, mycophenolate mofetil, methotrexate, and tacrolimus)
Health states	42 health states including: relapse-free, relapse without long-term disability (20 states defined by number of relapses); relapse with long-term disability (20 states defined by number of relapses) and death.
Cycle length	30 days (with no half-cycle correction)
Transition probabilities	Treatment persistence to ravulizumab was estimated assuming that no patients would discontinue therapy in the first year of therapy, with treatment persistence in subsequent years estimated based on the annualised discontinuation rate (excluding discontinuation due to personal reasons) reported in the ravulizumab and eculizumab studies. The risk of adverse events in the ravulizumab arm was based on the incidence of serious treatment-related adverse events reported in the CHAMPION-NMOSD study. All adverse events were assumed to occur in the first cycle. The risk of relapse in the placebo arm was estimated based on the time to first adjudicated relapse in the PREVENT trial ITT population. Estimates were extrapolated over time using an exponential function. The risk of subsequent relapses was assumed to be the same as the risk of first relapse.

Component	Description
	The risk of relapse in the ravulizumab arm was estimated by applying the hazard ratio for the time to first adjudicated relapse with ravulizumab compared to placebo based on the naïve indirect comparison of treatment arms in the subgroup of patients with multiple relapses and prior rituximab use (CHAMPION-NMOSD post hoc analysis). The risk of immediate permanent disability with each relapse (17.5%) was estimated based on a retrospective review of disabling attacks at disease onset in Korean NMOSD patients (Seok 2016). The risk of gradual permanent disability was estimated assuming a fixed increase in EDSS (+0.56) with each relapse (based on a post hoc analysis of the PREVENT trial and extension data) which was applied to the baseline distribution of EDSS scores in the CHAMPION-NMOSD study in order to determine the probability that a relapse would have caused a patient's EDSS to exceed the nominated threshold of 5.5 for permanent disability. The risk of death without permanent disability in the placebo arm was estimated based on the crude annual death rate reported in an observational study of the Oxford and Liverpool cohorts of NMOSD patients in the UK (Francis 2024) and assumed to remain constant over time. The risk of death with permanent disability in the placebo arm was estimated based on the standardised mortality rate reported in an observational study of non-traumatic spinal cord injury in Switzerland (Buzzell 2020) which was applied as a risk multiplier to the risk of death in the placebo arm. The risk of death without permanent disability in the ravulizumab arm was estimated based on the standardised mortality rates reported in the Oxford and Liverpool cohort (Francis 2024). The submission then assumed the hazard ratio for the time to first adjudicated relapse could be applied as a mortality hazard ratio to adjust the standardised mortality rates. Adjusted standardised mortality rates were then applied to Australian life table data. The risk of death with permanent disability in the ravulizumab arm was estimated based on the standardised mortality rate reported in an observational study of non-traumatic spinal cord injury in Switzerland (Buzzell 2020) which was applied as a risk multiplier to the risk of death in the ravulizumab arm. (Refer to Table 10 and paragraph 6.52 for the evaluation and ESC's comments on this approach.)
Utility values	Adverse event disutility values for serious infections were estimated based on published EQ-5D-3L estimates (US value set) for chronic conditions from the 2000-2002 US Medical Expenditure Panel Survey (Sullivan 2006). The duration of each adverse event was assumed. Disutility values associated with adjudicated relapses were estimated based on a linear mixed effect regression of EQ-5D-3L scores (Australian value set) from a pooled analysis of the CHAMPION-NMOSD study, the PREVENT trial and the PREVENT extension study. The estimated utility value for relapse-free patients was 0.66 based on the linear mixed effect regression. The regression model separated the utility loss associated with relapse into separate acute (-0.04) and chronic (-0.06) disutility values. Acute disutility values were applied for 50 days after an event (consistent with the PREVENT trial data), while chronic relapse disutility values were applied as lifetime estimates following a relapse event. The disutility value associated with permanent disability (-0.264) was estimated based on EQ-5D-5L scores (UK value set) reported from a UK survey (conducted 2016-2018) of NMOSD patients with mild, moderate, severe or very severe disability as assessed using the EDSS instrument (Hughes 2022). The disutility of adverse events, relapses (patients may have up to 20 relapses) and permanent disability was assumed to be additive. (Refer to Table 10 and paragraph 6.49 for the evaluation and ESC's comments on this approach.)
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 365

Source: Table 3-1, p142 of the submission

Abbreviations: EDSS, Expanded Disability Status Scale; ITT, intention-to-treat; NMOSD, neuromyelitis optica spectrum disorders.

6.44 The economic evaluation was based on a Markov cohort model with 42 health states including: relapse-free, relapse without long-term disability (20 states defined by number of relapses); relapse with long-term disability (20 states defined by number of relapses) and death. All patients (mean age 47 years) begin the model in the relapse-free health state. During each cycle of the model, patients may remain in their current health state, experience a disease relapse or die. Each disease relapse is associated with worsening disability with an immediate risk of permanent disability and a gradual risk of permanent disability based on EDSS progression (which increases by fixed increments with each relapse). Over the course of the model, patients can have a maximum of 9 relapses before permanent disability and a maximum of 20 relapses overall.

6.45 Patients may also experience adverse events in the first cycle and may discontinue ravulizumab treatment after the first year which has no impact on other transition probabilities.

6.46 The ESC considered the structure of the economic model was overly complex with 42 health states, consistent with the ESC's previous advice that a model submitted for eculizumab for NMOSD was overly complex with 20 health states (paragraph 6.34, eculizumab PSD, November 2021 PBAC meeting). The ESC considered that there may be insufficient clinical data to inform transitions between the different health states given the clinical studies informing the model had a small number of participants as NMOSD is a rare condition. The pre-PBAC response argued that sub-states were required within the post-relapse health states to describe the clinical status of patients given the risk of permanent disability is driven by the number of relapses. The pre-PBAC response acknowledged the limitations of the data to inform the economic model in this rare condition.

6.47 Key drivers of the economic model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment persistence	The submission assumed all patients would be fully persistent with therapy in the first year of treatment. The submission estimated treatment persistence in subsequent years (2% per year) based on the annualised discontinuation rate (after excluding discontinuations due to personal reasons) reported with ravulizumab in the CHAMPION-NMOSD study and extension as well as with eculizumab and placebo in the PREVENT trial and extension. The evaluation and the ESC considered that the assumption of no discontinuations in the first year of treatment was not justified and the estimated rate in subsequent years was highly uncertain given the substantial variation in discontinuation rates for any cause reported in the included studies (2-9% per year). The PSCR considered the persistence rates in the model were conservative and that persistence is expected to be high in clinical practice as ravulizumab would be the first access to a targeted, trialled treatment for Australian patients. Additionally, the evaluation and the ESC considered that it was unclear whether discontinuation rates from the CHAMPION-NMOSD and PREVENT studies (observed in a tightly regulated study setting) would be representative of clinical practice. It was also unclear whether patients in clinical practice who have not experienced a relapse in 5, 10 or 20 years (as occurs in the modelled analysis) would remain persistent with therapy. The submission assumed that treatment discontinuations would only affect drug costs with no impact on the modelled benefits of ravulizumab treatment. The evaluation and the ESC considered that this assumption was inappropriate and strongly biased the analysis in favour of ravulizumab. The PSCR disagreed and claimed the hazard ratio already accounted for discontinuations observed in the study; however, the ESC considered the impact beyond the trial duration was unclear. Overall, the ESC agreed with the evaluation that it was unclear whether the trial-based discontinuation rates would be representative of clinical practice.	High, favours ravulizumab
Relapse rates	The submission estimated the risk of relapse in the placebo arm based on the time to first adjudicated relapse in the overall population of the historical placebo arm of the PREVENT trial. The evaluation and the ESC considered that the relapse risk in the historical placebo arm may not be representative of the target PBS population as concomitant medication use in the PREVENT trial (including 27.7% no therapy; 23.4% corticosteroid monotherapy; 23.4% immunosuppressant monotherapy; 25.5% corticosteroids with immunosuppressants; 0% rituximab) did not appear to be consistent with current treatment guidelines, particularly in the second-line treatment setting. The submission estimated the risk of relapse in the ravulizumab arm based on the naïve indirect comparison of time to first adjudicated relapse with ravulizumab and placebo in the subgroup of patients with multiple relapses and prior rituximab use (HR = 0.085; 95% CI: 0.001, 0.708) CHAMPION-NMOSD post hoc analysis). The hazard ratio from this analysis was then applied to the relapse risk from the overall population in the historical placebo arm of the PREVENT trial. The submission did not adequately justify using the overall population to derive placebo relapse risk and the subgroup population to derive ravulizumab treatment effects. The submission assumed the risk of subsequent relapses was the same as the risk of first relapse. The evaluation and the ESC considered that this assumption was not reasonable as it seems highly unlikely that there would be no change in therapy for patients experiencing multiple disease relapses.	High, favours ravulizumab
Relapse and permanent disability disutility values	The submission estimated acute and chronic disutility values associated with adjudicated relapses based on a linear mixed effect regression of EQ-5D-3L (Australian value set) scores from a pooled analysis of the CHAMPION-NMOSD	High, favours ravulizumab

Description	Method/Value	Impact
	study, the PREVENT trial and the PREVENT extension study. This analysis was poorly documented and the validity of these estimates was unclear. The economic model applied acute relapse disutility values for 50 days following a relapse event while chronic relapse disutility values were applied as lifetime estimates following a relapse event (i.e. for the first 50 days both disutility values apply). The disutility value associated with permanent disability was estimated based on EQ-5D-5L scores (UK value set) reported from a UK survey (conducted 2016-2018) of NMOSD patients with mild, moderate, severe or very severe disability as assessed using the EDSS instrument (Hughes 2022). The submission assumed that disutility values associated with relapse events (acute and chronic) and permanent disability could be combined in an additive manner. The evaluation and the ESC considered that this assumption was not justified in the submission and a multiplicative approach may be more appropriate, particularly for chronic relapse disutility values, as it reduces the number of extreme negative utility values in the model (see Table 11). Additionally, the submission did not address the potential for overlap between the chronic disutility associated with relapse (presumably associated with the gradual accrual of disability) and the disutility associated with permanent disability.	
Mortality	The submission estimated treatment-specific mortality rates based on a longitudinal observational study of NMOSD patients using data from the UK National NMOSD data set (Oxford cohort) and the Walton Centre NHS Foundation Trust (Liverpool cohort) over a 7-year period (2014–2020) (Francis 2024). The submission estimated the mortality rate in the placebo arm based on the crude annual mortality rate (1.92% per year) reported in the study. The submission estimated the mortality rate in the ravulizumab arm based on the standardised mortality rate (3.04) reported in the study. The submission assumed that the estimated reduction in relapse risk with ravulizumab compared to placebo in the subgroup of patients with multiple historical relapses and rituximab use prior to their last relapse could also be used as a reduction in mortality risk (HR = 0.085; 95% CI: 0.001, 0.708) on the basis that relapses were the primary driver of mortality. The submission applied the 'mortality' hazard ratio to the excess risk of death to derive an adjusted standardised mortality rate for ravulizumab which was then applied to Australian life tables. The submission did not justify using a crude annual mortality rate for placebo and a standardised mortality rate for ravulizumab. The evaluation and the ESC considered that this approach was inappropriate and accounted for a substantial proportion of the difference in incremental survival between treatment arms. Further, the evaluation and the ESC considered that the assumption that the estimated reduction in relapse risk could also be applied to mortality risk was not reasonable given that the available data from Francis 2024 suggested that the main causes of excess mortality in NMOSD patients were complications of severe disability and long-term immunosuppression. The submission estimated the risk of death associated with permanent disability based on a retrospective review of medical records from patients undergoing rehabilitation for non-traumatic spinal cord injury in Switzerland between 1990 and 2011 (Buzzell 2020). The submission used the standardised mortality rate associated with non-traumatic spinal cord injury of non-malignant origin as a risk multiplier that was applied to treatment-specific mortality rates to estimate the excess mortality associated with permanent disability. The treatment-specific rates already included the excess mortality associated with complications of disability. The PSCR stated that sensitivity analyses applying the same methodology for each arm and removing the disability mortality multiplier did not meaningfully change the ICER, and argued that	High, favours ravulizumab

Description	Method/Value	Impact
	disease-specific mortality is primarily driven by relapses. However, the ESC considered the application of a standardised mortality rate as a risk multiplier to treatment-specific mortality rates was not appropriate and resulted in the economic model estimating a large overall survival benefit that was not adequately supported by the data presented in the submission.	

Source: Constructed during the evaluation
Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMOSD, neuromyelitis optica spectrum disorders; PSCR, pre-subcommittee response.

6.48 Patients in the ravulizumab arm spent an average of 16.8 life years in the relapse-free state while patients in the placebo arm spent an average of 2.2 life years in the relapse-free state. The time spent in various relapse health states and the utility values associated with these states are summarised in Table 11.

Table 11: Time spent in relapse health states

Number of relapses	Without disability			With disability		
	Utility	Ravulizumab life years	Placebo life years	Utility	Ravulizumab life years	Placebo life years
1	0.6020	5.25074	1.41288	0.3378	2.35652	0.63953
2	0.5399	1.30274	0.98705	0.2757	1.25297	0.95497
3	0.4778	0.25069	0.67941	0.2136	0.42488	1.15119
4	0.4157	0.03936	0.46511	0.1515	0.10713	1.25458
5	0.3536	0.00525	0.31980	0.0894	0.02161	1.28934
6	0.2915	0.00062	0.22236	0.0273	0.00364	1.27468
7	0.2294	0.00006	0.15664	-0.0348	0.00053	1.22351
8	0.1673	0.00001	0.11138	-0.0969	0.00007	1.14362
9	-	-	-	-0.1590	0.00001	1.11761
10	-	-	-	-0.2211	0.00000	0.97098
11	-	-	-	-0.2832	0.00000	0.81864
12	-	-	-	-0.3453	0.00000	0.66675
13	-	-	-	-0.4074	0.00000	0.52274
14	-	-	-	-0.4695	0.00000	0.39352
15	-	-	-	-0.5316	0.00000	0.28398
16	-	-	-	-0.5937	0.00000	0.19628
17	-	-	-	-0.6558	0.00000	0.12989
18	-	-	-	-0.7179	0.00000	0.08230
19	-	-	-	-0.7800	0.00000	0.04996
20	-	-	-	-0.8421	0.00000	0.06257

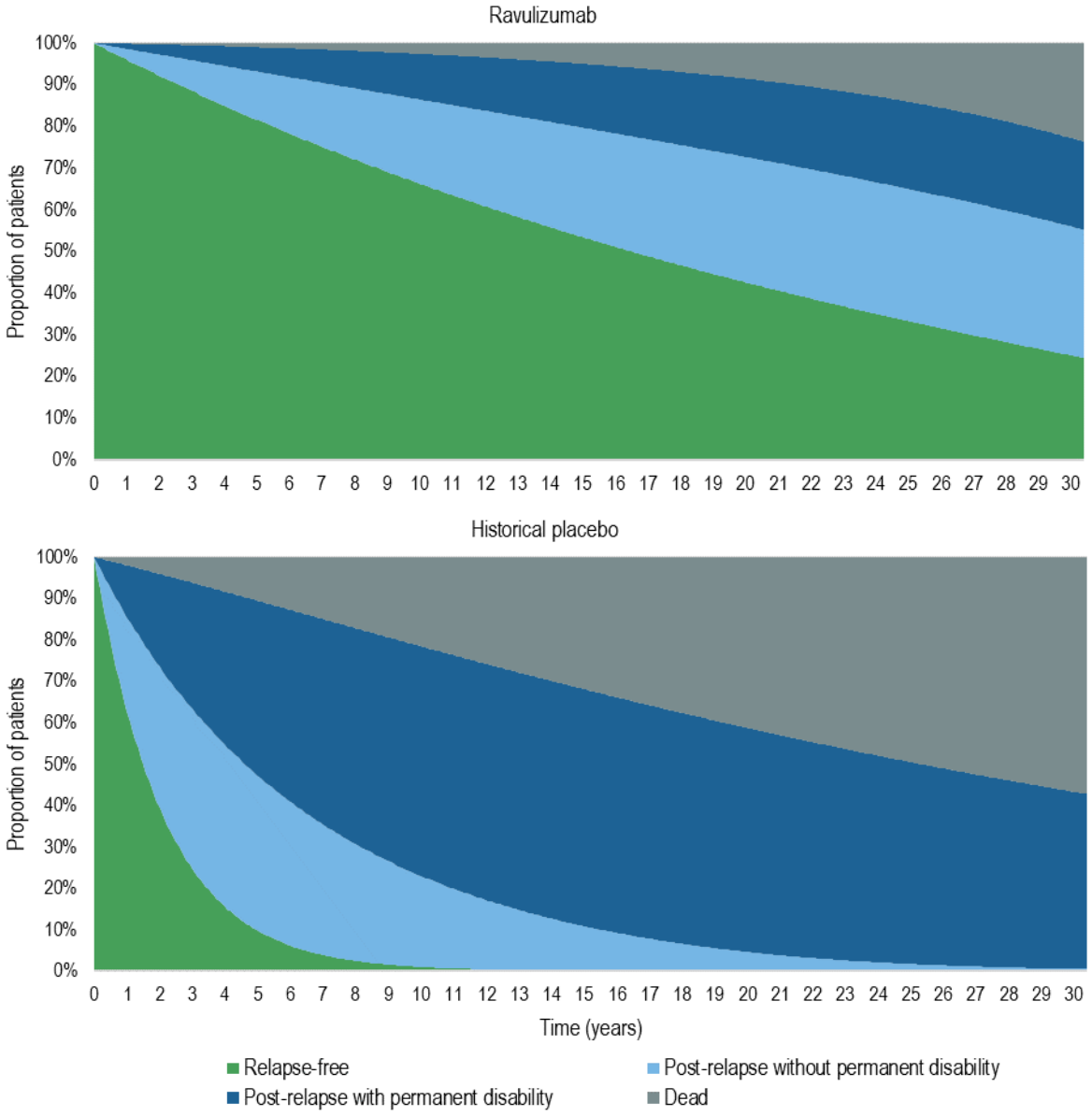
Source: Constructed during the evaluation based on Attachment 10 Section 3 Excel workbook
Note: Shaded cells indicate health states with negative utility values
Note: At 9 relapses all patients must switch to the 'with disability' states in the economic model

6.49 The submission claimed that utility predictions below zero were reasonable for patients with NMOSD, with published negative values as low as -0.29 (Hughes 2022). While negative values have been reported for NMOSD patients, it should be noted that Hughes 2022 reported a mean utility value of 0.20 (95% central range 0.02-0.38) for patients with very severe disability (EDSS 8.0-9.5) which was substantially higher than many of the health state utility values used in the model. Additionally, the negative values produced from the economic model are substantially lower (with estimates as low as -0.8421 for the 20th relapse) than the minimum values previously reported in the published literature. The PSCR stated that a patient in the 20th relapse

health state would be scored as EDSS 9.5 - confined to bed, totally dependent, unable to communicate effectively or eat/swallow. The PSCR considered it was reasonable to assume this health state would be worse than death and argued that a utility value of -0.8421 for the 20th relapse may be appropriate as the value of -0.29 reported in Hughes 2022 was based on patients who had experienced fewer relapses (up to 10 relapses). Overall, the ESC considered that while negative utility values would be appropriate for some health states, the magnitude of the negative utility values applied lacked face validity, and the additive method for calculating these negative values appeared inappropriate (as outlined in Table 10). The pre-PBAC response argued that the utility weight of -0.8421 would apply only to a patient experiencing 20 relapses, and was modelled as applying for 0.02 years (less than one week) across the time horizon of the model. The pre-PBAC response further argued that if the lower utility weight were capped at -0.29 (consistent with Hughes 2022) this would only have a minimal impact on the ICER (it would reduce the ICER/QALY by 2% to $455,000 to < $555,000). Conversely, the PBAC noted that other sensitivity analyses relating to the estimation of the utility values had a larger impact on the ICER/QALY (e.g. assuming relapse utility values are multiplicative would increase the ICER/QALY by 15% to $555,000 to < $655,000).

6.50 A Markov trace of the proportion of patients in each health state over time is presented in Figure 3.

Figure 3: Proportion of patients in each health state over time



Source: Constructed during the evaluation based on Attachment 10 Section 3 Excel workbook

6.51 The Markov traces indicate a rapid divergence in health outcomes between treatment arms, with ravulizumab patients having a substantially longer relapse-free time (median time of 16.2 years with ravulizumab and 1.5 years with placebo), a longer time without permanent disability (median time not reached with ravulizumab compared to 4.6 years with placebo) and longer life expectancy (median time not reached with ravulizumab compared to 24.9 years with placebo). By the end of the model, approximately 60% of patients in the ravulizumab arm were alive without disability, while nearly all patients in the placebo arm were dead or disabled.

6.52 The ESC considered it was inappropriate to apply the relative reduction in relapse directly to mortality. Although the ESC agreed with the PSCR that relapse events would

likely contribute to increased mortality, the ESC considered the relationship between the risk of relapse and the risk of death is not direct because NMOSD relapses vary in their clinical effects, and therefore vary in the risk of mortality. The ESC noted that directly applying the relative reduction in relapse to mortality resulted in the economic model estimating that patients using ravulizumab would, on average, experience an additional 7 years of life expectancy (undiscounted) over a 30-year time horizon. The ESC considered this lacked face validity and was not adequately justified by the data presented in the submission. While the pre-PBAC response argued that mortality in NMOSD is driven by relapses, the PBAC considered that it was the way in which the submission's model had applied the mortality risk that was problematic.

6.53 During the evaluation, it was noted that 99.1% of incremental QALYs in the model are accrued in the extrapolated period beyond 1.45 years (76 weeks).

6.54 The results of the stepped economic evaluation are summarised in Table 12.

Table 12: Stepped economic evaluation of ravulizumab compared to placebo

Type of resource item	Ravulizumab	Placebo	Increment
Step 1: Modelled estimate based on study duration of 1.4476 years (76 weeks) including drug acquisition costs only			
Costs	$	$0	$
Relapses	0.0513	0.5762	-0.5248
Incremental cost-per-relapse avoided			$[1]
Step 2: Modelled estimate extrapolated to 30 years including drug acquisition costs only			
Costs	$	$0	$
Relapses	1.0849	9.1572	-8.0723
LYs	27.8319	20.7399	7.0920
Incremental cost-per-relapse avoided			$[2]
Incremental cost per LY gained			$[1]
Step 3: Modelled estimates extrapolated to 30 years including both drug acquisition and other costs			
Costs	$	$508,390	$
LYs	27.8319	20.7399	7.0920
Incremental cost per LY gained			$[1]
Step 4: Modelled estimates extrapolated to 30 years including drug acquisition and other costs with utility weights applied			
Costs	$	$508,390	$
QALYs	15.9098	2.6072	13.3026
Incremental cost per QALY gained			$[3]
Step 5: Modelled estimates extrapolated to 30 years including drug acquisition and other costs with utility weights and discounting applied			
Costs	$	$284,705	$
QALYs	8.9830	2.9206	6.0625
Incremental cost per QALY gained			**$**[4]

Source: Table 3-24, p183 of the submission
Abbreviations: LY, life year; QALY, quality-adjusted life year
The redacted values correspond to the following ranges:
1 $655,000 to < $755,000
2 $555,000 to < $655,000
3 $355,000 to < $455,000
4 $455,000 to < $555,000

6.55 Based on the economic model, treatment with ravulizumab was associated with a cost per QALY gained of $455,000 to < $555,000 compared to placebo for the treatment of

NMOSD. The PBAC previously noted that ICERs in the range of $95,000 to < $115,000 to $255,000 to < $355,000 per QALY gained were considered acceptable for rare diseases (para 7.13 eculizumab PSD, November 2021 PBAC meeting). The ESC considered that although the economic model was implausibly optimistic, the ICER substantially exceeded the range that the PBAC previously considered would be appropriate. The ESC considered a substantial cost reduction would likely be required for ravulizumab to be considered cost-effective.

6.56 On average, for every patient treated with ravulizumab versus placebo and followed up for 30 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- A decrease in NMOSD relapse events (8 fewer events) with a linked reduction in the risk of permanent disability.
- An increase in life expectancy of approximately 7 years.
- A decrease in the time spent in health states worse than death of approximately 7.5 years.
- Additional drug acquisition costs of $[redacted].

6.57 The ESC considered the modelled benefits associated with ravulizumab treatment appeared optimistic and highly implausible based on currently available data.

6.58 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Results of key sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALYs	ICER	Change from base case ICER
Base case	[redacted]	**6.0625**	[redacted]1	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate	[redacted]	7.5359	[redacted]1	[redacted]%
0% discount rate		13.3026	[redacted]2	[redacted]%
Time horizon (base case: 30 years)				
53 years	[redacted]	7.2699	[redacted]2	[redacted]%
25 years		5.2793	[redacted]1	[redacted]%
20 years		4.2750	[redacted]3	[redacted]%
10 years		1.7581	[redacted]4	[redacted]%
Treatment discontinuations (base case: assume no discontinuations in first year and a 2% annual discontinuation rate in subsequent years; only applied to ravulizumab drug costs)				
Assume no discontinuations	[redacted]	6.0625	[redacted]3	[redacted]%
Apply 2% discontinuation rate in all years (to costs only)		6.0625	[redacted]1	[redacted]%
Assume the 2% annual discontinuation rate affects both costs and outcomes		5.2067	[redacted]3	[redacted]%
Relapse rates (base case: constant risk based on the historical placebo arm overall population in the PREVENT trial with ravulizumab treatment effects estimated based on a naïve comparison in the subgroup of patients with multiple relapses and prior rituximab use, risk of subsequent relapses assumed to be the same as first relapse; maximum relapses capped at 20)				
Ravulizumab treatment effect based on upper CI in subgroup analysis	[redacted]	1.5588	[redacted]5	[redacted]%

Analyses	Incremental cost ($)	Incremental QALYs	ICER	Change from base case ICER
Base case	[redacted]	**6.0625**	[redacted][1]	-
Ravulizumab treatment effect based on lower CI in subgroup analysis		6.9162	[redacted][2]	[redacted]%
Ravulizumab treatment effect based on ITT population		6.7800	[redacted][2]	[redacted]%
Decrease relapse risk in placebo arm by 10%		5.7341	[redacted][1]	[redacted]%
Decrease relapse risk in placebo arm by 20%		5.3881	[redacted][3]	[redacted]%
Decrease relapse risk in placebo arm by 30%		5.0219	[redacted][3]	[redacted]%
Decrease relapse risk in placebo arm by 40%		4.6323	[redacted][6]	[redacted]%
Decrease relapse risk in placebo arm by 50%		4.2148	[redacted][6]	[redacted]%
Maximum relapses capped at 15		6.0407	[redacted][1]	[redacted]%
Maximum relapses capped at 10		5.8571	[redacted][1]	[redacted]%
Maximum relapses capped at 5		4.8075	[redacted][3]	[redacted]%
Mortality rates (base case: mortality risk in placebo arm based on crude published mortality rates; mortality risk in ravulizumab arm based on adjusted mortality rates and assuming the relapse treatment effect also applies to death; applies a mortality multiplier for permanent disability based on published literature)				
Placebo mortality based on standardised rate	[redacted]	5.9356	[redacted][1]	[redacted]%
No ravulizumab treatment effect on death (same as placebo crude rate)		4.7318	[redacted][1]	[redacted]%
No ravulizumab treatment effect on death (same as placebo standardised rate)		5.4268	[redacted][1]	[redacted]%
Remove mortality multiplier for permanent disability		6.1855	[redacted][1]	[redacted]%
Utility values (base case: relapse disutility values based on pooled analysis of CHAMPION-NMOSD and PREVENT trial data; permanent disability disutility values based on published estimates; assumed disutility values of multiple events were additive)				
Cap lower bound of utilities to zero	[redacted]	5.4101	[redacted][3]	[redacted]%
Estimate relapse disutilities based on subgroup of patients with multiple relapses and prior rituximab use		8.9417	[redacted][7]	[redacted]%
Remove permanent disability disutility values		4.8986	[redacted][3]	[redacted]%
Assume relapse disutility values are multiplicative		5.2571	[redacted][3]	[redacted]%
Assume relapse and permanent disutility values are multiplicative		4.5223	[redacted][6]	[redacted]%
Perspective (base case: health system perspective)				
Societal perspective (patient productivity loss, non-medical direct costs, carer productivity loss and carer disutility values)	[redacted]	6.3121	[redacted][2]	[redacted]%

Source: Table 3-29, p188 of the submission

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; ICER, incremental cost effectiveness ratio; ITT, intention-to-treat; QALYs, quality adjusted life years

The redacted values correspond to the following ranges:

1 $455,000 to < $555,000

2 $355,000 to < $455,000

3 $555,000 to < $655,000

4 $955,000 to < $1,055,000

5 > $1,055,000

6 $655,000 to < $755,000

7 $255,000 to < $355,000

6.59 The results of the sensitivity analyses indicate that the model is most sensitive to the discount rate, time horizon, treatment discontinuation rate, ravulizumab treatment effects, placebo relapse rates, maximum relapse caps, relapse disutility values,

permanent disability disutility value, the method of combining disutility values, and the perspective of the economic analysis.

6.60 The model was relatively insensitive to mortality despite the substantial impact of survival on the incremental health outcomes between treatment arms. This insensitivity appeared to be due to the extreme negative utility values produced by the model which results in a negative association between improved survival and quality of life in the placebo arm (e.g. increasing survival in the placebo arm results in a reduction in quality-adjusted life years as patients spend more time with negative utility values).

6.61 Overall, the ESC advised that the ICER presented in the submission was not a reliable estimate of the cost effectiveness of ravulizumab. The ESC considered that a revised economic evaluation would be required and should be based on a simplified model structure that addresses the issues regarding disutility values and mortality benefit (as outlined in Table 10 and paragraphs 6.49 and 6.52).

6.62 In the absence of a reliable estimate of the cost-effectiveness of ravulizumab in this condition, the ESC noted that the cost-per-relapse avoided at 76 weeks was $655,000 to < $755,000 (Step 1 of Table 12, based on an incremental cost of $ and 0.52 relapses avoided).

6.63 The pre-PBAC response outlined that the cost-per-relapse avoided at 76 weeks would reduce to $455,000 to < $555,000 if the societal perspective were included.

6.64 The PBAC noted previous recommendations it had made using an incremental cost-per-responder analyses, as outlined in Table 14.

Table 14: Examples of cost-per-responder analyses previously considered by the PBAC

Drug & condition (PBAC meeting)	Cost-per-responder
Bevacizumab for relapsed or refractory glioblastoma (May 2019)	The cost-per-responder (ORR) was [redacted as per PSD]
Brentuximab vedotin for refractory or relapsed CD30 positive cutaneous T-cell lymphomas (CTCL). (Nov 2018)	The cost-per-responder (ORR) was $45,000 - $75,000 and the cost per additional year without progression was $15,000 - $45,000
Vorinostat for refractory or relapsed cutaneous T-cell lymphoma (CTCL) (March 2017)	Cost-per-responder was [redacted as per PSD]
Clostridium botulinum type A toxin-haemagglutinin complex (Dysport®) for focal spasticity of the upper limb following a stroke, to also include spasticity following acute events other than stroke (March 2019)	Cost-per-responder: less than $15,000
Denosumab giant cell tumour of bone (November 2013)	Incremental cost-per-responder of less than $15,000
Etanercept severe chronic plaque psoriasis in patients under the age of 18 years (March 2012)	Incremental cost-per-PASI 75 response: less than $15,000
Tiotropium severe asthma in children and adolescents aged 6-17 years who have not achieved adequate asthma control. (November 2018)	Incremental cost-per-symptomatic exacerbation avoided: less than $15,000

Source: constructed from PSDs

6.65 The PBAC noted the incremental cost-per-responder proposed in this resubmission was considerably higher than the precedents previously noted for other therapies, which had been in the range of $15,000 to $75,000. However, the PBAC also acknowledged that there was considerable variation in these analyses in terms of: the clinical meaningfulness of response, including the long-term impact of a response; the timeframe over which the 'response' was achieved; and the duration of therapy. The PBAC noted that many of the previous cost-per-responder analyses had been for time-limited therapies, with response assessed at 26 weeks or one year.

Drug cost/patient/year

6.66 The estimated drug costs per patient per year for ravulizumab are presented in Table 15. The commentary estimated that the average cost per patient per year for ravulizumab was around $ in Year 2 onwards (excluding the loading dose, based on 6.25 maintenance doses per year).

Table 15: Drug cost per patient per year for ravulizumab

	CHAMPION-NMOSD	Economic model	Financial estimates
Effective AEMP per 300 mg vial	-	$	$
Effective AEMP per 1,100 mg vial	-	-	$
Adherence	100%	100%	100%
Cost per year	-	Year 1: $[a] Year 2: $[b] Year 3: $[c] Year 4: $[b] Year 5: $[c] Year 6: $[b]	Year 1: $[d] Years 2-6: $[e]
Treatment discontinuation	2.5% per year (primary study period) or 2% per year (including extension data)	2% per year	0% per year

Source: Constructed during the evaluation based on Attachment 10 Section 3 Excel workbook and Attachment 11 Section 4 Excel workbook
Abbreviations: AEMP, approved ex-manufacturer price; PNH, paroxysmal nocturnal haemoglobinuria
[a] Based on patients receiving 1 loading dose and 7 maintenance doses, assuming the same distribution of patients across weight categories as the CHAMPION-NMOSD study, assuming a private/public hospital distribution based on the PBS utilisation of ravulizumab for PNH.
[b] Based on patients receiving 6 maintenance doses, with the same assumptions as the first year calculations.
[c] Based on patients receiving 7 maintenance doses, with the same assumptions as the first year calculations.
[d] Based on patients receiving 1 loading dose and 6.25 maintenance doses, assuming the same distribution of patients across weight categories as the CHAMPION-NMOSD study, assuming a private/public hospital distribution based on the PBS utilisation of ravulizumab for PNH.
[e] Based on patients receiving 6.5 maintenance doses, with the same assumptions as the first year calculations.

6.67 For comparison, the estimated annual drug cost of rituximab treatment would be $ (based on the average dose of 2 g every 6 months used in the pre-PBAC response for the November 2021 eculizumab submission; and using the current private DPMQ of $ for 2 x 500 mg vials).

6.68 The submission assumed no intervention costs were associated with best supportive care.

Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC.

6.70 The submission used an epidemiological approach to estimate the utilisation and financial implications of listing ravulizumab on the PBS/RPBS for the treatment of adult patients with NMOSD who are AQP4 positive and who have experienced a recent relapse event, despite prior treatment with rituximab or who cannot tolerate rituximab.

6.71 Key inputs to the budget impact model are summarised in Table 16.

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

Parameter	Value/Source	Comment
Prevalence of NMOSD	1.04 per 100,000 population. Based on a selected subset of studies identified in a systematic review of NMOSD epidemiology studies (Papp 2021). The submission claimed that the individual studies were selected on the basis of including predominantly White populations with adequate sample sizes (Aboul-Enein 2013; Sepulveda 2018; Papp 2018; Jonsson 2019; Papp 2020; Bukhari et al. 2017). Studies that reported estimates for AQP4 positive disease only were inflated to an overall NMOSD prevalence (estimate divided by 90.12%). The estimate used in the submission was based on the median value across all the selected studies.	DUSC has previously noted an Australian NMOSD epidemiology study which reported the prevalence of NMOSD as 0.70 per 100,000 (Bukhari et al. 2017) but considered that the methodology used in the study may underestimate disease prevalence (Table 12, eculizumab PSD, November 2020 PBAC meeting). The evaluation and the ESC considered that the prevalence of NMOSD was uncertain, with prevalence estimates in predominantly White populations ranging from 0.7 to 4.4 per 100,000 population with higher prevalence estimates observed in predominantly Black or Asian populations. (Papp 2021). A more recent systematic review of epidemiology studies estimated a global prevalence of 1.51 (95% CI 1.21, 1.81) per 100,000 population using the 2015 NMOSD diagnostic criteria (Bagherieh 2023). The PBAC considered that the prevalence value applied in the submission was appropriate.
Proportion of patients with first-line rituximab treatment Proportion with contraindication to rituximab	95% receive first-line rituximab treatment while the remaining 5% have contraindications. Based on expert advice that all patients without contraindications would receive first-line treatment with rituximab.	The PBAC considered this was likely appropriate.
Patients experiencing a serious adverse event with rituximab requiring discontinuation	3.2% of patients. Based on a retrospective longitudinal study of NMOSD patients attending hospitals in France between 1993 and 2018 (Poupart 2020). The estimate used in the submission was based on the proportion of patients who discontinued rituximab due to any adverse event	The proportion of patients with a qualifying serious adverse event with rituximab treatment was uncertain and could be higher than estimated, particularly as the availability of a new antibody therapy may reduce the tolerance for adverse events associated with existing therapies. Poupart 2020 noted that 8.1% of rituximab-treated patients experienced a serious infection event over a median of 2.6 years of follow-up (however, none of these patients discontinued therapy). This was in addition to the other 3.2% who discontinued therapy due other safety reasons (severe agranulocytosis, recurrent non-serious infection). A recent systematic review of azathioprine, mycophenolate mofetil and rituximab as first-line treatments for NMOSD noted that data on the tolerance of these therapies remains scarce (Giovanelli 2021). Overall, the PBAC considered that the value applied in the submission was appropriate.

Parameter	Value/Source	Comment
Patients experiencing a relapse event with rituximab	31.5% of patients. Based on a systematic review of studies comparing the time to first relapse with azathioprine, mycophenolate mofetil and rituximab as first-line treatments for NMOSD (Giovannelli 2021). <u>Rituximab</u> Jeong 2016: 18/52 patients (34.6%) experienced a relapse over a median follow-up time of 41 months. Stellmann 2017: 23/62 patients (37.1%) experienced a relapse over a median follow-up time of 6 months. Yang 2018: 7/20 patients (35.0%) experienced a relapse over a median follow-up time of 28.5 months. McCreary 2018: 13/36 patients (36.1%) experienced a relapse over a median follow-up time of 8 months. Poupart 2020: 11/62 patients (17.7%) experienced a relapse over a median follow-up time of 31 months. The submission also identified an additional observational study of rituximab. Nasir 2024: 25/77 patients (32.5%) experienced a relapse over a median follow-up time of 44 months. The estimate used in the submission was based on the weighted average proportion of patients with relapse across the included studies.	The commentary and the ESC considered that the applicability of this estimate was unclear as the proposed restriction does not require patients to be actively using rituximab at the time of relapse (patients only require a prior history of rituximab use). The weighted average proportion used in the submission does not adequately account for the difference in follow-up time between studies and it is likely that annualised relapse rates would vary substantially between each of the included study populations. Given that preventative treatments such as rituximab only reduce but do not eliminate the risk of relapse it is likely than many patients will eventually experience a qualifying relapse event. The PSCR stated that the estimate that 31.5% of patients would relapse on rituximab was supported by a real world NMOSD cohort (n=111) which reported that rituximab had a 30% failure rate despite suppressed B cells (Bilodeau 2024). However, the ESC noted that the cited reference appeared to indicate that rituximab was associated with a 40% relapse rate over a median treatment duration of 5.8 years, which would result in a much lower annualised relapse rate than estimated in the submission. Overall, the PBAC considered that the proportion of patients experiencing a relapse while on rituximab of should be applied in a stepwise fashion (i.e. 15% in Year 1, 25% in Year 2, 31.5% from Year 3 onwards).
Proportion of patients with a relapse in prior 12 months	Not estimated.	The patient population estimates presented in the submission do not account for the proposed clinical criterion requiring patients to have had a recent relapse in the prior 12 months. The PBAC considered this could be addressed by applying the proportion of patients experiencing a relapse while on rituximab in a stepwise fashion (see above).
Ravulizumab uptake rate	[redacted]% in Year 1 increasing [redacted]% in Year 2 and to [redacted]% in Years 3+. Assumption. Based on the clinical need in the target patient population and the reduction in relapse risk associated with ravulizumab treatment.	The evaluation and the ESC considered that it was unclear whether this assumption was reasonable given that the choice of therapy may involve other clinical and non-clinical factors and rituximab as a component of best supportive care is likely to remain a treatment option for a substantial proportion of patients in the second line setting. However, the PBAC considered that the uptake rate applied in the submission was likely reasonable given the severe nature of relapses.

Parameter	Value/Source	Comment
Grandfathered population	The submission stated that the sponsor currently supports [redacted] [1]patients via a compassionate supply program. These patients were assumed to be a subset of the eligible patient population.	No details on patient eligibility to the compassionate supply program were provided. The evaluation considered that it was unclear whether these patients should be considered as additional patients, or a subset of the eligible patient population, as the submission's proposed restriction did not require grandfathered patients to have met the requirements to have a contraindication, serious adverse event or a relapse with rituximab therapy. However, the ESC and the PBAC considered that the submission's approach of assuming these patients are a subset of the eligible population was reasonable given the restriction would require these patients to have met the PBS eligibility criteria at the time of ravulizumab initiation.

Source: Section 4, pp196-2015 of the submission; Attachment 11 Section 4 Excel workbook.
Abbreviations: AEMP, approved ex-manufacturer price; AQP4, aquaporin-4; DUSC, Drug Utilisation Sub Committee; MBS, Medicare Benefits Schedule; NMOSD, neuromyelitis optica spectrum disorder; PBS, Pharmaceutical Benefits Scheme; PNH, paroxysmal nocturnal haemoglobinuria; PSD, Public Summary Document.
The redacted values correspond to the following ranges:
1 <500

6.72 The estimated use and financial implications of listing ravulizumab as a second-line treatment option for NMOSD, as estimated in the submission, are summarised in Table 17.

Table 17: Estimated use and financial impact of ravulizumab (effective price) for NMOSD

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total treated population	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
300 mg loading dose scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
300 mg maintenance dose scripts	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
1,100 mg maintenance dose scripts	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Cost to PBS less copayment	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Cost to the MBS for drug administration	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to PBS/MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Table 4-5, p207; Table 4-6, p207; Table 4-7, p208; Table 4-8, p208; Table 4-10, p211; Table 4-11, p211; Source: Table 4-14, p214 of the submission
Abbreviations: NMOSD, neuromyelitis optica spectrum disorder; PBS, Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
1 <500
2 500 to < 5,000
3 $20 million to < $30 million
4 $0 to < $10 million

6.73 The submission estimated that the cost to the PBS of listing ravulizumab for NMOSD would be $20 million to < $30 million in Year 1, increasing to $20 million to < $30 million in Year 6, with a cumulative total of $100 million to < $200 million over 6 years.

6.74 The evaluation and the ESC considered that there was uncertainty associated with the available published estimates of NMOSD prevalence and the proportion of patients:

who are contraindicated to rituximab; who have experienced a serious adverse event with rituximab; or who have experienced a relapse with rituximab (see Table 16).

6.75 Overall, the ESC considered that the eligible patient population was likely to have been overestimated given the submission did not account for the requirement for patients to have had a relapse in the prior 12 months. To appropriately accommodate this criterion would require the inclusion of annualised relapse rates for patients with and without rituximab treatment. The requirement to have a recent relapse is likely to reduce the number of eligible patients in any given year, resulting in a gradual accrual of treated patients over time rather than a large prevalent pool of patients in Year 1 as estimated in the submission. The PBAC considered that, to address this issue, the proportion of patients experiencing a relapse while on rituximab should be applied in a stepwise fashion (i.e. 15% in Year 1, 25% in Year 2, 31.5% from Year 3 onwards).

6.76 The ESC noted that the estimated number of patients was substantially higher than was estimated in the November 2021 submission for eculizumab (refer to Table 2) however the November 2021 submission had targeted patients with a higher number of prior relapses.

6.77 The ESC considered that it was unclear whether the submission's assumption (in the financial estimates) of no treatment discontinuations and 100% adherence was reasonable. The PBAC considered that a discontinuation rate should be applied in the financials, of at least 2% per year consistent with the economic model (while the submission did not apply the discontinuation rate in the first year of the economic model, the PBAC considered the discontinuation rate should apply in Year 1 of the financial estimates noting the economic model was not considered sufficiently reliable for decision-making).

6.78 The evaluation and the ESC considered that it was unclear whether uptake rates would be representative of clinical practice given that rituximab may remain a treatment option following relapse for many patients. However, the PBAC considered that the uptake rate applied in the submission was likely reasonable given the severe nature of relapses.

Quality Use of Medicines

6.79 The submission detailed the implementation of risk minimisation measures, including targeted education materials, controlled distribution in Australia, and annual meningococcal vaccination reminders, to be managed via a digital risk minimisation platform. The sponsor will require a completed certificate of vaccination against N. meningitides and/or treatment with prophylactic antibiotics to allow distribution to occur.

Financial Management – Risk Sharing Arrangements

6.80 The submission noted the sponsor's intention to enter a risk sharing arrangement (RSA) should ravulizumab be listed on the PBS, with Commonwealth payment thresholds based on agreed financial estimates. The PSCR stated the sponsor was

willing to enter an RSA with a 100% rebate on utilisation above the expenditure caps to provide financial certainty. However, the ESC noted that the PSCR did not provide any further discussion regarding RSA proposals.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of ravulizumab for the treatment of neuromyelitis optica spectrum disorder (NMOSD) on the basis that it should be available only under special arrangements under Section 100. The PBAC recognised the very high unmet need for treatments for NMOSD which is a rare condition with substantial impacts on quality of life. The PBAC was satisfied that ravulizumab provides, for some patients, a significant improvement in efficacy over best supportive care. The PBAC considered that the economic model presented in the submission was not sufficiently reliable for decision-making in part due to the limited long-term data available and the complex and unpredictable nature of the condition. Overall, the PBAC considered that in the context of this rare and severe condition, ravulizumab would be considered acceptably cost-effective with a reduction in treatment cost that would result in an acceptable cost-per-relapse avoided. The PBAC considered that any remaining uncertainties should be managed by a risk sharing arrangement (RSA).

7.2 The PBAC welcomed the consumer input received from individuals, health professionals and organisations which described the debilitating nature of NMOSD and the substantial impact it can have on quality of life including through reduced mobility, a decreased ability to participate in the activities of daily life, pain, vision loss, fear of relapse, and a significant impact on families and carers. The PBAC recognised the importance of avoiding relapses given the potential for permanent disability. The PBAC considered there was a very high unmet need for effective therapies for NMOSD in patients who have relapsed on rituximab, or in whom rituximab is contraindicated/intolerant.

7.3 The PBAC noted the submission was based on the CHAMPION-NMOSD study, which was designed as single-arm study with a historical external control arm (from the pivotal randomised controlled trial for eculizumab, PREVENT). There were no adjudicated relapses associated with ravulizumab treatment in the CHAMPION-NMOSD study or during the longer-term extension study of ravulizumab (median follow-up 138.4 weeks). In comparison, in the PREVENT trial, 37% of placebo patients had relapsed by 48 weeks, 44% by 72 weeks and 48% by 96 weeks.

7.4 The PBAC noted that there were limitations associated with the data presented (non-randomised comparison with a historical control) including that: (i) the PREVENT trial appeared to have enrolled a more severely affected patient population compared to the CHAMPION-NMOSD study (refer to paragraph 6.10); (ii) patients in the PREVENT trial and CHAMPRION-NMOSD study were not permitted to use other antibody therapies (such as rituximab), IVIg/PLEX, mitoxantrone or immunomodulatory therapy

for relapse prevention; and (iii) the primary analysis was based on adjudicated relapses (assessed using an external committee).

7.5 Overall, the PBAC considered that the evidence presented clearly demonstrated that ravulizumab was associated with a meaningful reduction in relapse frequency compared with best supportive care. However, noting the limitations, the PBAC considered that the magnitude of benefit associated with ravulizumab was potentially overestimated.

7.6 The PBAC considered that ravulizumab was non-inferior to best supportive care in terms of comparative safety.

7.7 The PBAC noted that the submission presented a cost-utility analysis based on data from the CHAMPION-NMOSD study, the PREVENT trial and additional modelled data. The base case ICER was high at $455,000 to < $555,000/QALY. The PBAC agreed with the ESC that the economic model was unreliable and implausibly optimistic because:

- the incremental difference in survival was likely to have been overestimated due to the way in which mortality risks were applied including the: unsupported assumption that the reduction in relapse risk with ravulizumab could also be applied directly to mortality; inappropriate use of different methodologies to calculate mortality rates in each arm; and incorrect application of a disability mortality multiplier to mortality rates that already include deaths due to disability.
- the magnitude of the negative utility values associated with some health states (with estimates as low as -0.8421, which was substantially lower than reported in the literature) and the duration of time spent in health states worse than death (average of 7.5 years in the placebo arm, undiscounted) appeared implausible. Further, the PBAC noted the ESC's advice that the additive method for calculating these negative values appeared inappropriate.
- the relapse rate in the historical placebo arm of the PREVENT trial may not be representative of best supportive care in the second-line setting given that no patients were receiving rituximab, and a substantial proportion were receiving either no therapy (27.7%) or corticosteroid monotherapy only (23.4%).
- the application of treatment persistence estimates to drug costs only, with no impact on modelled health outcomes, was inappropriate and biased the analysis in favour of ravulizumab.

7.8 Further, the PBAC considered the economic model was not sufficiently reliable for decision-making due to the lack of long-term data available and the complex and unpredictable nature of the condition (e.g. the relapses which cause disability are unpredictable with respect to timing, frequency, severity and degree of recovery). As such, the PBAC considered the uncertainty in the ICER was unlikely to be adequately resolved with further revisions to the model structure. The PBAC acknowledged the very high unmet need, the importance of reductions in relapse rates, and the potential for substantial improvements in the quality of life for patients and carers. In this

overall context, the PBAC considered that the cost-per-relapse avoided would provide a reasonable alternative assessment of cost-effectiveness in this instance.

7.9 However, the PBAC considered the cost-per-relapse avoided at 76 weeks was unacceptably high at $655,000 to < $755,000 (Step 1 of Table 12). The PBAC noted previous cost-per-responder analyses which it had accepted were in the range of $15,000 to $75,000, with considerable variation between these analyses in terms of: the clinical meaningfulness of response, including the long-term impact of a response; the timeframe over which the 'response' was achieved; and the duration of therapy. The PBAC acknowledged that many of the previous cost-per-responder analyses had been for time-limited therapies, with response captured at 26 weeks or one year.

7.10 The PBAC considered that in order to accept the value proposition, a reduction in treatment cost would be required to achieve a cost-per-relapse avoided of $255,000 to < $355,000 at 76 weeks (based on step 1 of the stepped economic evaluation outlined in Table 12 i.e. the modelled estimate based on study duration of 76 weeks including drug acquisition costs only), given this would correspond with a cost-per-relapse avoided of around $115,000 to < $135,000 per 26 weeks (if relapses and costs were accrued in a uniform manner over that time period). The PBAC noted that, even with this reduction in treatment costs, the cost-per-response was very high in the context of previous recommendations, but considered it was adequately supported given the substantial and potentially irreversible impact of NMOSD relapses on patient quality of life, and the impact on families and carers.

7.11 The PBAC noted that the reduction in treatment costs as outlined in paragraph 7.10 would result in a cost per patient per year of ravulizumab of approximately $ (in Year 2 onwards, i.e. excluding the loading dose, based on 6.25 maintenance doses per year).

7.12 The PBAC considered the submission targeted a well-defined population and the utilisation estimates provided in the submission were generally reasonable except:

- the proportion of patients experiencing a relapse while on rituximab should be applied gradually in the first two years (i.e. 15% in Year 1, 25% in Year 2, 31.5% from Year 3 onwards); and
- a ravulizumab discontinuation rate should be applied (at least 2% per year, each year).

7.13 The PBAC considered that a 100% rebate would be required for expenditure above the utilisation estimates (i.e. based on the submission's utilisation estimates, adjusted for the issues outlined in paragraph 7.12, and acknowledging the treatment costs outlined in paragraph 7.10) to manage the total financial expenditure.

7.14 The PBAC requested that DUSC review the utilisation of ravulizumab after an appropriate period of time post-listing to ensure that patient numbers in practice are consistent with the estimates to ensure an appropriate ravulizumab treatment cost is achieved in this condition.

7.15 The PBAC advised the restriction:

- should clearly define the requirement for patients to have had a recent relapse event in the previous 12 months while receiving treatment with rituximab (unless intolerant or contraindicated).
- should specify that ravulizumab treatment must be discontinued if the patient's Expanded Disability Status Scale (EDSS) score exceeds 7 points and if they suffer a relapse whilst receiving treatment with ravulizumab.
- should remain silent with respect to age.
- should specify that "this drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting."
- should be Authority Required (delayed assessment) for initial induction and grandfather therapy, and an Authority Required (immediate assessment – telephone/online assessment) listing for continuing therapy.
- should include an "Initial 1 - induction dose" listing for the loading dose with zero repeats to fulfil initial PBS criteria; and a merged balance of supply and continuing restriction labelled as "continuing treatment" with two repeats for all maintenance treatment.
- is considered to be complex.

7.16 The PBAC considered that a grandfather restriction was reasonable and advised that it should require the patient to have: had at least one relapse in the 12 months prior to initiation of ravulizumab; and received treatment with rituximab immediately prior to the most recent relapse (unless intolerant/contraindicated). The PBAC advised that the grandfather listing should be in operation for 12 months from the date of listing.

7.17 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for ravulizumab:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy, over best supportive care on the basis of the reduction in the rate of relapses observed in the CHAMPION-NMOSD study;

b) The treatment is expected to address a high and urgent unmet clinical need;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.18 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive PBAC recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№. of Rpts	Available brands
RAVULIZUMAB					
ravulizumab 1.1 g/11 mL injection, 11 mL vial	NEW HSD (Public) NEW HSD (Private)	1	1	0	Ultomiris
ravulizumab 300 mg/3 mL injection, 3 mL vial	NEW HSD (Public) NEW HSD (Private	1	1	0	Ultomiris
	Category / Program: Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)				
	Prescriber type: Medical Practitioners				
	Restriction type: Authority Required (FULL assessment) in writing only via post/HPOS upload)				
	Authority type: Complex Authority Required (CAR)				
	Administrative Advice: *See the following article/website for details on Expanded Disability Status Scale (EDSS):* https://www.ncbi.nlm.nih.gov/books/NBK222389/				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special Pricing Arrangements apply.				
	Caution: C5 inhibitors increase increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.				
Restriction Summary [new1] / Treatment of Concept: [new1A]					
	Episodicity: blank				
	Severity: blank				
	Condition: Neuromyelitis optica spectrum disorder (NMOSD)				
	Indication: Neuromyelitis optica spectrum disorder (NMOSD)				
	Treatment Phase: Initial treatment – loading dose				
	Clinical criteria:				
	Patient must have a confirmed diagnosis of NMOSD with aquaporin-4 immunoglobulin G auto-antibody (AQP4-IgG)				
	AND				
	Clinical criteria:				
	Patient must have an Expanded Disability Status Scale (EDSS) score of no higher than 7				
	AND				
	Clinical criteria:				
	Patient must have had at least one relapse in the last 12 months				
	AND				
	Clinical criteria:				
	Patient must have experienced the most recent relapse while receiving treatment with rituximab; or				
	Patient must have a documented intolerance to rituximab of a severity necessitating permanent treatment withdrawal; or				
	Patient must have a documented contraindication to rituximab therapy				
	AND				
	Clinical criteria				
	Patient must not receive more than 2 weeks of treatment under this restriction.				

	AND
	Treatment criteria:
	Must be treated by a neurologist; or
	Must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.
	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for a single loading dose for induction therapy, according to the specified dosage in the approved Product Information (PI). Refer to the approved PI for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested. Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.
	Prescribing Instructions: The authority application must be in writing and must include all of the following: (1) Details of the proposed authority prescription; (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes: (i) the patient's Expanded Disability Status Scale (EDSS) score (ii) details of prior rituximab treatment [dosage, date of commencement and duration of therapy], or details of contraindications or developed intolerances necessitating treatment withdrawal.
	Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
RAVULIZUMAB					
ravulizumab 1.1 g/11 mL injection, 11 mL vial	NEW HSD (Public) NEW HSD (Private)	1	1	2	Ultomiris
ravulizumab 300 mg/3 mL injection, 3 mL vial	NEW HSD (Public) NEW HSD (Private	1	1	2	Ultomiris

)	**Category / Program:** ☒ Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (immediate assessment) telephone/online
	Authority type: ☒ Complex Authority Required (CAR)

		Administrative Advice: See the following article/website for details on Expanded Disability Status Scale (EDSS): https://www.ncbi.nlm.nih.gov/books/NBK222389/
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Caution: C5 inhibitors increase increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Restriction Summary [new2] / Treatment of Concept: [new2A]		
		Episodicity: blank
		Severity: blank
		Condition: Neuromyelitis optica spectrum disorder (NMOSD)
		Indication: Neuromyelitis optica spectrum disorder (NMOSD)
		Treatment Phase: Continuing treatment
		Clinical criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must have an Expanded Disability Status Scale (EDSS) score of no higher than 7
		AND
		Clinical criteria:
		Patient must not have experienced a relapse while receiving treatment with this drug for this condition
		AND
		Clinical criteria:
		Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction
		AND
		Treatment criteria:
		Must be treated by a neurologist; or
		Must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.
		Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for 8 weeks of treatment and up to 2 repeats, according to the specified dosage in the approved Product Information (PI). With 2 repeat prescriptions, this treatment phase listing intends to provide approximately 24 weeks of treatment. Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved. An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
		Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Restriction Summary [new3] / Treatment of Concept: [new3A]		
		Episodicity: blank

	Severity: blank
	Condition: Neuromyelitis optica spectrum disorder (NMOSD)
	Indication: Neuromyelitis optica spectrum disorder (NMOSD)
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfather arrangements
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of PBS listing]
	AND
	Clinical criteria:
	Patient must have a confirmed diagnosis of NMOSD with AQP4-IgG prior to commencing treatment with this drug
	AND
	Clinical criteria:
	Patient must have recorded baseline Expanded Disability Status Scale (EDSS) score of no higher than 7 prior to commencing treatment with this drug
	AND
	Clinical criteria:
	Patient must not have experienced a relapse while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have a current Expanded Disability Status Scale (EDSS) score of no higher than 7
	AND
	Clinical criteria:
	Patient must have had at least one relapse in the 12 months prior to commencing treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must have received treatment with rituximab immediately prior to the most recent relapse prior to initiation of ravulizumab; OR
	Patient must have a documented intolerance to rituximab of a severity necessitating permanent treatment withdrawal; OR
	Patient must have a documented contraindication to rituximab therapy
	AND
	Clinical criteria
	Patient must not receive more than 24 weeks of treatment under this restriction
	AND
	Treatment criteria:
	Must be treated by a neurologist; OR
	Must be treated by a medical practitioner who has consulted a neurologist, with agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.

	Prescribing Instructions: At the time of authority application, medical practitioners must request the appropriate number of vials to provide sufficient drug for 8 weeks of treatment and up to 2 repeats, according to the specified dosage in the approved Product Information (PI). With 2 repeat prescriptions, this treatment phase listing intends to provide approximately 24 weeks of treatment. Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the TGA PI will not be approved. An appropriate amount of drug (maximum quantity in units) may require prescribing both strengths. Consider strengths and combinations that minimise drug wastage. A separate authority prescription form must be completed for each strength requested.
	Prescribing Instructions: This drug is not PBS-subsidised if it is prescribed to an in-patient in a public hospital setting.
	Prescribing Instructions: The authority application must be in writing and must include all of the following: (1) Details of the proposed authority prescription; (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) which includes: (i) the patient's baseline Expanded Disability Status Scale (EDSS) score before commencement with this drug for drug for this condition (ii) the patient's current Expanded Disability Status Scale (EDSS) score (iii) details of prior rituximab treatment [dosage, date of commencement and duration of therapy], or details of contraindications or developed intolerances necessitating treatment withdrawal.
	Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

Alexion is pleased with the recommendation and is now looking forward to working with the Department of Health to ensure Australians living with Neuromyelitis Optica Spectrum Disorder (NMOSD), an ultra-rare disease, can access Ultomiris on the PBS at the earliest opportunity