

6.07 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 generalised myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.
- 1.2 The submission claimed that there is an unmet clinical need for additional treatment options for the management of myasthenia gravis given the limitations of current treatments including inadequate symptom control, slow onset of action, high treatment burden as well as significant side effects and risk of developing comorbidities.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus placebo.

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

Component	Description
Population	Adult patients with generalised myasthenia gravis who are AChR-positive and remain symptomatic despite standard therapy.
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). In combination with standard therapy (including anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, ciclosporin)
Comparator	Placebo in combination with standard therapy (including anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, ciclosporin)
Outcomes	Reduction in functional impairments, reduction in clinical exacerbations and myasthenic crisis events, improvements in quality of life
Clinical claim	Ravulizumab in combination with standard therapy is superior in terms of efficacy and inferior in terms of safety compared to placebo in combination with standard therapy

Source: Table 1-1, p25 of the submission

Abbreviations: AChR, acetylcholine receptor antibody

2 Background

Registration status

- 2.1 Ravulizumab was approved by the TGA on 22 May 2023 ‘as an add-on to standard therapy for the treatment of adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive’.
- 2.2 Ravulizumab is also currently TGA approved and PBS listed for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome.

Stakeholder meeting for generalised Myasthenia Gravis (AChR+)

- 2.3 A stakeholder meeting was held on 3 May 2024 to discuss the current clinical management of gMG and the role of emerging new treatments.
- 2.4 At the stakeholder meeting:
 - the consumer representatives outlined that gMG places a substantial burden on patients particularly when symptoms are not well-controlled e.g. during disease fluctuations. Current treatment regimens can be intrusive, time-consuming, and can have a range of adverse events. Quality of life and participation in the workforce and society can be significantly impacted and this impact can extend to a patient’s family.
 - The consumer representatives highlighted that ideally clinicians would be able to offer access to newer medications based on individual patient needs and benefits, for all disease severities and for all disease settings.
 - Although there are ongoing complexities for patients, the clinicians present at the stakeholder meeting noted that at present approximately 70% of patients experience on-treatment remission, while 30% are treatment refractory. The clinicians outlined that the majority of patients will respond/achieve remission

with the classic treatment options (i.e. pyridostigmine and/or corticosteroids and/or non-steroid immunosuppressants), although some patients require high doses of steroids to achieve remission.

- Some patients require combination therapy with the classic treatment options from early on and, often, bridging therapies to provide relief from symptoms whilst remission induction occurs. It was stated that it can take up to two years for the non-steroid immunosuppressants to induce remission.
- It was noted that at present, the only bridging therapies available are intravenous immunoglobulin (IVIg) and plasma exchange (PLEX). The evidence for rituximab in this setting is poor. Clinicians advised that the availability of PLEX was not equitable as it is available mostly in metropolitan hospitals across Australia. In addition, PLEX treatment is very intensive. For IVIg, there is only limited long-term evidence of its benefit, the dosing schedule is demanding, it is expensive, and it is associated with safety issues and side effects.
- The newer agents (ravulizumab and zilucoplan, also known as complement inhibitors, along with the FcRn-targeted immunosuppressive therapies, efgartigimod and rosanolixizumb) have not yet been incorporated into key treatment guidelines.
- The clinicians present at the meeting stated that the new treatments have rapid onsets of action and considered that complement inhibitors should be available to be used early in combination with standard therapy i.e. as a bridging therapy with specific patient criteria to be determined (e.g. a hypothetical case study of a typical patient who could benefit from the new therapies was discussed which took into account the patient's response to standard therapy). The clinicians noted that there is also a role for complement inhibitors later in the disease course in refractory patients and in patients requiring rescue therapy for myasthenic crisis.
- The clinicians considered there should be robust stopping rules to prevent ongoing use. It was noted that it would be harder to cease treatment in refractory patients.
- The clinicians outlined the following potential stopping rules when used early in disease:
 - Given that it appears that these agents work quickly, it was stated that it would be possible to determine whether they were having an effect within 12 weeks.
 - If it was established that an agent was effective in improving symptoms, patients could remain on treatment for 12 months, as it usually takes at least 12 to 24 months for the standard disease modifying agents to have an effect.
 - At 12 months, treatment with the complement inhibitor should be ceased. If the patient deteriorated, the complement inhibitor could be restarted, with 6-monthly rechallenges up to 2 years of total treatment. At that point treatment with the complement inhibitor would cease.

Public Summary Document - July 2024 PBAC meeting

- The clinicians proposed that patients may access re-treatment with a complement inhibitor if the disease is refractory, or if the patient experiences an exacerbation or is at risk of a myasthenia crisis.
- In all disease settings, the clinicians and consumer representatives stated that patients would have to be assessed for treatment response via measures that provided a robust, yet wholistic reflection, of the disease state. It was suggested that this would likely consist of the Myasthenia Gravis-Activities of Daily Living (MG-ADL) and/or Myasthenia Gravis Composite (MGC) score tools.

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

3 Requested listing

3.1 The restriction requested in the submission is outlined below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough (noting these changes are administrative in nature only).

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. 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
Restriction Summary / Treatment of Concept:					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)				
	Caution: <i>C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.</i>				
	Episodicity: blank				
	Severity: blank				
	Condition: generalised myasthenia gravis (gMG)				
	Indication: generalised myasthenia gravis (gMG)				
	Treatment phase: Initial treatment - <i>loading dose</i>				
	Clinical criteria:				
	Patient must have a diagnosis of generalised myasthenia gravis <i>that is not pure ocular myasthenia gravis made by or in consultation with a neurologist.</i>				
	AND				
	Clinical criteria:				
	The condition must not be pure ocular myasthenia gravis				
	AND				
	Clinical criteria:				

Public Summary Document - July 2024 PBAC meeting

	Patient must have been confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (anti-AChR antibodies)
	AND
	Clinical criteria:
	Patient must be experiencing symptoms consistent with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 6 points despite treatment with standard therapy
	AND
	Clinical criteria:
	<i>Patient must not receive more than 2 weeks of treatment under this restriction</i>
	AND
	Treatment criteria:
	Must be treated by a neurologist, or a non-specialist medical physician who has consulted a neurologist on the patient's drug treatment details
	<i>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.</i>
	AND
	Population criteria:
	Patients must be aged 18 years or older
	Prescribing Instructions: Standard therapy is defined as any of: pyridostigmine, oral corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclosporin.
	<p>Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate number of vials to cover the loading dose and 3 maintenance doses based on the patient's weight and as per the Product Information. Refer to the Product information for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). <i>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).</i> <i>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.</i> <i>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</i></p>
	<p>Prescribing Instructions: <i>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.</i></p>
	<p><i>The authority application must be in writing and must include all of the following:</i> <i>(1) A completed authority prescription form(s);</i> <i>(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);</i> <i>(3) The baseline MG-ADL profile score</i></p>

Public Summary Document - July 2024 PBAC meeting

	<p>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</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>NOTE: <i>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) can be calculated here [sponsor advised: Muppidi 2022 available at https://onlinelibrary.wiley.com/doi/10.1002/mus.22140]. The MG-ADL scale assesses the impact of MG on daily functions, based on the patient's recall of symptoms during the prior week. The MG-ADL is an eight-item patient-reported outcome measure assessing symptom severity, with each response graded from 0 (normal) to 3 (most severe). The eight components are: talking; chewing; swallowing; breathing; impairment of ability to brush teeth or comb hair; impairment of ability to arise from a chair; double vision; and eyelid droop. MG-ADL Items are linearly scored and not weighted. Cumulative MG-ADL scores range from 0 to 24, with higher scores indicating greater severity. Document the MG-ADL in the patient's medical records.</i></p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. 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
Restriction Summary / Treatment of Concept:					
	Category / Program: Section 100 – Highly Specialised Drugs Program				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate assessment by Services Australia				
	Caution: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.				
	Episodicity: blank				
	Severity: blank				
	Condition: generalised myasthenia gravis (gMG)				
	Indication: generalised myasthenia gravis (gMG)				
	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 up to 24 weeks treatment under this restriction				
	AND				

Public Summary Document - July 2024 PBAC meeting

	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.
	AND
	Population criteria:
	Patients must be aged 18 years or older
	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate number of vials to cover 3 maintenance doses based on the patient's weight and as per the Product Information. Refer to the Product information 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.
	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 / Treatment of Concept:	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)
	Caution: C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
	Episodicity: blank
	Severity: blank
	Condition: generalised myasthenia gravis (gMG)
	Indication: generalised myasthenia gravis (gMG)
	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 continue to demonstrated a clinical improvement based on a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 2 points from baseline.
	AND
	Clinical criteria:
	Patients who are clinically stable should be considered for a trial of cessation of therapy to identify disease remission.
	AND
	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 a non-specialist medical physician who has consulted a neurologist on the patient's drug treatment details

Public Summary Document - July 2024 PBAC meeting

	<i>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.</i>
	AND
	Population criteria:
	Patients must be aged 18 years or older
	Prescriber instructions: <i>Patients who are clinically stable should be considered for a trial of cessation of therapy to identify disease remission.</i>
	<i>The authority application must be in writing and must include all of the following:</i> <i>(1) A completed authority prescription form(s);</i> <i>(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);</i> <i>(3) The current MG-ADL profile score</i>
	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
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	NOTE: <i>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) can be calculated here [sponsor to advise]. The MG-ADL is an eight-item patient-reported outcome measure assessing symptom severity, with each response graded from 0 (normal) to 3 (most severe). The eight components are: talking; chewing; swallowing; breathing; impairment of ability to brush teeth or comb hair; impairment of ability to arise from a chair; double vision; and eyelid droop. Cumulative MG-ADL scores range from 0 to 24, with higher scores indicating greater severity.</i> <i>Document the MG-ADL in the patient's medical records.</i>
Restriction Summary / Treatment of Concept:	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart; requires at least one concept ID to be marked as 'FULL' for full assessment by Services Australia)
	Caution: <i>C5 inhibitors increase the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.</i>
	Episodicity: blank
	Severity: blank
	Condition: generalised myasthenia gravis (gMG)
	Indication: generalised myasthenia gravis (gMG)
	Treatment phase: Transition from non-PBS subsidised to PBS subsidised treatment (grandfather)
	Clinical criteria:

Public Summary Document - July 2024 PBAC meeting

	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior [date of PBS listing]
	AND
	Clinical criteria:
	Patient must have a diagnosis of generalised myasthenia gravis <i>that is not pure ocular myasthenia gravis made by or in consultation with a neurologist.</i>
	AND
	Clinical criteria:
	The condition must not be pure ocular myasthenia gravis
	AND
	Clinical criteria:
	Patient must have been confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (anti-AChR antibodies)
	AND
	Clinical criteria:
	Patient must have recorded baseline symptoms consistent with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 6 points despite treatment with standard therapy prior to initiation of ravulizumab.
	AND
	Clinical criteria:
	Patient must have continue to demonstrated a clinical improvement based on a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 2 points from baseline <i>after 26 weeks of treatment.</i>
	AND
	Treatment criteria:
	Must be treated by a neurologist, or a non-specialist medical physician who has consulted a neurologist on the patient's drug treatment details
	<i>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.</i>
	AND
	Population criteria:
	Patients must be aged 18 years or older
	Prescribing Instructions: Standard therapy is defined as any of: pyridostigmine, oral corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclosporin.
	Prescribing Instructions: At the time of the authority application, medical practitioners should request the appropriate number of vials to cover 3 maintenance doses based on the patient's weight and as per the Product Information. Refer to the Product information for patient weight ranges for the 100mg/mL doses (consisting of 300 mg in 3 mL and 1.1 g in 11 mL vials). <i>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</i>
	<i>The authority application must be in writing and must include all of the following:</i> (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); (3) The baseline MG-ADL profile score (4) The current MG-ADL profile score

Public Summary Document - July 2024 PBAC meeting

	<p>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</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>NOTE: <i>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) can be calculated here [sponsor to advise]. The MG-ADL is an eight-item patient-reported outcome measure assessing symptom severity, with each response graded from 0 (normal) to 3 (most severe). The eight components are: talking; chewing; swallowing; breathing; impairment of ability to brush teeth or comb hair; impairment of ability to arise from a chair; double vision; and eyelid droop. Cumulative MG-ADL scores range from 0 to 24, with higher scores indicating greater severity. Document the MG-ADL in the patient's medical records.</i></p>

- 3.2 The ESC noted that the proposed restriction would allow ravulizumab to be used in any combination with standard therapy at any place in therapy (including the first- and second-line settings and the treatment-refractory setting), which is considerably broader than the requested place in therapy and the setting in which the submission's model assessed cost-effectiveness (refer to Paragraphs 4.14 and 6.42, respectively). Overall, the ESC considered that the intended place in therapy was highly uncertain and required substantial additional clinical input, which would be required to further inform the restriction. Subsequent to ESC consideration of this submission, a stakeholder meeting was held to discuss the clinical management of gMG and the role of new treatments (refer to paragraphs 2.3 and 2.4).
- 3.3 The pre-PBAC response proposed amending the requested initial restriction to clarify that ravulizumab should be used as add-on to immunosuppressive therapy (i.e. to require that the patient must have an MG-ADL score of ≥ 6 points despite at least one 'immunosuppressive therapy', rather than despite 'standard therapy').

Instrument to determine eligibility (MG-ADL versus MGC)

- 3.4 The proposed restriction uses the Myasthenia Gravis Activities of Daily Living instrument (MG-ADL) to determine eligibility for treatment initiation and continuation, consistent with key clinical trial data. The MG-ADL instrument is an 8-item assessment tool capturing patient-reported outcomes of functional disability related to different domains including ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items). Each item is scored on a 0-4 scale, with a total score ranging from 0 to 24, where lower scores indicate better functional outcomes. The submission claimed the instrument would be easy to administer in clinical practice and would be consistent with the key clinical data. The

- ESC noted that a 2-point change in the MG-ADL scale is considered clinically meaningful.¹
- 3.5 The National Blood Authority (NBA) listing of chronic IVIg for myasthenia gravis uses a different instrument, the Myasthenia Gravis Composite (MGC) score, to determine treatment initiation and continuation. The MGC instrument is a 10-item assessment tool capturing both patient-reported outcomes and physician assessments of impairment to different domains including ocular (2 items), bulbar (3 items), respiratory (1 item) and generalised (4 items). Each item is scored on an ordinal scale with 4 possible categories (variable scores between items), with a total score ranging from 0 to 50, where lower scores indicate better functional outcomes. The ESC noted that a 3-point change in the MGC scale is considered clinically meaningful.¹
- 3.6 Data from the MGBase registry presented with the submission suggest that the MGC instrument is more commonly used than the MG-ADL instrument in Australian clinical practice.
- 3.7 The Pre-Sub-Committee Response (PSCR) re-iterated the submission's view that the MG-ADL instrument should be used in the PBS restriction, stating "the construct validity, responsiveness to clinical improvement, simplicity, and ease-of-use of the MG-ADL are attractive attributes for use in the clinic and in clinical trials." However, the ESC considered it would be more appropriate for the PBS restriction to be based on the MGC score as: (a) it would be consistent with the NBA criteria for IVIg; (b) MGC appears to be more commonly used in clinical practice; and (c) MGC includes elements of both physician and patient assessment.
- 3.8 The PSCR stated that the MG-ADL is strongly correlated with the MGC ($r = 0.85$, $P < 0.001$),² where a score greater than 0.81 indicates almost perfect agreement. However, the ESC noted that a recent publication using data from a Phase II trial of rozanolixizumab reported a much lower correlation ($r = 0.57$; 95% CI 0.32, 0.74) between these instruments.³
- 3.9 The pre-PBAC response reiterated the appropriateness of the MG-ADL instrument for inclusion in the restriction, stating the 'construct validity, responsiveness to clinical improvement, simplicity, and ease-of-use of the MG-ADL are attractive attributes for use in the clinic' and that the CHAMPION-MG study was powered for the change in MG-ADL score (which was the primary endpoint). Further, the pre-PBAC response stated that 'at the Myasthenia Gravis Stakeholder meeting, the MG-ADL was considered an appropriate assessment tool for a robust, yet wholistic reflection of the disease state'.

¹ Thomsen JLS, Andersen H. Outcome Measures in Clinical Trials of Patients With Myasthenia Gravis. *Front Neurol.* 2020 Dec 23;11:596382. doi: 10.3389/fneur.2020.596382. PMID: 33424747; PMCID: PMC7793650

² Muppidi, S., G. I. Wolfe, M. Conaway, T. M. Burns, C. Mg and G. Mg-Qol15 Study (2011). "MG-ADL: still a relevant outcome measure." *Muscle Nerve* 44(5): 727-731.

³ Regnault A, et al. Measuring Overall Severity of Myasthenia Gravis (MG): Evidence for the Added Value of the MG Symptoms PRO. *Neurol Ther.* 2023 Oct;12(5):1573-1590. doi: 10.1007/s40120-023-00464-x.

Continuation and cessation criteria

- 3.10 The submission stated that the proposed continuation criterion (≥ 2 -point reduction in MG-ADL score) was based on the minimal clinically important difference for this instrument. However, the key clinical trial indicated that a similar proportion of patients in both treatment arms achieved this outcome, with no statistically significant difference between ravulizumab and placebo (63.9% versus 53.0% at Week 26; nominal p-value = 0.1621). Therefore, the evaluation considered that it may be appropriate to consider more stringent criteria to assess treatment response. Further, the ESC considered that the scoring instrument was subjective, which is particularly concerning in the context of determining eligibility for continuing treatment, given it may increase the risk of leakage outside the intended restriction. Further, given the placebo response rate, it will be difficult in clinical practice to attribute functional improvements to ravulizumab over continuing treatment with standard therapy.
- 3.11 The proposed restriction stated “patients who are clinically stable should be considered for a trial of cessation of therapy to identify disease remission”. The wording of this criterion is ambiguous as it does not mandate cessation nor provide sufficient detail on when and how stable disease should be assessed. In contrast, the economic model and financial estimates assumed that all patients using ravulizumab for two years will achieve disease remission and cease ravulizumab treatment, despite the lack of data regarding the optimal duration of ravulizumab for generalised myasthenia gravis, with the available clinical data limited to 60 weeks of ongoing therapy. The ESC considered that, if ravulizumab is intended to be ceased after two years of therapy, then this must be clearly articulated in the restriction. However, even with clear discontinuation requirements, the ESC considered that it would be unlikely that all patients would cease ravulizumab after two years, unless the restriction was strictly time limited.
- 3.12 The clinicians present at the stakeholder meeting outlined potential stopping rules for newer agents when used early in disease (refer to paragraph 2.4) The pre-PBAC response stated that it expected the average time on treatment with ravulizumab to be two years, and stated that work would be required to define appropriate criteria such as recommencement provisions and that patients with more severe symptoms should be considered for a longer time on treatment.
- 3.13 The requested restriction does not prevent patients who discontinue ravulizumab from re-starting therapy. This is consistent with the product information which states that ravulizumab can be restarted if symptoms occur after discontinuation. However, the proposed restriction is inconsistent with the economic analysis which assumed that patients treated with ravulizumab who relapsed after achieving remission would move onto other treatment options. The PSCR argued that it would be unlikely for patients to recommence ravulizumab as the “small proportion of patients” who respond to ravulizumab but later become symptomatic would use therapies such as IVIg, but argued that the selection of therapy in this instance should be reserved for clinician discretion. The ESC felt that patients who responded to ravulizumab but then

stopped it and subsequently relapsed, would be highly likely to recommence ravulizumab.

- 3.14 The submission proposed a grandfathering restriction and predicted that approximately < 500 patients would receive ravulizumab under the sponsor's familiarisation program and < 500 of these patients would achieve a response and be eligible for treatment under the grandfathering restriction.

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

4 Population and disease

- 4.1 Myasthenia gravis is a chronic autoimmune disorder caused by antibodies attacking components of the neuromuscular junction leading to impaired signal transmission between nerves and muscles. Patients can be classified into subgroups based on the antibodies involved, with the majority of patients (approximately 80%) having autoantibodies against acetylcholine receptors (AChR).
- 4.2 Myasthenia gravis can develop at any age (including childhood) but more commonly impacts young adult women (under 40) and older men (over 60). The worldwide prevalence of myasthenia gravis ranges from approximately 15 to 20 patients per 100,000 population. An analysis conducted for the submission indicated an annual incidence of 5 patients per 100,000 population and a prevalence of 20 patients per 100,000 population in Australia.
- 4.3 Myasthenia gravis is characterised by muscle weakness which may be localised to ocular muscles (ocular myasthenia gravis) or generalised to include other muscles such as limbs, bulbar and respiratory system (generalised myasthenia gravis). Typical symptoms associated with myasthenia gravis include drooping eyelids, blurred or double vision, shortness of breath, difficulty chewing and swallowing, impaired speech, fatigue, pain, muscle spasms and general muscle weakness.
- 4.4 The intensity of muscle weakness can fluctuate from day to day and can be worsened due to fatigue, stress, current illness and other factors. Transient periods of rapid symptom worsening are referred to as disease exacerbations. Of particular concern, are myasthenic crises which are severe, life-threatening exacerbations that are due to weakness in respiratory muscles which results in respiratory failure requiring mechanical ventilation. However, the submission noted that the mortality of patients with myasthenia gravis has decreased over the years and most patients have a normal lifespan.
- 4.5 Patient perspectives included in the submission indicate that myasthenia gravis has substantial impacts on activities of daily living, quality of life, workplace participation and carer burden. Impacts on physical functioning included an inability to participate in hobbies/sports, need for increased planning, and difficulties performing activities of daily living such as personal hygiene, cooking and driving. Many patients also reported emotional/social impacts including anxiety, fear, depression, frustration,

embarrassment and feeling misunderstood. The submission highlighted that the treatments used to manage this condition may also have substantial negative impacts to patients, particularly the side-effects associated with the use of chronic corticosteroids.

4.6 Current treatment guidelines for AchR positive generalised myasthenia gravis recommend the use of:

- anti-cholinesterases i.e. pyridostigmine. While pyridostigmine has a rapid onset of action, its efficacy commonly decreases over time.
- immunosuppressive therapy, with corticosteroids used as the main first-line treatment option. The guidelines state that other immunosuppressive agents (e.g. mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclosporin) may also be used as monotherapies (for patients who refuse corticosteroids or who are contraindicated to corticosteroids) or in combination with corticosteroids (for patients with an inadequate response, for patients with significant steroid side-effects or who require high corticosteroid doses that cannot be tapered down). The PSCR stated that symptom control with immunosuppressive therapies can take 18 to 24 months for optimisation (refer to Paragraph 4.11) without providing adequate supportive evidence for this claim. Further the ESC noted that response to immunosuppressive therapies often occurs earlier than this in clinical practice e.g. typically within six months of therapy.
- chronic plasma exchange (PLEX) and chronic intravenous immunoglobulin (IVIg) can be used (a) as bridging therapies while patients adjust to other slower-acting immunosuppressive agents; and/or (b) in patients with treatment-refractory disease (variable definitions in the literature). The ESC noted that IVIg is funded by the NBA for the indication: As maintenance therapy for moderate to severe myasthenia gravis when other treatments have been ineffective or caused intolerable side effects. The NBA criteria for IVIg requires (a) a patient to have a MGC score ≥ 4 points; and (b) ≥ 2 other treatments to have been ineffective, contra-indicated, unavailable or caused intolerable side effects. The NBA criteria state 'IVIg should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy' and requires evidence of response for ongoing therapy after 4 months and then annually thereafter.⁴
- Patients with refractory disease can receive treatment with chronic PLEX/IVIg, eculizumab (not registered in Australia for myasthenia gravis), cyclophosphamide or rituximab.

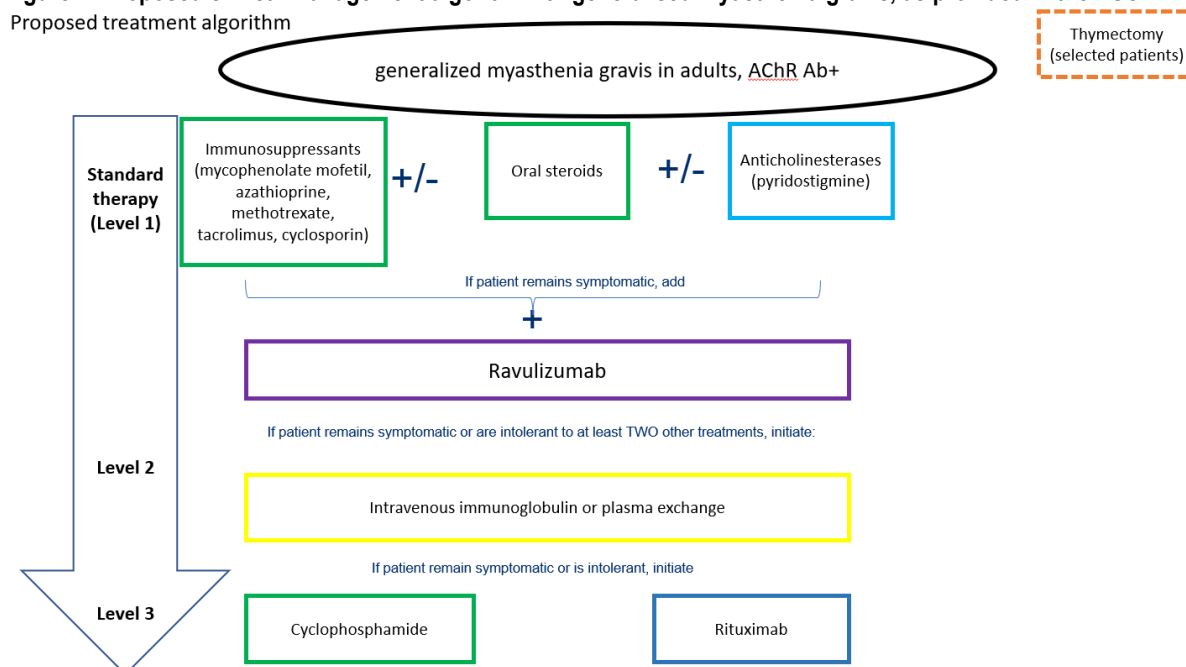
⁴ <https://www.criteria.blood.gov.au/MedicalCondition/View/2681>

- Acute management of exacerbations typically involves the use of high dose corticosteroids, IVIg or PLEX in the community or hospital setting depending on severity.
- Thymectomy can be considered in a small subset of patients, particularly younger patients.

4.7 The PSCR stated “the goal of treatment is to reduce or eliminate symptoms and functional limitations, while avoiding treatment side effects and, importantly, minimising myasthenic exacerbation (clinical deterioration of myasthenia gravis symptoms) and myasthenic crisis where intubation/mechanical ventilation is necessary”.

4.8 Figure 1 presents the proposed clinical algorithm provided in the PSCR.

Figure 1: Proposed clinical management algorithm for generalised myasthenia gravis, as provided in the PSCR



Source: PSCR Figure 1, p5.

*Note: Treatment with ravulizumab is expected to occur for an average of 2 years to allow time for the onset of effect from immunosuppression therapies (noting the fast onset of action with ravulizumab and that symptom control with ISTs can take 18 to 24 months for optimisation)

4.9 The evaluation considered that the inclusion of anticholinesterases, corticosteroids and immunosuppressive therapies in a single line of therapy was not adequately justified given that these therapies are typically used in a stepwise manner. Additionally, the separation of therapies for treatment-refractory disease into two lines of therapy was not adequately justified as there is no established treatment sequencing for these patients.

4.10 The PSCR stated the intended place in therapy for ravulizumab was as an add-on therapy in patients currently treated with at least one standard therapy whilst

symptoms persist. It further stated that ravulizumab is intended as a bridging therapy (with an average treatment duration of two years) that can be used ‘early and upfront’ for symptom reduction until immunosuppressive therapies can achieve optimal control.

- 4.11 With regard to the proposed duration of ravulizumab treatment of two years, the PSCR stated that generalised myasthenia gravis “reaches maximum, or near maximum, severity in the first two years after onset of symptoms... Generalised myasthenia gravis is not a progressive disease, and the stepwise approach to current therapies is driven by safety concerns and symptom control relating to those therapies rather than disease progression. Patients generally require some level of immunosuppression for many years, but achieving the balance of appropriate immunosuppression with acceptable safety is challenging and slow – on average taking 18-24 months”.
- 4.12 The PSCR stated that symptom control with immunosuppressive therapies can take 18 to 24 months for optimisation, while ravulizumab has a fast onset of action. However, the ESC considered this claim was inadequately justified and noted that response to immunosuppressive therapies often occurs earlier than this in clinical practice e.g. typically within six months of therapy.
- 4.13 The evaluation considered that the appropriate clinical place in therapy for ravulizumab was unclear, noting ravulizumab (and other similar agents for the treatment of myasthenia gravis) is yet to be incorporated into recognised treatment guidelines. Further, the ESC considered the clinical place outlined in the PSCR may be inappropriately broad particularly given the risk-benefit profile of ravulizumab in this condition (i.e. as outlined in Paragraph 6.34).
- 4.14 The ESC considered there were additional issues with the place in therapy proposed in the PSCR including:
- it did not align with the proposed restriction, which is substantially broader as it allowed ravulizumab to be used in any combination with standard therapy at any place in therapy. While the pre-PBAC response proposed an amendment to the requested restriction to require patients to have an MG-ADL score of ≥ 6 points despite at least one immunosuppressive therapy, the PBAC noted the proposed restriction did not specify a timeframe for assessing response to optimised immunosuppressive therapy prior to commencing ravulizumab.
 - it was inconsistent with the clinical data provided. Patients in CHAMPION-MG trial had a mean time since diagnosis of 9.9 years (median 6.5 years), with many patients having extensive treatment histories; and therefore trial participants are unlikely to be representative of newly diagnosed patients. This extensive pre-trial burden of disease in CHAMPION-MG is at odds with the PSCR claim that most patients stop progression after 2 years. Additionally, the CHAMPION-MG trial and extension were designed to assess the use of ravulizumab as an ongoing maintenance therapy rather than a bridging therapy, and the trial protocol did not

require the optimisation of background therapies over the course of the trial (changes to immunosuppressive therapy occurred in 24% of trial participants but most of these changes related to the use of rescue medications or were not clinically significant).

- it would be difficult to differentiate the contribution of each agent (ravulizumab versus immunosuppressive therapy) to response.
- it was inconsistent with the economic analysis presented in the submission (refer to Paragraph 6.42).

4.15 The ESC considered there are some patients who do not achieve adequate symptom control with any standard treatment and there is a high unmet need for effective therapies in this group of patients. However, the ESC considered:

- there was a lack of evidence specifically in this patient group, given the broad inclusion criteria of the pivotal trial.
- this place in therapy may overlap with the current use of chronic IVIg and PLEX. However, the ESC considered that the advantages of ravulizumab versus IVIg were unclear as both have a fast onset of action, while ravulizumab is associated with a risk of infection including meningococcal infection. The pre-PBAC response stated that IVIg has a demanding dosing schedule, has no clear benefit at six months, can be difficult to access and is associated with adverse events. Further, the pre-PBAC response stated PLEX is very intensive to administer and is only available in a limited number of outpatient clinics in Australia.

4.16 The pre-PBAC response re-iterated that ravulizumab should be added to immunosuppressive therapies early in the treatment algorithm, prior to consideration of chronic IVIg. While the pre-PBAC response acknowledged that the majority of patients achieve remission with standard therapy (i.e. pyridostigmine and/or corticosteroids and/or non-steroid immunosuppressants), it argued that some patients require high doses of corticosteroids, and the full effect of non-steroid immunosuppressive therapies may take up to approximately two years to manifest.

4.17 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 (potentially by reducing membrane attack complex-mediated destruction of the neuromuscular junction) although the exact mechanism of action in generalised myasthenia gravis is currently unknown.

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

5 Comparator

5.1 The submission nominated standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil,

azathioprine, methotrexate, tacrolimus, cyclosporin) as the main comparator. The main argument provided in support of this nomination was that ravulizumab will be used as an add-on therapy that would not directly substitute for any of the currently used therapies for myasthenia gravis.

- 5.2 The evaluation considered that the claim that ravulizumab would not substitute for existing therapies was inadequately supported. The PBS restriction proposed in the submission did not specify lines of therapy and allows use of ravulizumab in any combination with standard therapy at any point of the treatment pathway (including for first- or second-line therapy or for treatment-refractory patients). The evaluation and the ESC considered that, in each of these settings, ravulizumab as an add-on therapy would displace existing treatment options which should therefore be considered as treatment comparators including existing immunosuppressive therapies, chronic PLEX/IVIg, rituximab and cyclophosphamide.
- 5.3 The PSCR acknowledged that use of ravulizumab may displace downstream therapies (e.g. patients may no longer require subsequent treatments such as IVIg), but argued these treatments represent different “levels of therapy” and would not directly substitute for ravulizumab. The ESC considered that, while ravulizumab may delay (rather than replace) existing therapies, the appropriate comparator would be contingent on the clinical place of ravulizumab in therapy.
- 5.4 The pre-PBAC response reiterated that the intended place in therapy for ravulizumab was prior to consideration of chronic IVIg. However, the PBAC noted that the proposed restriction would also enable use of ravulizumab in later lines of therapies, including in those patients who would otherwise be treated with chronic IVIg/PLEX.
- 5.5 The submission also identified a number of newer therapies for myasthenia gravis including zilucoplan (FDA and EMA approved, under TGA review), efgartigimod (FDA and EMA approved) and rozanolixizumab (FDA and EMA approved) but argued that these treatments were not near-market comparators as their timeframe for marketing approval in Australia was unknown. However, the evaluation and the ESC considered these therapies may be considered potential near-market comparators and may help inform the clinical place for new gMG treatment options.

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 outlined that there is a significant unmet need for effective therapies for gMG, particularly therapies that have a fast onset of action. The clinician described that gMG is best treated with upfront combination therapy because the autoimmune aspect of the disease is slow to respond to remission-inducing therapies. The alternatives such as high dose steroids and IVIg have substantial adverse effects. Further, the benefits of IVIg are

heterogenous with no clear benefit after six months. The clinician noted that complement inhibitors such as ravulizumab offer advantages compared to IVIg, such as a shorter infusion time. Only a small number of hospitals in Australia provide PLEX as an outpatient therapy, and thus it is inaccessible to around 90% of people.

- 6.2 The clinician outlined that the ideal place in therapy for ravulizumab is as a first-line combination therapy, as an alternative to IVIg, although IVIg is likely to be tried first in the majority of cases. The clinician expected the average treatment length for ravulizumab would be one to two years, although some patients would use it for longer.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (36), health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the significant impact that gMG can have on quality of life such as an inability to: perform daily tasks; work; study; drive; or participate in social activities. Patients outlined that the fluctuating nature of gMG can create uncertainty. The comments noted that existing treatment options can be ineffective or have significant adverse events including the potential for osteoporosis, diabetes, hypertension and weight gain with corticosteroids. The comments also highlighted that there are some patients who are unable to tolerate high doses of corticosteroids or in whom corticosteroids are contraindicated.
- 6.4 The comments described a range of potential benefits of ravulizumab compared to IVIg and PLEX, in terms of ease of administration. Input discussed that IVIg and PLEX are very intensive, for example IVIg administration can require half-day hospital attendance every few weeks (or more frequently), with the potential for adverse events such as headaches and fevers. Input outlined the benefits of a treatment that is accessible at a local health facility, especially for those who live in rural or remote areas.
- 6.5 The comments discussed a range of potential benefits of ravulizumab including an improvement in symptoms such as fatigue, swallowing, speech, eye droop and vision problems. The comments also noted the need for other treatment options in the long-term, since ravulizumab is not a remission-inducing therapy.
- 6.6 The PBAC noted the advice received from Myasthenia Alliance Australia (MAA) which outlined the results of a recent online survey that was conducted. Forty-four percent of the 194 respondents indicated their current treatment regimen was not keeping them stable or allowing them to undertake daily activities including family and work commitments. MAA stated that, from the patient perspective, the benefits of ravulizumab outweigh the disadvantages.
- 6.7 The PBAC also noted the advice received from Myasthenia Gravis Association of Queensland noting the increasing prevalence of gMG and thus the increasing burden of disease. The comments highlighted the debilitating nature of gMG, the barriers to

accessing current therapies and the substantial out-of-pocket costs associated with gMG in the context of a reduced capacity to work.

Clinical studies

6.8 The submission was based on one head-to-head randomised trial comparing ravulizumab to placebo in patients with generalised myasthenia gravis (CHAMPION-MG). The submission also presented an interim analysis from an open-label extension study of patients previously enrolled in the CHAMPION-MG trial as supportive data.

6.9 Details of the included studies are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ALXN1210-MG-306 (CHAMPION-MG)	Alexion (2021). A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab in complement-inhibitor-naïve adult patients with generalized myasthenia gravis.	Internal study report
	Alexion (2022). A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab in complement-inhibitor-naïve adult patients with generalized myasthenia gravis. Clinical study report addendum (60-week data).	Internal study report
	Vu et al (2022). Terminal complement inhibitor ravulizumab in generalized myasthenia gravis.	New England Journal of Medicine Evidence 1(5)
	Vu et al (2023). Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis	Journal of Neurology 270: 3129-3137
	Meisel et al (2023). Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension	Journal of Neurology 270: 3862-3875

Source: Table 2-3, p56 of the submission

Note: Abstracts of studies with full publications are not presented

6.10 The key features of the CHAMPION-MG trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ravulizumab vs. placebo						
CHAMPION-MG	175	MC, R, DB, PC, 26 weeks duration with open-label extension to 60 weeks	Low ^a	AchR+ generalised myasthenia gravis with functional impairment (MG-ADL \geq 6) with stable background therapy	Primary: Change in MG-ADL score. Other outcomes: Change in other functional measures (MGC, QMG), global assessments (MGFA-PIS), quality of life (EQ-5D-5L, MG-QoL15r, Neuro-QoL Fatigue) and incidence of clinical deterioration events.	Baseline characteristics, treatment response, treatment discontinuations, adverse events, clinical events, and utility values for clinical events and health states

Source: Source: Table 2-4, p59; Section 2.4, pp64-77 of the submission.

Abbreviations: AchR+, anti-acetylcholine receptor antibody positive; DB, double-blind; MC, multicentre; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, myasthenia gravis composite score; MGFA-PIS, modified Myasthenia Gravis Foundation of America Post-Intervention Status; MG-QoL15r, revised Myasthenia Gravis Quality of Life; Neuro-QoL Fatigue, Quality of Life in Neurological Disorders Fatigue subscale; PC, placebo-controlled; QMG, Quantitative Myasthenia Gravis score; R, randomised.

^a The CHAMPION-MG trial had a low risk of bias. However, 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.

6.11 The ESC noted that the inclusion criteria for the CHAMPION-MG trial encompassed a broad patient population with mild to severe symptoms, however a relatively treatment-experienced and potentially treatment refractory population were enrolled as indicated by a mean time since diagnosis of 9.9 years (refer to Paragraph 4.14). The ESC considered this may have been indicative of a large incident population seeking alternative treatment options. The trial did not require any specific prior therapies or optimisation of current therapies, with 10.3% of patients not on immunosuppressive therapies at baseline. The ESC felt that the trial population was not reflective of the eligible population under the proposed restriction.

Comparative effectiveness

6.12 The mean change in functional outcome measures from baseline to Week 26 with ravulizumab and placebo in the CHAMPION-MG trial are summarised in Table 4.

Table 4: Mean change in functional outcome measures from baseline to Week 26 with ravulizumab and placebo

Treatment arm	Baseline, Mean (SD)	Final, Mean (SD)	LS mean change (95% CI)	Treatment difference (95% CI)
Myasthenia Gravis Activities of Daily Living (MG-ADL) score [primary outcome]				
Ravulizumab N = 78	9.2 (2.63)	5.9 (4.00)	-3.1 (-3.8, -2.3)	-1.6 (-2.6, -0.7)
Placebo N = 82	8.8 (2.07)	7.3 (3.82)	-1.4 (-2.1, -0.7)	
Quantitative Myasthenia Gravis (QMG) score				
Ravulizumab N = 76	14.8 (5.22)	11.6 (6.16)	-2.8 (-3.7, -1.9)	-2.0 (-3.2, -0.8)
Placebo N = 78	14.1 (5.03)	13.3 (5.63)	-0.8 (-0.7, 0.1)	
Myasthenia Gravis Composite (MGC) score				
Ravulizumab N = 77	16.6 (6.70)	9.7 (7.41)	-6.1 (-7.6, -4.7)	-2.9 (-4.8, -1.1) ^a
Placebo N = 81	16.4 (4.95)	12.7 (7.14)	-3.2 (-4.6, -1.8)	

Source: Table 2-18, p78; Table 2-20, p82 of the submission; Table 14.2.1.1.15.1, pp719-721; Table 14.2.2.1.1.11.1, pp771-773; Table 14.2.3.1.1.1, p1025; Table 14.2.3.1.3.1, pp1029-1031 of the CHAMPION-MG trial report

Abbreviations: CI, confidence interval; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, myasthenia gravis composite score; QMG, Quantitative Myasthenia Gravis score; SD, standard deviation

^a Change in MGC score was an exploratory outcome with no adjustment for multiplicity and therefore no further inference on statistical significance should be made for this outcome

Note: MG-ADL scores range from 0 to 24 with lower scores indicating better functional outcomes

Note: QMG scores range from 0 to 39 with lower scores indicating better functional outcomes

Note: MGC scores range from 0 to 50 with lower scores indicating better functional outcomes

6.13 Treatment with ravulizumab was associated with modest but statistically significant improvements in functional outcome measures compared to placebo over 26 weeks. Differences between treatment arms were observed by Week 1 and were maintained over the 26-week randomised treatment period. The ESC considered that, while the primary outcome was statistically significant (mean difference in the MG-ADL score of -1.6 (95% CI: -2.6, -0.7)), the clinical relevance of this to individual patients was unclear as it failed to meet the MCID, recognising that some patients would have surpassed the MCID. The ESC reflected that this represented a considerable heterogeneity in effect and reinforced that the population most likely to benefit was not adequately identified. The pre-PBAC response stated that using the MCID in isolation to interpret average changes between groups does not provide the full context and that responder analyses using these thresholds provides context as to the clinical relevance of the treatment effect.

6.14 A substantial proportion of patients in both treatment arms reported changes in MG-ADL scores from baseline that met the nominated minimal clinically important difference, as shown in Table 7, a 2-point reduction was achieved by 63.9% of ravulizumab patients and 53.0% of placebo patients; nominal p-value = 0.1621. The ESC noted the proportion of patients achieving this outcome was similar between arms and the difference was not statistically significant. The ESC considered the benefit of ravulizumab demonstrated in the trial appeared to be modest and many patients (36.1%) who would be eligible under the restriction will fail to meet the

nominated MCID and very few additional patients (10.9%) would achieve the MCID compared to current therapies.

- 6.15 Data from the ongoing extension study suggest that the improvement in functional measures observed with ravulizumab treatment may be sustained over the longer term, with follow-up data indicating no loss of effect for up to 60 weeks (mean change from baseline to Week 60 in the ravulizumab/ravulizumab arm was -4.0; 95% CI -4.8, -3.1).
- 6.16 Results numerically favoured ravulizumab, particularly when stricter definitions of response were used (3-point reduction achieved by 56.7% of ravulizumab patients and 34.1% of placebo patients; nominal p-value = 0.0049). Treatment with ravulizumab was also associated with a higher proportion of responders compared to placebo based on QMG and MGC scores (see Table 7).
- 6.17 The mean change in quality of life measures from baseline to Week 26 with ravulizumab and placebo in the CHAMPION-MG trial are summarised in Table 5.

Table 5: Mean change in quality of life scores from baseline to Week 26 with ravulizumab and placebo

Treatment arm	Baseline, Mean (SD)	Final, Mean (SD)	LS mean change (95% CI)	Treatment difference (95% CI)
Revised Myasthenia Gravis Quality of Life score (MG-QoL15r)				
Ravulizumab N = 78	15.6 (5.37)	11.8 (7.18)	-3.3 (-4.7, -1.9)	-1.7 (-3.4, 0.1)
Placebo N = 82	16.3 (6.77)	14.1 (7.70)	-1.6 (-3.0, -0.3)	
Quality of Life in Neurological Disorders Fatigue score (Neuro-QoL Fatigue)				
Ravulizumab N = 77	59.0 (12.22)	51.1 (18.30)	-7.0 (-10.7, -3.2)	-2.2 (-6.9, 2.6)
Placebo N = 82	59.9 (18.26)	54.7 (21.10)	-4.8 (-8.5, -1.1)	
EQ-5D-5L visual analogue scale				
Ravulizumab N = 77	60.2 (19.22)	65.0 (21.83)	4.0 (-0.2, 8.2)	1.3 (-4.0, 6.6)
Placebo N = 82	60.6 (18.41)	63.8 (19.43)	2.7 (-1.3, 6.8)	
EQ-5D-5L health state index (US weights)				
Ravulizumab N = 76	0.59 (0.28)	0.67 (0.26)	0.06 (0.01, 0.12)	0.07 (0.00, 0.14)
Placebo N = 82	0.60 (0.30)	0.59 (0.35)	-0.01 (-0.07, 0.04)	

Source: Table 14.2.2.3.1.1.1, p885; Table 14.2.2.3.1.11.1, pp897-898; Table 14.2.2.4.1.1.1, p920; Table 14.2.2.4.1.11.1, pp932-933; Table 14.2.3.3.1.1, p1035; Table 14.2.3.3.3.1, pp1038-1039; Table 14.2.3.3.4.1, p1040; Table 14.2.3.3.6.1, pp1043-1044 of the CHAMPION-MG trial report

Abbreviations: CI, confidence interval; LS, least squares; MG-QoL15r, revised Myasthenia Gravis Quality of Life; Neuro-QoL Fatigue, Quality of Life in Neurological Disorders Fatigue subscale; SD, standard deviation; US, United States

Note: The CHAMPION-MG trial used a hierarchical testing order for outcomes to account for multiplicity of testing (with MG-QoL15r assessed before other quality of life outcomes). As the difference between arms was non-significant for MG-QoL15r, no further inferences should be made for other quality of life outcomes

Note: MG-QoL15r scores range from 0 to 30 with lower scores indicating better quality of life

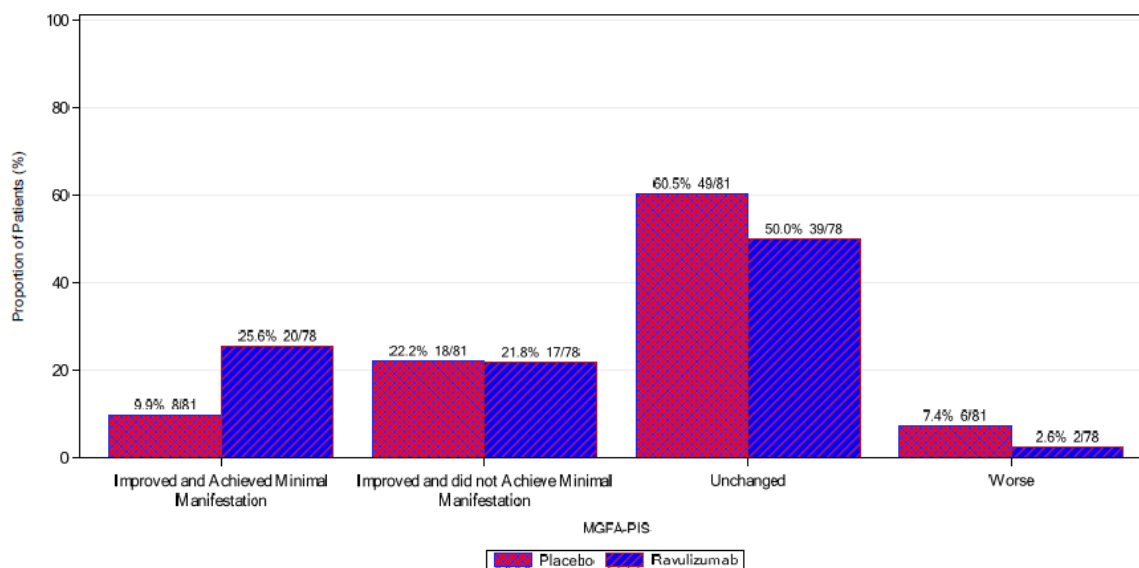
Note: Neuro-QoL Fatigue range from 19 to 95 with lower scores indicating better quality of life

Note: EQ-5D-5L visual analogue scores range from 0 to 100 with higher scores indicating better quality of life

Note: EQ-5D-5L health state index scores range from 0 to 1 with higher scores indicating better quality of life

- 6.18 There were no statistically significant differences in quality of life between treatment arms although results numerically favoured ravulizumab.
- 6.19 The proportion of patients classified with improved, unchanged or worsening disease at 26 weeks compared to their pre-treatment assessment in the CHAMPION-MG trial using the modified Myasthenia Gravis Foundation of America Post-Intervention Status (MGFA-PIS) instrument is summarised in Figure 2.

Figure 2: Proportion of Patients in Each Category of the MGFA-PIS at Week 26



Source: Figure 2-14, p87 of the submission

Abbreviations: MGFA-PIS, modified Myasthenia Gravis Foundation of America Post-Intervention Status

- 6.20 Treatment with ravulizumab was associated with a numerically higher proportion of patients achieving improvement with minimal manifestation (patient has no functional limitations but may have some residual muscle weakness) compared to placebo. More patients in the placebo arm also reported unchanged or worsening disease.
- 6.21 There were no statistically significant differences in clinical deterioration events (significant symptom worsening, use of rescue medication, myasthenic crisis events) between treatment arms although results numerically favoured ravulizumab. The PSCR emphasized the importance of reducing the frequency of exacerbations and myasthenic crises and of improving quality of life, although the clinical trial failed to demonstrate these benefits.
- 6.22 The submission noted that the efficacy of ravulizumab was consistent across pre-specified subgroups including immunosuppressant use at baseline (based on four categories: only corticosteroid; only non-steroid immunosuppressive therapy; corticosteroid + non-steroid immunosuppressive therapy; and none). However, the pre-PBAC response stated the greatest reduction of MG-ADL score was observed when ravulizumab was added early to standard therapy including in patients who had not received prior chronic IVIg/PLEX, referencing 'data on file'. Further, the pre-PBAC

response stated that a *post hoc* subgroup analysis of time from gMG diagnosis (≤ 2 , > 2 years) found a trend toward a greater improvement in MG-ADL in patients who initiated ravulizumab earlier after MG diagnosis compared with later. However, the PBAC noted no treatment interaction testing was presented in the submission and these analyses were not adjusted for multiplicity.

- 6.23 During the evaluation, a recently published network meta-analysis (Sacca 2023) was identified which compared ravulizumab with near-market comparators (zilucoplan, efgartigimod and rozanolixizumab) and other therapies (eculizumab and rituximab) for the treatment of myasthenia gravis.
- 6.24 The complement inhibitor trials (ravulizumab, eculizumab, zilucoplan) generally used similar study designs although there were some differences between trials in baseline disease severity, background therapies and trial durations. However, transitivity between complement inhibitor trials and the other trials was less clear, with major differences in study designs and patient populations. In particular, neonatal Fc receptor blockers (efgartigimod, rozanolixizumab) are administered as cyclical therapies with on/off treatment periods however treatment effects were assessed at their peak efficacy timepoint (4-6 weeks, at the end of a treatment cycle) which does not account for the gradual loss of effect over time in the off-treatment period. Additionally, the rituximab trials allowed for changes in background therapies over time (which is likely to impact the comparative efficacy of treatments) while trials of newer agents typically required patients to remain on stable background therapies.
- 6.25 A simple meta-analysis of trials within each drug class suggested that treatment effects were broadly similar between members of each drug class. The network meta-analysis suggested that neonatal Fc receptor blockers may be slightly more effective than complement inhibitors, while rituximab was the least effective treatment for generalised myasthenia gravis. However, the results of the network meta-analysis should be interpreted with caution given that it is unclear whether trials were sufficiently similar to justify their use in a network meta-analysis.

Comparative harms

- 6.26 An overall summary of the adverse events reported in the CHAMPION-MG trial is presented in Table 6.

Table 6: Summary of key adverse events in the CHAMPION-MG trial

Patients, n (%)	Ravulizumab N = 86	Placebo N = 89
Any adverse event	78 (90.7%)	77 (86.5%)
Treatment-related adverse event	29 (33.7%)	30 (33.7%)
Serious adverse event	20 (23.3%)	14 (15.7%)
Adverse events leading to treatment discontinuation	2 (2.3%)	3 (3.4%)
Deaths	2 (2.3%)	0 (0.0%)
Adverse events of special interest		
Meningococcal infection	0 (0.0%)	0 (0.0%)
Infusion-related reactions	28 (32.6%)	28 (31.5%)
Selected treatment-emergent adverse events		
Infections and infestations	38 (44.2%)	28 (31.5%)
COVID-19	5 (5.8%)	3 (3.4%)
Urinary tract infection	5 (5.8%)	4 (4.5%)
Nasopharyngitis	3 (3.5%)	5 (5.6%)

Source: Table 2-26, p91 of the submission, Table 2-28, pp92-93 of the submission

- 6.27 The most frequently reported adverse events (> 5% of patients) in either treatment arm were COVID-19, urinary tract infection, nasopharyngitis, headache, dizziness, diarrhoea, nausea, abdominal pain, back pain, arthralgia, fatigue and pyrexia.
- 6.28 Treatment with ravulizumab was associated with a higher rate of serious adverse events compared to the placebo arm. The ESC noted ravulizumab was associated with a higher rate of infections and infestations (44.2% versus 31.5% for treatment-emergent adverse events). The ESC considered this was a particular concern in the context of concomitant use of immunosuppressive therapies.
- 6.29 Two serious adverse events were considered related to ravulizumab including one case each of dysphagia and tendonitis. Two patients died in the ravulizumab treatment arm, one due to cerebral haemorrhage and one due to COVID-19 infection.
- 6.30 The 60-week interim analysis of the CHAMPION-MG open-label extension study was suggestive of declining adverse event rates over time and did not identify any additional safety concerns with ravulizumab treatment.

Benefits/harms

- 6.31 A summary of the comparative benefits and harms for ravulizumab versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits and harms for ravulizumab and placebo

Subgroup	Ravulizumab	Placebo	Treatment difference
Proportion of patients with ≥ 2-point reduction in MG-ADL scores from baseline to Week 26	63.9%	53.0%	10.9%
Proportion of patients with ≥ 3-point reduction in MG-ADL scores from baseline to Week 26	56.7%	34.1%	22.6%
Proportion of patients with ≥ 3-point reduction in QMG scores from baseline to Week 26	44.8%	24.2%	20.6%
Proportion of patients with ≥ 5-point reduction in QMG scores from baseline to Week 26	30.0%	11.3%	18.7%
Proportion of patients with ≥ 3-point reduction in MGC scores from baseline to Week 26	71.1%	50.3%	20.8%
Proportion of patients with serious adverse events	23.3%	15.7%	7.6%
Proportion of patients with a treatment-emergent infection	44.2%	31.5%	12.7%

Source: Figure 2-10, p83; Section 2.5.1.2.4, p84; Table 2-21, p85; Table 2-26, p91; Table 2-28, pp92-93 of the submission
 Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, myasthenia gravis composite score; QMG, Quantitative Myasthenia Gravis score

Note: All changes in functional measures met or exceed the nominated minimal clinically important difference for each outcome (MCID for MG-ADL ≥ 2 point reduction; MCID for QMG ≥ 3 point reduction; MCID for MGC ≥ 3 point reduction). The proportion of patients with ≥ 3 point reduction in MG-ADL and the proportion of patients with ≥ 5 point reduction in QMG were key secondary outcomes of the CHAMPION-MG trial. The other thresholds were reported as exploratory outcomes.

6.32 On the basis of direct evidence presented in the submission, for every 100 patients treated with ravulizumab in comparison with placebo for 26 weeks:

- Approximately 11 additional patients would experience a clinically important improvement in functional outcomes (> 2-point reduction in MG-ADL scores).
- Approximately 8 additional patients would experience a serious adverse event.
- Approximately 13 additional patients would experience an infection (treatment-emergent).

Clinical claim

6.33 The submission described ravulizumab in combination with standard therapy as superior in terms of efficacy and inferior in terms of safety compared to placebo in combination with standard therapy. The evaluation and the ESC considered that, while this claim was reasonable:

- The ESC noted that a similar proportion of patients in both treatment arms achieved a ≥ 2-point reduction in MG-ADL scores from baseline to Week 26, with no statistically significant difference between ravulizumab and placebo (63.9% versus 53.0% at Week 26; nominal p-value = 0.1621). The ESC considered that the benefit of ravulizumab versus placebo was modest and the clinical meaningfulness to the proposed PBS population was unclear.
- The ESC considered that the placebo response rates were high which may have been due to: disease variability; the potentially subjective nature of the instruments used to assess response; and patients in the placebo arm continuing to receive active background therapy.

- The ESC noted the inferior safety of ravulizumab versus placebo, particularly the potential for serious infections and the known risk of *Neisseria meningitidis*.
- 6.34 Overall, the ESC considered that, given the availability of effective therapies for many patients, the modest treatment benefit shown in the key trial and the inferior safety (particularly the risk of serious infections), the most appropriate patient population would need to be identified.
- 6.35 The PBAC considered that while the claim of superior comparative effectiveness versus standard therapy alone was adequately supported, the incremental benefit shown in the trial was modest.
- 6.36 The PBAC considered that the claim of inferior comparative safety versus standard therapy alone was reasonable.

Economic analysis

- 6.37 The submission presented a stepped economic evaluation of ravulizumab in combination with standard therapy compared to placebo in combination with standard therapy for the treatment of AchR positive generalised myasthenia gravis in patients with functional impairment. The economic evaluation was based on a direct randomised trial (CHAMPION-MG) with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.
- 6.38 Key components of the economic evaluation are summarised in Table 8.

Table 8: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Patients with response; responder years; quality adjusted life years
Time horizon	15 years
Methods used to generate results	Markov cohort model
Treatments	Ravulizumab and placebo. For both treatment arms second-line therapy included chronic IVIg and chronic PLEX, and third-line therapy included rituximab and cyclophosphamide. All patients also continued to receive standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, tacrolimus) for all lines of therapy
Health states	9 health states defined by treatment status (treatment initiator, responder, non-responder) and lines of therapy (first-line, second-line or third-line treatment) and death.
Cycle length	13-weeks (with no half-cycle correction)
Circumstances of use	Ravulizumab was positioned as a new line of therapy immediately prior to the classification of patients as having treatment-refractory disease. The model assumed limited treatment durations for all therapies (1-2 years) with the exception of standard therapy which was assumed to have perfect compliance (adherence and persistence) for the duration of the model. It was assumed that ravulizumab is the only treatment capable of inducing remission (minimal manifestations of disease). The model assumed that no patients who relapse after ravulizumab treatment would restart treatment with ravulizumab.

Public Summary Document - July 2024 PBAC meeting

Component	Description
Transition probability	<p>All first-line patients were assumed to remain in the treatment initiator state for 6 months (consistent with the duration of the CHAMPION-MG trial).</p> <p>Treatment response rates for ravulizumab and placebo were based on the CHAMPION-MG trial (based on the proportion of patients achieving a ≥ 2-point reduction in MG-ADL scores from baseline to Week 26 in the CHAMPION-MG trial). Response rates for chronic IVIg (Zinman 2007, Barth 2011) and rituximab (Zhao 2021, Li 2021) were based on published literature. The response rate for chronic PLEX was assumed to be the same as chronic IVIg and the response rate for cyclophosphamide was assumed to be the same as rituximab.</p> <p>Patients in the treatment initiation health states were assumed to not discontinue therapy. Discontinuation rates in the responder states were based on the CHAMPION-MG extension study for ravulizumab and assumed for other therapies. All patients in the non-responder states were assumed to have discontinued therapy.</p> <p>The submission assumed that all patients with treatment response at 2 years in the ravulizumab arm achieved disease remission (i.e. they remain in the response health state) and no longer required any further therapy with ravulizumab. The submission estimated the risk of relapse using a linear function assuming all patients will have relapsed by 15 years.</p> <p>Patients who discontinue therapy (all therapies) or experience relapse (ravulizumab only) were assumed to initiate later lines of therapy after a 1 cycle break in therapy. Patients who discontinue third-line therapy are assumed to remain on standard therapy alone.</p> <p>The incidence of adverse events with ravulizumab and placebo were based on the CHAMPION-MG trial. Adverse events for chronic IVIg (Bril 2022), chronic PLEX (MSAC Assessment Report 1566), cyclophosphamide (Buzzard 2015) and rituximab (Nowak 2021) were based on published literature. Adverse events were assumed to only occur in the first cycle of each therapy.</p> <p>The risk of disease exacerbations and myasthenic crisis were based on a post hoc analysis of CHAMPION-MG trial and extension using a Poisson regression on data from both treatment arms to determine an association between disease exacerbations and MG-ADL score. Responders/non-responders to second/third-line therapies were assumed to have the same change in MG-ADL scores as first-line therapies for calculating event risk.</p> <p>Transition probabilities for myasthenic crisis-related death were based on published estimates (Alshekhlee 2009). Transition probabilities for general mortality were based on Australian life tables.</p>

Public Summary Document - July 2024 PBAC meeting

Component	Description
Utility values	<p>The health state utility value for first-line treatment initiators was estimated based on the pooled baseline EQ-5D-5L values (Australian weights, Norman 2023) from both treatment arms of the CHAMPION-MG trials (0.740). First-line health state utilities for responders and non-responders were based on a post hoc analysis of EQ-5D-5L data (Australian weights, Norman 2023) from each treatment arm of the CHAMPION-MG trial (ravulizumab responder: 0.830; ravulizumab non-responder: 0.730; placebo responder: 0.810; placebo non-responder: 0.650). Health state utility values for treatment initiators to second/third-line therapy were assumed to be equivalent to the non-response value of the preceding line of therapy. Utility values for responders to second/third-line therapy were assumed to be equivalent to published estimates for mild myasthenia gravis while non-responders were assumed to have utility values equivalent to severe myasthenia gravis (responder: 0.766; non-responder: 0.530; Dewilde 2023).</p> <p>Utility values were age-adjusted based on Australian general population EQ-5D-3L data (Clemens 2014).</p> <p>Exacerbation and myasthenic crisis disutility values were based on a post hoc analysis of EQ-5D-5L data from the combined treatment arms of the CHAMPION-MG trial. The duration of events was assumed based on published literature (Ramsaroop 2023).</p> <p>The disutility for adverse events was assumed to be included in health state utility values for first-line therapies. Adverse event QALY decrements for chronic PLEX were derived from MSAC Assessment Report 1566. The QALY decrement associated with adverse events for other therapies was assumed to be equivalent to an exacerbation.</p>
Costs	<p>Treatment costs (drug, vaccination, administration, procedure and monitoring costs) were based on proposed or current PBS/MBS items.</p> <p>The costs associated with exacerbations and myasthenic crises were calculated assuming all patients are hospitalised and receive rescue IVIg or PLEX. Costs for IVIg and PLEX were based on MSAC Assessment Report 1566. The cost of hospitalisation was based on AR-DRG weights (B81A/B, B42A) with myasthenic crisis assumed to require ventilator support.</p> <p>The cost of serious adverse events was based on AR-DRG cost weights (B81A, B81B). The cost of retroperitoneal haematoma, femoral thrombosis and sepsis associated with chronic PLEX treatment were based on MSAC Assessment Report 1566.</p> <p>Disease management costs were based on expert opinion of resource use (GP and specialist visits) for treatment responders and non-responders. The costs of physician visits were based on MBS items (Items 23 and 105).</p> <p>Terminal care costs were based on AR-DRG sub-acute cost weights (4BT1) and were assumed to apply to all patients that died in the model.</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 365

Source: Section 3, pp106-149 of the submission

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; GP, general practitioner; IVIg, intravenous immunoglobulin; MBS, Medicare Benefits Schedule; MG-ADL, Myasthenia Gravis Activities of Daily Living; MSAC, Medicare Services Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PLEX, plasma exchange; QALY, quality-adjusted life year.

- 6.39 All patients begin the model in the first-line treatment initiator health state. Patients can remain in this state for up to 6 months or die due to general mortality or crisis-related mortality but cannot discontinue therapy due to other reasons. During this period, patients may experience adverse events (first cycle only) and exacerbations or myasthenic crisis events.
- 6.40 After 6 months, patients are assigned to the response and non-response health states. Responders may remain in this state, die due to general mortality or crisis-related

mortality, or prematurely discontinue therapy (with different therapies having different maximum treatment durations). Patients who discontinue therapy switch to the non-response health state with the exception of patients who have been treated with ravulizumab for 2 years who are assumed to achieve disease remission. Patients in disease remission are assumed to remain in the response health state but no longer require active treatment with ravulizumab. Patients in disease remission have a risk of disease relapse over time requiring the initiation of a new line of therapy. All patients in the non-response health state are assumed to discontinue therapy. During this period, patients may experience exacerbations or myasthenic crisis events.

- 6.41 After premature discontinuation, patients are assumed to enter a subsequent treatment initiator health state for up to 3 months before being assigned to response and non-response health states similar to first-line therapy (however no therapy other than ravulizumab can achieve disease remission). During this period, patients may die due to general mortality or crisis-related mortality and may experience adverse events (first cycle of treatment only) and exacerbations or myasthenic crisis events. Patients who have discontinued three lines of therapy are assumed to remain on treatment with standard therapy alone.
- 6.42 The economic model assessed the use of ravulizumab as a new line of therapy immediately prior to 'treatment-refractory' disease, using a sequential treatment model (i.e. where patients start on first line therapy and then move to subsequent lines as each line of therapy fails). The ESC considered that this did not reflect the proposed restriction nor the PSCR's intended place in therapy. While the PSCR stated that ravulizumab could be used as a bridging therapy for symptom reduction until immunosuppressive therapies can achieve optimal control, the economic analysis assumed that patients on standard therapy alone, including immunosuppressive therapy, would never achieve long-term symptom control (i.e. in the economic model only patients on ravulizumab could achieve remission, as shown in Figure 3).
- 6.43 Additionally, there were insufficient clinical data to populate a sequential treatment model and therefore the economic analysis required the use of a substantial number of data assumptions. Finally, despite the added complexity of including lines of therapy in the model, most of the additional variables had only a modest impact on the economic analysis, with the exception of the utility value for non-response to second/third-line therapies (assumed to be the same as severe disease), which was a key driver of the economic analysis. The ESC considered that these assumptions were poorly justified and the complexity of the model with 9 health states compounded the uncertainty and limited the usefulness of the estimated ICER.
- 6.44 Key drivers of the economic model are summarised in Table 9.

Public Summary Document - July 2024 PBAC meeting

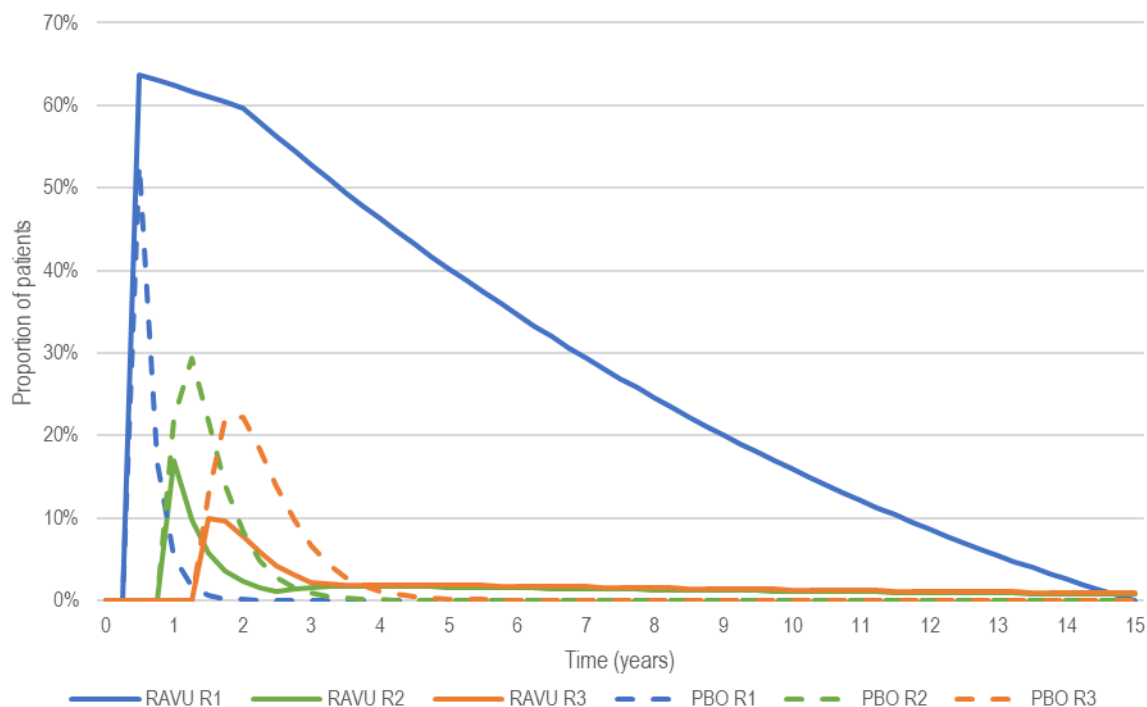
Table 9: Key drivers of the model

Description	Method/Value	Impact
Ravulizumab responder treatment duration	<p>The submission assumed that treatment responders to ravulizumab would have a maximum treatment duration of 2 years on the basis that patients treated with ravulizumab for this length of time would achieve disease remission (minimal manifestations of disease) and would not require any further treatment with ravulizumab. The submission argued that a 2-year treatment window was consistent with the natural history of myasthenia gravis and aligns with the general management principles for myasthenia gravis which are to manage symptoms with the lowest treatment burden. The PSCR (p3) stated that it estimated that “a patient on average will be treated for 2 years (not a maximum of 2 years)”. However, the ESC noted that the economic model used a maximum treatment duration of 2 years (i.e. patients could receive less than 2 years of treatment but could not receive more than 2 years of treatment).</p> <p>The submission provided no clinical data on the duration of ravulizumab therapy required to induce remission. While it is plausible that ravulizumab may induce remission in some patients, it is unlikely to occur in all treatment responders, and the submission provided no clinical data to support this assumption. It should be noted that while many patients experienced an improvement in functional outcomes during the CHAMPION-MG trial (ravulizumab: 63.9%) only a minority of patients achieved minimal manifestations of disease (ravulizumab: 25.6%) at the end of 26 weeks. Therefore, it is unclear whether the majority of treatment responders would meet clinical definitions for disease remission.</p>	High, favours ravulizumab
Placebo responder treatment duration	<p>The submission assumed that treatment responders to placebo would have a maximum treatment duration of 1 year. The submission claimed that this argument was reasonable as patients were only receiving active therapy with stable doses of standard therapy and therefore discontinuation rates would be expected to be high. All patients discontinuing placebo were switched to non-response health states. The evaluation and the ESC considered that this assumption was implausible as treatment responders in the placebo arm had achieved a clinically important improvement in functional outcomes using the same thresholds as applied to ravulizumab. There are no clinical data to support differential handling of ravulizumab and placebo arm treatment durations after the clinical trial period.</p>	High, favours ravulizumab
Ravulizumab remission duration	<p>The submission predicted that patients in disease remission would gradually relapse over time which was modelled using a linear function based on the assumption that all patients in remission at 2 years had relapsed by 15 years. No clinical data were provided to support this assumption. The ESC considered this highly simplistic and not supported by clinical data or evidence from the literature.</p>	High, favours ravulizumab
Health utility for 2 nd /3 rd line non-responders	<p>In the absence of any available clinical data, the submission assumed that second/third-line treatment non-responders would have the same utility value as patients with severe (MGFA Class IV) myasthenia gravis. The evaluation and the ESC considered this assumption was implausible as the vast majority of patients in the CHAMPION-MG trial only had mild-to-moderate disease (44.6% mild, 49.1% moderate).</p>	High, favours ravulizumab

Source: Constructed during the evaluation

6.45 A model trace of the proportion of responders over time is summarised in Figure 3.

Figure 3: Model trace of responders by line of therapy



Source: Constructed during the evaluation based on Attachment 7 Economic Model Excel Spreadsheet

Abbreviations: PBO, placebo; R1, responders to first-line treatment; R2, responders to second-line treatment; R3, responders to third-line treatment; RAVU, ravulizumab.

6.46 The Markov trace indicates that a substantial proportion of patients in both treatment arms achieve a response to first-line therapy (consistent with the clinical trial data) but arms rapidly separate after 6 months due to different assumptions in the extrapolated period (all placebo patients discontinue by one year, ravulizumab patients responding at 6 months will maintain response for 2 years unless discontinued for other reasons, ravulizumab patients responding for 2 years will achieve disease remission). The trace also indicates that patients rapidly progress through later lines of therapy.

6.47 The results of the stepped economic evaluation are summarised in Table 10.

Table 10: Stepped economic evaluation of ravulizumab compared to placebo

Type of resource item	Ravulizumab	Placebo	Increment
Step 1: Modelled estimate based on trial duration of 26 weeks			
Costs	\$█	\$4,948	\$█
Patients with response	0.639	0.530	0.109
Incremental cost per additional patient with response			\$ ¹
Step 2: Modelled estimate extrapolated to 15 years			
Costs	\$█	\$251,052	\$█
Responder years	4.749	0.753	3.996
Incremental cost per year in response			\$ ²
Step 3: Modelled estimate extrapolated to 15 years with utility weights applied			
Costs	\$█	\$251,052	\$█
QALYs	8.949	7.651	1.298
Incremental cost per QALY gained			\$ ³
Step 4: Modelled estimate extrapolated to 15 years with utility weights and discounting applied			
Costs	\$█	\$182,986	\$█
QALYs	6.589	5.557	1.032
Incremental cost per QALY gained			\$ ⁴

Source: Table 3-33, p146 of the submission

Abbreviations: QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$75,000 to < \$95,000

³ \$155,000 to < \$255,000

⁴ \$255,000 to < \$355,000

6.48 Based on the economic model, treatment with ravulizumab in combination with standard therapy was associated with a cost per QALY gained of \$255,000 to < \$355,000 compared to placebo in combination with standard therapy for the treatment of myasthenia gravis. The ESC noted that the trial-based (26 weeks) estimate was > \$1,055,000 per responder.

6.49 The evaluation and the ESC considered that the estimated ICER was highly uncertain as it was dependent on three highly optimistic and implausible core assumptions:

- All patients in the ravulizumab arm who maintain response for two years will achieve disease remission (i.e. remain in a response health state) and will require no further treatment with ravulizumab. The model also assumed that if relapse occurs then patients would use other non-ravulizumab therapies.
- All patients in the placebo arm will lose treatment response within one year and can never achieve disease remission. The ESC considered this was inconsistent with the PSCR's description of the natural history of generalised myasthenia gravis, which outlined that the condition reaches maximum or near-maximum severity in 37% of patients within six months of symptom onset, in 29% during the next six months, in 17% during the next year, and in only 18% after two years from onset.⁵

⁵ Grob, D., N. Brunner, T. Namba and M. Pagala (2008). "Lifetime course of myasthenia gravis." *Muscle & Nerve* 37(2): 141-149.

- Patients with non-response to second/third-line treatments have the same utility values as patients with severe myasthenia gravis (0.53) despite the vast majority of patients having mild to moderate disease. The assumed utility for non-response to second/third-line therapy was substantially lower than trial-based estimates of non-response (0.69) from the CHAMPION-MG trial.
- 6.50 Additionally, the model only estimated the cost-effectiveness of ravulizumab when used as a new line of therapy immediately prior to the classification of patients as having treatment-refractory disease and does not assess the use of ravulizumab in other clinical roles covered by the proposed PBS listing. The pre-PBAC response stated that the structure of the model is aligned with the proposed restriction for ravulizumab use early and upfront as an add-on to immunosuppressive therapy (Level 1 of the treatment algorithm proposed in Figure 1), and that the proposed restriction 'ensures that ravulizumab is not used as an add-on to Level 2 (chronic IVIg or PLEX) or Level 3 (rituximab or other) treatments. Therefore, add-on to Level 2 or 3 treatments have not been displayed in the economic evaluation'. However, the PBAC noted that the proposed restriction would allow use of ravulizumab in later-lines of therapy.
- 6.51 The results of key univariate sensitivity analyses are summarised in Table 11.

Public Summary Document - July 2024 PBAC meeting

Table 11: Results of univariate sensitivity analyses

Analyses	Incr. cost	Incr. QALYs	ICER	Change from base case ICER
Base case	\$█	1.0319	\$█ ¹	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate	\$█	1.1011	\$█ ¹	-%
0% discount rate	\$█	1.2982	\$█ ²	-%
Time horizon (base case: 15 years)				
20 years	\$█	1.1805	\$█ ¹	-%
10 years	\$█	0.8311	\$█ ³	+%
5 years	\$█	0.5426	\$█ ⁴	+%
2 years	\$█	0.2916	\$█ ⁵	+%
Response rates (base case: ravulizumab and placebo response rates based on proportion of patients with ≥ 2-point reduction in MG-ADL scores in the CHAMPION-MG trial)				
Ravulizumab and placebo response rates based on proportion of patients with ≥ 3-point reduction in MGC scores	\$█	1.0361	\$█ ¹	+%
Circumstances of use (base case: ravulizumab maximum treatment duration of 2 years; placebo maximum treatment duration of 1 year; all other therapies maximum treatment duration of 2 years)				
Ravulizumab maximum treatment duration 3 years	\$█	1.0915	\$█ ³	+%
Ravulizumab maximum treatment duration 5 years	\$█	1.1982	\$█ ⁶	+%
Ravulizumab maximum treatment duration 10 years	\$█	1.4012	\$█ ⁷	+%
Ravulizumab maximum treatment duration 15 years	\$█	1.5164	\$█ ⁸	+%
Placebo maximum treatment duration 3 years	\$█	0.9737	\$█ ¹	+%
Placebo maximum treatment duration 5 years	\$█	0.9164	\$█ ¹	+%
Placebo maximum treatment duration 10 years	\$█	0.7835	\$█ ³	+%
Placebo maximum treatment duration 15 years	\$█	0.6664	\$█ ⁶	+%
Duration of remission (base case: linear function assuming all ravulizumab patients with remission at 2 years have relapsed by 15 years)				
Linear function assuming all ravulizumab patients with remission at 2 years have relapsed by 11.5 years	\$█	0.9049	\$█ ¹	+%
Linear function assuming all ravulizumab patients with remission at 2 years have relapsed by 9 years	\$█	0.7935	\$█ ³	+%
Linear function assuming all ravulizumab patients with remission at 2 years have relapsed by 6 years	\$█	0.6348	\$█ ⁶	+%
Linear function assuming all ravulizumab patients with remission at 2 years have relapsed by 3 years	\$█	0.4440	\$█ ⁷	+%
Utility values (base case: second/third-line responder utility values assumed to be the same as mild disease and second/third-line non-responder utility values assumed to be the same as severe disease)				
Second/third-line non-responder utility value decreased by 5% (0.505)	\$█	1.1022	\$█ ¹	-%
Second/third-line non-responder utility value increased by 5% (0.557)	\$█	0.9580	\$█ ¹	+%
Assume second/third-line non-responder utility value is the same as pooled first-line estimates (0.69)	\$█	0.5686	\$█ ⁶	+%

Source: Table 3-37, p149 of the submission

Abbreviations: CI, confidence interval; AEMP, approved ex-manufacturer price; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$155,000 to < \$255,000

³ \$355,000 to < \$455,000

⁴ \$555,000 to < \$655,000

⁵ > \$1,055,000

⁶ \$455,000 to < \$555,000

⁷ \$655,000 to < \$755,000

- 6.52 The results of the sensitivity analyses indicate that the model is most sensitive to ravulizumab and placebo treatment durations, ravulizumab remission duration, time horizon (as a consequence of sensitivity to treatment/remission durations), utility and the values for second/third-line treatment non-responders.
- 6.53 However, due to the limitations of the model structure and data inputs it was not possible to assess the impact of multiple episodes of care (i.e. ravulizumab re-treatment), use of other responder definitions (MG-ADL \geq 3, QMG \geq 3, QMG \geq 5 reduction from baseline; the proportion of patients achieving minimal manifestations of disease) or the use of ravulizumab in different clinical roles covered by the proposed PBS listing.
- 6.54 The ESC noted that the base case ICER was approximately \$255,000 to < \$355,000/QALY but considered this was likely underestimated and driven by clinically implausible assumptions around treatment duration, duration of remission, and utilities for non-responders. Given the assumptions made in the model and thus uncertainty in their true parameter values, the ESC considered the univariate sensitivity analyses around each of these factors were highly informative, noting they resulted in ICERs over \$355,000 to < \$455,000/QALY. Multivariate sensitivity analyses addressing all three of these factors would result in substantially higher ICERs/QALY. However, overall, the ESC considered that such multivariate sensitivity analyses would not address the fundamental issue that the model structure, the modelled population and the treatment setting would need to be based on an appropriate place in therapy.

Drug cost/patient/course

- 6.55 The estimated drug cost for ravulizumab in the first year of treatment was \$ [REDACTED] (based on patients receiving 1 loading dose and 7 maintenance doses, assuming the same distribution of patients across weight categories as the CHAMPION-MG trial, and using the effective AEMP of \$ [REDACTED] for the 300 mg vial with additional fees and markup for use in the private hospital setting). The estimated drug cost for ravulizumab in the second year of treatment was \$ [REDACTED] (based on patients receiving 6 maintenance doses with the same assumptions as the first year calculations).
- 6.56 The estimated annual drug cost for standard therapy (anticholinesterases, corticosteroids and other immunosuppressive agents) was \$2,444 per year. The estimated annual cost for chronic IVIg therapy (including procedure costs) was \$ [REDACTED] per year. The estimated annual costs for chronic PLEX (including procedure costs) was \$ [REDACTED] per year. The estimated annual cost for cyclophosphamide was \$989 in the first year and \$1,143 in subsequent years. The estimated annual cost for rituximab was \$865 per year.
- 6.57 A comparison of ravulizumab drug costs (based on effective AEMP) across different sections of the submission is presented in Table 12.

Table 12: Drug cost per patient for ravulizumab

	Clinical trial	Economic model	Financial estimates
Initial treatment prior to response assessment at 6 months			
Dose intensity	96.5% of patients were 100% adherent with scheduled doses during the trial	100%	91.7%
Persistence	91.9%	99.9%	100%
Average total dose administered (mg)	12,759 mg (dispensed as approximately 42.5 x 300 mg vials)	12,905 mg (dispensed as approximately 43.0 x 300 mg vials)	11,837 mg (dispensed as approximately 12.3 x 300 mg vials and 7.4 x 1,100 mg vials)
Cost per vial (AEMP)	-	300 mg vial: \$	300 mg vial: \$ 1,100 mg vial: \$
Cost of 6 months initial treatment (AEMP)	-	\$	\$
Continuing treatment in treatment responders between 6 months and 2 years			
Proportion responders	63.9%	63.9%	63.9%
Dose intensity	-	91.7%	91.7%
Persistence	-	94.7% at 2 years	100% for 2 years
Average total dose administered (mg)	-	30,214 mg (dispensed as approximately 100.7 x 300 mg vials)	30,968 mg (dispensed as approximately 12.7 x 300 mg vials and 24.7 x 1,100 mg vials)
Cost per vial (AEMP)	-	300 mg vial: \$	300 mg vial: \$ 1,100 mg vial: \$
Cost of continuing treatment (AEMP)	-	\$	\$
Total ravulizumab costs at 2 years			
Total cost for non-responders (AEMP)	-	\$	\$
Total cost for responders (AEMP)	-	\$	\$

Source: constructed during the evaluation based on Attachment 7 Economic Model Excel Spreadsheet and Attachment 8 Financial utilisation model spreadsheet

Abbreviations: AEMP, approved ex-manufacturer price

Estimated PBS usage & financial implications

6.58 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications of listing ravulizumab on the PBS for the treatment of adult patients with anti-acetylcholine receptor positive generalised myasthenia gravis who have functional impairments. The key inputs used to derive the financial implications are presented in Table 13.

Public Summary Document - July 2024 PBAC meeting

Table 13: Key inputs for financial estimates

Parameter	Value/Source	Comment
Prevalence of myasthenia gravis	20 per 100,000 population. Based on a sponsor-commissioned analysis of PBS data for the cholinesterase inhibitor pyridostigmine, based on the methodology reported in Gattellari 2012. Estimated pyridostigmine patients were divided by ABS population data to determine prevalence. The estimated prevalence of treated myasthenia gravis ranged from 16.7 to 20.3 per 100,000 population between 2018 and 2022 (an average annual increase of 5%).	The commentary and DUSC considered the prevalence of myasthenia gravis may be underestimated as not all treated patients will be treated with pyridostigmine (patients treated with another cholinesterase inhibitor, or other treatments). Data from the Australian MGBase cohort indicated that 51.9% of patients with myasthenia gravis were currently treated with pyridostigmine. Additionally, the submission's prevalence estimate may also include use of pyridostigmine for other conditions (only use for orthostatic hypotension was excluded). The commentary and DUSC considered that the submission inappropriately assumed a constant prevalence over time, which was inconsistent with data from the commissioned analysis indicating increasing prevalence. DUSC noted the prevalence in Australian studies was between 52 to 66%.
Proportion with generalised myasthenia gravis	79% Based on various studies reporting the proportion of myasthenia gravis which is generalised. Estimates ranged from 69% to 89%; the submission stated that the midpoint was selected.	The commentary and DUSC considered there was a wide range of estimates from the included studies based on a variety of study designs, over different time periods, in different settings and patient populations; that were not assessed for their applicability to the proposed eligible population. The commentary and DUSC considered that the proportion of Australian patients with gMG, based on a population treated with pyridostigmine, is currently unclear.
Proportion with functional impairment	17%. Based on the proportion of patients with MG-ADL ≥ 6 , with ≥ 1 point from non-ocular items from Petersson 2021, a Swedish cross-sectional cohort study of 1,077 patients with myasthenia gravis (2018-2019).	The commentary noted the estimate was applied to pyridostigmine-treated patients with AChR positive generalised myasthenia gravis, however, the treatment status of patients in the Petersson 2021 study is unknown and the population was not specifically AChR positive generalised myasthenia gravis patients. The commentary therefore considered that it was unclear whether the resulting eligible population would be representative of the proposed population of patients with MG-ADL ≥ 6 despite treatment with standard therapy. DUSC considered that this could be an underestimate given the subjective nature of the scale used to measure functional impairment.
Uptake	█% in Year 1, increasing to █% in Years 4-6. The submission stated that market uptake was informed by uptake of ocrelizumab for multiple sclerosis on the PBS (28% of the biologics market in Year 1; increasing to 60% in Year 3; based on Figure 2, DUSC 2020 Ocrelizumab predicted versus actual analysis), as well as local expert opinion and international experience.	The submission acknowledged that ocrelizumab is not a perfect analogue, as it provided substitution of existing medicines rather than incremental use, but claimed it provides some guidance on uptake of a new treatment for a neurological condition. The commentary noted that no details were provided on the expert opinion or commercial experience. DUSC considered that uptake rates were uncertain and an underestimate given uncertainty of place in therapy and unmet need.

Public Summary Document - July 2024 PBAC meeting

Parameter	Value/Source	Comment
Treatment responders at 6 months	63.9%. Based on the response rate (proportion of patients with ≥ 2 point decrease in MG-ADL) in CHAMPION-MG.	The commentary considered it was unclear whether the response rate in a clinical trial would be representative of the response rate in clinical practice, used to determine ongoing treatment eligibility. DUSC considered that the proportion of treatment responders was likely to be lower than that seen in the trial.
Proportion of treatment responders completing 2 years of therapy	100%, Assumption.	The commentary considered that this assumption was unlikely to reflect clinical practice and was inconsistent with treatment persistence in the CHAMPION-MG trial and the economic model. DUSC agreed with the commentary and considered that there was uncertainty in the proportion of treatment responders given its likely use in clinical practice and the assumptions of the economic model.
Grandfathered patients	█ ¹ patients. The submission stated that █ ¹ patients are expected to enrol in an early access program; 63.9% of whom will achieve response (based on the response rate in CHAMPION-MG). The submission assumed that patients would complete the initial treatment period in the early access program and complete a further 78 weeks of PBS funded treatment (6 doses in Year 1; 4 doses in Year 2).	The submission claimed that grandfathered patients do not contribute to the number of initiating patients, only continuing patients in Years 1 and 2, and do not require removal from the prevalent population in Year 1. However, the commentary considered there is likely to be substantial overlap between the eligible prevalent populations from year to year and it would be more appropriate to remove the grandfathered patients from the eligible prevalent pool. The commentary considered that it is likely that a proportion of continuing therapy would occur during the early access program, rather than as PBS-subsidised therapy only. DUSC agreed with the commentary and considered that the grandfathered patient should be removed from the prevalent estimates.
Number of scripts per patient	Initial scripts: 4 × 300 mg and 4 × 1,100 mg Continuing scripts: 10 × 300 mg and 10 × 1,100 mg.	The treatment duration was based on the assumption that all treatment responders would achieve remission and no longer require ravulizumab treatment after 2 years. The commentary considered that this was inadequately justified as the clinical data are limited to 60 weeks of therapy with no evidence that ravulizumab can achieve clinical remission without ongoing treatment. The assumption that patients receive 2 scripts for each dose was inconsistent with the calculation of the number of vials per dose, which estimated all loading doses would use the 300 mg vial; and only patients in the highest weight category (≥ 100 kg) would require 2 scripts for maintenance doses (representing 36% of patients, based on data from CHAMPION-MG). DUSC considered that there was uncertainty in the number of scripts due to uncertainties in duration of treatment and possible retreatment.

Source: Section 4, pp150-160 of the submission; 'Attachment 8 Financial utilisation model' spreadsheet provided with the submission, Table 1 of ravulizumab DUSC Advice, March 2024.

Abbreviations: AChR, anti-acetylcholine receptor antibody; DUSC, Drug Utilisation Sub-Committee; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PBS; Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ < 500

Public Summary Document - July 2024 PBAC meeting

6.59 Table 14 summarises the estimated patients treated, scripts dispensed and net cost to the PBS of listing ravulizumab for gMG.

Table 14: Estimated use and financial implications of ravulizumab (effective price) for generalised myasthenia gravis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initiating patients	1	1	1	1	1	1
Responders at 6 months (63.9%)	a 1	1	1	1	1	1
Continuing patients (responders from previous year; 2 nd year only)	-	a 1	1	1	1	1
Total treated patients	1	1	2	2	2	2
Initial scripts ^b	2	2	2	2	2	2
Continuing scripts ^c	2	2	2	2	2	2
Number of scripts dispensed	2	3	3	3	3	3
Net financial implications to the PBS/MBS						
Net cost to the PBS	\$ 4	\$ 5	\$ 6	\$ 6	\$ 6	\$ 6
Cost to the MBS ^d	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Total cost to PBS/MBS	\$ 4	\$ 5	\$ 6	\$ 6	\$ 6	\$ 6

Source: Table 4-6, p155; Table 4-7, p157; Table 4-12, p161; Table 4-15, p164 of the submission; 'Attachment 8 Financial utilisation model' spreadsheet provided with the submission.

Note: An error in the calculation of MBS costs (the number of administrations for continuing patients was applied to grandfathered patients) was corrected during the evaluation.

^a Includes < 500 grandfathered patients who received initial treatment as part of an early access program and met the response continuation criterion.

^b 8 scripts per initiating patient (4 scripts of 300 mg dose; 4 scripts of 1,100 mg dose); adjusted for 91.7% adherence.

^c Includes 8 scripts per responding patient in their 1st year of treatment (4 scripts of 300 mg dose; 4 scripts of 1,100 mg dose); 12 scripts per responding patient in their 2nd year of treatment (6 scripts of 300 mg dose; 6 scripts of 1,100 mg dose); 12 scripts per grandfathered patient in their 1st year of treatment (6 scripts of 300 mg dose; 6 scripts of 1,100 mg dose); 8 scripts per grandfathered patient in their 2nd year of treatment (4 scripts of 300 mg dose; 4 scripts of 1,100 mg dose); adjusted for 91.7% adherence.

^d Administration costs for ravulizumab, based on the cost of a subsequent specialist consultation (\$47.80; 80% of the fee for MBS item 105), applied to the number of doses per year.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$40 million to < \$50 million

⁵ \$90 million to < \$100 million

⁶ \$100 million to < \$200 million

⁷ \$0 to < \$10 million

6.60 The total cost to the PBS of listing ravulizumab for gMG was estimated to be \$40 million to < \$50 million in Year 1, increasing to \$100 million to < \$200 million in Year 6; a total of \$600 million to < \$700 million in the first 6 years of listing.

6.61 DUSC considered that the financial estimates presented in the submission were uncertain and underestimated. The DUSC considered the main issues were:

- there was uncertainty in the estimates of the prevalence of myasthenia gravis and the proportion of myasthenia gravis patients with gMG due to the method in deriving the prevalent population and the range of estimates for the proportion with gMG.

- the prevalence of myasthenia gravis may be underestimated as it was based on the use of pyridostigmine on the PBS though not all treated patients will be treated with pyridostigmine.
 - the submission inappropriately assumed a constant prevalence over time, which was inconsistent with data from the commissioned analysis indicating increasing prevalence.
 - the proportion of patients with the relevant functional impairment were an underestimate due to the subjective nature of the measuring instrument (MG-ADL) as it only incorporates patient subjective assessment of their functional impairment.
 - the uptake rate was uncertain and was probably an underestimate due to the unmet clinical need, uncertainty of ravulizumab's place in therapy, and the subjective nature of the MG-ADL instrument.
 - there was uncertainty in duration of therapy and in treatment continuation beyond the time when a patient has likely achieved an appropriate level of immunosuppression with steroids or immunomodulatory therapy. DUSC considered that the 18-24 months stated in the submission to achieve adequate immunosuppression was unsupported and likely overestimated.
 - there was uncertainty in relation to treatment cessation after the patient becomes stable or does not show adequate symptom control and that a stopping rule should be included in the restriction.
- 6.62 The evaluation considered the assumption that patients receive a maximum of 2 years of ravulizumab (at which point they are assumed to be in remission and no longer require ravulizumab treatment) was inadequately justified. The available clinical data are limited to 60 weeks of ongoing therapy with no evidence that ravulizumab can achieve clinical remission without ongoing treatment. The optimal duration of ravulizumab therapy for generalised myasthenia gravis is currently unknown.

Quality Use of Medicines

- 6.63 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.
- 6.64 DUSC considered that, while *Meningococcus* prevention has been adequately addressed, the overall risk of other possible infections (such as those caused by other *Neisseria* species) also need QUM activities.

Financial Management – Risk Sharing Arrangements

- 6.65 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.
- 6.66 DUSC considered that an RSA would be appropriate.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of ravulizumab for the treatment of patients with generalised myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive. The PBAC considered that the incremental benefit shown in the trial was modest and that it was difficult to determine whether the incremental benefit would be clinically meaningful in the broad population requested for listing. Further, the PBAC considered the incremental cost-effectiveness ratio (ICER) presented in the submission was very high and likely to have been underestimated, and the proposed price was very high. The PBAC recognised the high clinical need for effective therapies for gMG, particularly in patients who are not responding to or are unable to use existing therapies, and for those with refractory disease.
- 7.2 The primary reason for this outcome was the comparative clinical evidence.
- 7.3 The PBAC noted the strong consumer and clinician support for ravulizumab received via the Consumer Comments facility on the PBS website (see paragraphs 6.3 to 6.7), the sponsor hearing (see paragraphs 6.1 and 6.2) and as part of the stakeholder meeting (see paragraphs 2.3 and 2.4). The PBAC appreciated the input provided by patients, carers and clinicians in these forums and found the comments very informative for understanding the high and unmet clinical need for new effective treatments and the potential use of complement inhibitors in the management gMG. The PBAC noted that the comments described the substantial adverse effects associated with current therapies particularly corticosteroids, and the limited options available for patients who are refractory to available treatments or who are not responding to or are unable to use existing therapies. The input outlined that there are many patients whose condition is not adequately controlled with currently available treatments (e.g. their condition is not stable, or they cannot undertake daily activities including work or family commitments). The PBAC noted that many of the comments described the hope that ravulizumab would improve quality of life, and safely and quickly relieve symptoms.
- 7.4 The PBAC noted that the PSCR and pre-PBAC response stated that the intended place in therapy for ravulizumab was prior to consideration of chronic IVIg. However, the PBAC noted that this was inconsistent with other elements of the submission, including the proposed restriction which would also allow use of ravulizumab in later lines of therapy, including in those patients who would otherwise be treated with

chronic IVIg/PLEX.

- 7.5 As such, the PBAC noted that the submission requested listing of ravulizumab in a broad patient population which comprised two key, distinct places in therapy:
- early in the treatment algorithm, initiated in combination with at least one immunosuppressive therapy; and
 - later in the disease course in refractory patients.

The PBAC noted this broad patient population aligned with the feedback received both at the stakeholder meeting and through the consumer comments regarding the ideal clinical positioning of the newer agents for gMG. As such, the PBAC expressed a preference for listing these therapies in this broad patient population. However, the PBAC considered it was unclear whether ravulizumab would be suitable for listing in this broad population given: the very modest clinical efficacy demonstrated in the CHAMPION-MG trial (noting that a similar proportion of patients in both treatment arms achieved the MCID threshold of a ≥ 2 -point reduction in the MG-ADL score); and the available therapies may be effective for many patients. Further, the PBAC considered that a substantially lower ICER (based on a model that incorporates the issues raised in paragraphs 7.15 and 7.16) would be required for listing in a broad patient population. Alternatively, the PBAC considered there could be potential for listing the newer gMG therapies in a distinct population where the alternative treatment options are more limited, if this were supported by clinical evidence. For example, the PBAC considered that the highest unmet clinical need is in patients who would otherwise be treated with chronic IVIg or PLEX (noting access to these therapies can be difficult).

- 7.6 The PBAC considered that it may have been preferable to have proposed separate initial and continuing treatment criteria for refractory and non-refractory patients. Further, the PBAC considered that it was unclear whether there is evidence to support use of ravulizumab in gMG exacerbations/crises or if this setting should have been explicitly excluded.
- 7.7 The pre-PBAC response proposed amending the requested initial restriction to require patients to have an MG-ADL score of ≥ 6 points despite 'at least one immunosuppressive therapy' (rather than despite 'standard therapy' to help clarify that ravulizumab should be used as add-on to immunosuppressive therapy). The PBAC considered that this remained broad given it did not require the immunosuppressive therapy to have been optimised, nor specify a timeframe for assessing response prior to commencing ravulizumab.
- 7.8 The PBAC noted that the proposed restriction stated 'patients who are clinically stable should be considered for a trial of cessation of therapy to identify disease remission'. The PBAC agreed with the clinicians present at the stakeholder meeting that there should be robust stopping rules (i.e. to require cessation in responding patients in order to prevent ongoing use that may be unnecessary), noting that it would be harder

to cease treatment in refractory patients. However, the PBAC considered that the wording in the proposed restriction was ambiguous as it did not mandate cessation nor provide sufficient detail as to when and how stable disease should be assessed. As such, the PBAC considered that based on the proposed restriction it would be unlikely that all patients would cease ravulizumab after a maximum of two years, as assumed in the economic model and financial estimates.

- 7.9 In terms of the continuation criteria for assessing response (i.e. to require cessation in patients who experience an inadequate response), the PBAC noted that the submission proposed that a 2-point reduction in MG-ADL from baseline would be required for on-going treatment. However, the PBAC considered this required further consideration as it would mean that over half of patients would be continuing based on the placebo effect alone, given 53.0% of patients in the placebo arm achieved this response level in the trial (versus 63.9% in the ravulizumab group, based on the proportion of patients with a ≥ 2 -point reduction in MG-ADL scores from baseline to Week 26).
- 7.10 The PBAC noted that the submission nominated standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclosporin) as the main comparator. The PBAC agreed with the evaluation and the ESC, that ravulizumab would displace existing treatment options which should therefore be considered as treatment comparators including existing immunosuppressive therapies and chronic PLEX/IVIg (refractory setting). As such, the PBAC considered for the non-refractory group, the comparator should be optimisation of existing therapies. For refractory patients and those who are unable to use or not responding to existing therapies, the PBAC acknowledged that there are variations in access to IVIg/PLEX and that any clinical comparisons may be limited by the lack of evidence for IVIg/PLEX. As such, the PBAC considered that placebo may be a reasonable comparator in this group. However, the PBAC considered that chronic IVIg/PLEX remained a relevant comparator for providing a frame of reference for interpreting the cost per patient of ravulizumab in the refractory setting.
- 7.11 The PBAC noted that the clinical claim was based on the CHAMPION-MG trial, a randomised, double-blind trial comparing ravulizumab with placebo for 26 weeks. The PBAC considered that, while the primary outcome was statistically significant (mean difference in the Myasthenia Gravis Activities of Daily Living instrument (MG-ADL) score of -1.6 (95% CI: -2.6, -0.7) from baseline to Week 26), the clinical relevance of this to individual patients was unclear. For context, the PBAC noted that the MCID in an individual patient is a ≥ 2 -point reduction in the MG-ADL score, and that a similar proportion of patients in both treatment arms achieved this MCID with no statistically significant difference between ravulizumab and placebo (63.9% versus 53.0% at Week 26; nominal p-value = 0.1621). Overall, the PBAC considered that, while the claim of superior comparative effectiveness versus standard therapy alone was adequately supported, the incremental benefit shown in the trial was modest. The PBAC

considered that it was difficult to determine whether the incremental benefit would be clinically meaningful, particularly in the broad population requested given effective therapies are available for many of these patients (e.g. given the high placebo response rates and the potential to optimise available therapies in these patients).

- 7.12 Further, the PBAC noted that clinicians and consumers had stated that the new therapies for gMG have rapid onsets of action and thus could be used early in combination with standard therapy while waiting for non-steroid immunosuppressants to induce remission. However, the PBAC noted that no evidence had been presented to specifically demonstrate the difference in onset of action between ravulizumab and non-steroid immunosuppressants.
- 7.13 The pre-PBAC response claimed that, in the CHAMPION-MG trial, the greatest reductions in MG-ADL scores were observed when ravulizumab was added early to standard therapy (in patients treated with only one immunosuppressive therapy who had not received chronic IVIg or PLEX) and in patients with a shorter time since diagnosis (refer to paragraph 6.22). However, as noted in paragraph 7.10, the PBAC considered that effective therapies may be available for many patients earlier in the disease course, and that optimisation of existing therapies would have been a more relevant comparison for some of the patients in these groups. Further, the PBAC noted that these appeared to be based on *post-hoc* analyses and no treatment interaction testing was presented.
- 7.14 The PBAC considered that the claim of inferior comparative safety versus standard therapy alone was reasonable. While ravulizumab appeared well-tolerated, the PBAC noted the requirement for patients to receive meningococcal vaccinations.
- 7.15 The PBAC noted that the base case ICER presented in the submission was \$255,000 to < \$355,000/QALY. The PBAC noted that, despite this very high ICER, the ESC had considered it was still highly likely to be underestimated and was implausible due to the assumptions around:
- the duration of remission in each arm. The ESC considered it was unreasonable to assume that: (a) all patients who respond and remain on ravulizumab for 2 years, cease ravulizumab, achieve disease remission and gradually relapse over the modelled time horizon of 15 years; while (b) all placebo patients lose treatment response within 1 year and can never achieve disease remission.
 - utilities for non-responders. The ESC considered that it was unreasonable to assume that patients with non-response to second/third-line treatments would have the same disutility as severe myasthenia gravis despite the vast majority of modelled patients having mild to moderate disease.

The PBAC agreed with the issues raised by ESC about the economic model.

- 7.16 The PBAC also noted that the economic model only estimated the cost-effectiveness of ravulizumab when used as a new line of therapy immediately prior to the classification of patients as having treatment-refractory disease and did not assess the

use of ravulizumab in other clinical roles covered by the proposed PBS listing.

- 7.17 The PBAC agreed with the issues with the financial estimates that were raised by DUSC as outlined in paragraph 6.61 including the significant uncertainties regarding the: prevalence of myasthenia gravis (potentially underestimated) and the proportion of myasthenia gravis patients with gMG; proportion of patients with MG-ADL ≥ 6 (likely underestimated); expected uptake of ravulizumab (potentially underestimated); and the likely duration of ravulizumab treatment.
- 7.18 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

Whilst Alexion is disappointed with the current outcome and its impact on patients living with gMG, they extend their sincere gratitude to all healthcare professionals, patient organisations and consumers for their invaluable input and support. Alexion is committed to working with the PBAC to ensure Australians living with gMG can access Ultomiris on the PBS at the earliest opportunity.