

**7.09 RAVULIZUMAB,**

**Solution concentrate for I.V. infusion 300 mg in 3 mL,  
Solution concentrate for I.V. infusion 1,100 mg in  
11 mL,  
Ultomiris<sup>®</sup>,  
ALEXION PHARMACEUTICALS AUSTRALASIA PTY LTD**

**1 Purpose of submission**

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for the treatment of newly diagnosed and treatment refractory patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody positive.
- 1.2 The resubmission claimed that there is an unmet clinical need in newly diagnosed patients for treatments which have a rapid onset of action so that patients can achieve minimal symptoms quickly and reduce the prolonged time and negative impacts of cycling through therapies until symptom control is established.
- 1.3 The resubmission claimed that there is an unmet clinical need for alternative treatment options in treatment refractory patients who remain symptomatic despite the use of optimised existing therapies.
- 1.4 Listing was requested on the basis of a cost-effectiveness analysis versus placebo.

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

Component	Description
Population	<ul style="list-style-type: none"> <li>• Adult patients within 2 years of a diagnosis of AChR+ myasthenia gravis who have developed generalised symptoms and who remain symptomatic (MG-ADL <math>\geq</math> 6) despite stable doses of corticosteroids and/or non-steroidal immunosuppressants and who have failed prior treatment with IVIg/PLEX (unable to access, intolerant or inadequate response).</li> <li>• Adult patients with AChR+ generalised myasthenia gravis who remain symptomatic (MG-ADL score <math>\geq</math> 6) despite at least 24 months of treatment with corticosteroids and/or non-steroidal immunosuppressants and who have failed prior treatment with IVIg/PLEX (unable to access, intolerant or inadequate response).</li> </ul>
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, p5 of the resubmission

Abbreviations: AChR+, acetylcholine receptor antibody positive; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PLEX, plasma exchange

## 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 (gMG) who are anti-acetylcholine receptor (AChR) antibody-positive'.
- 2.2 Ravulizumab is also currently TGA approved for the treatment of paroxysmal nocturnal haemoglobinuria, atypical haemolytic uraemic syndrome and neuromyelitis optica spectrum disorders.

### Previous PBAC consideration

- 2.3 Ravulizumab is currently listed on the PBS for the treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome and received a positive recommendation for the treatment of neuromyelitis optica spectrum disorders at the November 2024 PBAC meeting.
- 2.4 The sponsor presented a Category 2 submission to the March 2024 PBAC meeting (which was held over to the July 2024 PBAC meeting) requesting a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for ravulizumab as a treatment for adult patients with generalised myasthenia gravis who are AChR-positive and remain symptomatic despite standard therapy.
- 2.5 At its July 2024 consideration, the PBAC did not recommend ravulizumab for the requested listing with the primary reason being the limitations of the comparative clinical evidence. The PBAC noted that the broad requested listing in the submission

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was consistent with clinician and patient feedback but 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 given that the existing therapies may be effective for many patients. 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 (para 7.1-7.3, ravulizumab Public Summary Document, July 2024 PBAC meeting).

2.6 The key matters of concern from the November 2024 PBAC meeting are summarised in Table 2.

**Table 2: Summary of key matters of concern**

Component	Matter of concern	How the resubmission addresses it
Place in therapy	The PBAC expressed a preference for listing the new therapies in a broad patient population, but also considered that the highest unmet clinical need was in patients who would otherwise be treated with chronic IVIg or PLEX (noting access to these therapies can be difficult) (para 7.5).	The resubmission positioned ravulizumab as a treatment option after prior failure of IVIg/PLEX in newly diagnosed and treatment refractory patients.
Proposed restriction	The PBAC noted that the proposed clinical criteria needed further refinement regarding prior therapies, continuation criteria and stopping rules and should be broken up into separate restrictions for non-refractory and refractory populations (para 7.6-7.9).	<p>The resubmission provided separate PBS listings for newly diagnosed and treatment refractory patients.</p> <p>The clinical criteria now require patients to have previous treatment with immunosuppressive therapies and IVIg/PLEX.</p> <p>The clinical criteria now define response as a 3-point reduction in MG-ADL score at 12 weeks rather than a 2-point reduction at 26 weeks.</p> <p>The newly diagnosed population listing includes a stopping rule limiting treatment to a maximum of 2 years</p>
Comparator	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 (para 7.10).	The resubmission nominated placebo as the main comparator in patients who have failed previous IVIg/PLEX treatment.
Clinical evidence	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 given that the existing therapies may be effective for many patients (para 7.1-7.3).	The resubmission provided separate subgroup analyses for patients with newly diagnosed disease and treatment refractory disease.

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Component	Matter of concern	How the resubmission addresses it
Economic model	<p>The PBAC 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.</p> <p>The PBAC agreed with ESC that the base case ICER was highly likely to have been underestimated and was implausible due to the assumptions that:</p> <ul style="list-style-type: none"> <li>• 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 all placebo patients lose treatment response within 1 year and can never achieve disease remission.</li> <li>• 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 (para 7.15-7.16).</li> </ul>	<p>The resubmission provided two separate economic models for patients with newly diagnosed and treatment refractory disease.</p> <p>Transition probabilities for treatment response, treatment discontinuation and loss of response were extensively revised in the resubmission. Patients in the placebo arm in the newly diagnosed model can now achieve a pharmacological remission.</p> <p>The resubmission revised utility values for subsequent therapies based on the assumption that newly diagnosed non-responders have the same utility value as patients with moderate disease while treatment refractory non-responders have the same utility value as patients with moderate-to-severe disease.</p>
Cost effectiveness estimate	<p>The PBAC considered the ICER presented in the submission was very high and likely to have been underestimated, and the proposed price was very high (para 7.1-7.3).</p>	<p>The resubmission proposed a █████% reduction in the effective price of ravulizumab.</p>
Budget impact	<p>The PBAC agreed with DUSC regarding the significant uncertainties regarding the prevalence of myasthenia gravis (potentially underestimated), the proportion of patients with generalised symptoms; the proportion of patients with MG-ADL <math>\geq 6</math> (likely underestimated); the expected uptake of ravulizumab (potentially underestimated); and the likely duration of ravulizumab treatment (para 7.17).</p>	<p>The resubmission used the same sources for epidemiology data but now includes growth over time.</p> <p>The proportion of patients with generalised symptoms and MG-ADL <math>\geq 6</math> have remained the same.</p> <p>The assumed uptake rate of ravulizumab was substantially increased.</p> <p>The likely duration of treatment was better defined for newly diagnosed patients with a maximum treatment limit of 2 years.</p>

Source: Table ES-1, pp XVII-XVIII of the resubmission

Abbreviations: DUSC, Drug Utilisation Sub-Committee; ESC, Economic Sub-Committee; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; PBAC, Pharmaceutical Benefits Advisory Committee; PLEX, plasma exchange; PSD, Public Summary Document

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**3 Requested listing**

MEDICINAL PRODUCT medicinal product pack	Dispensed price for Max. qty		Max. qty packs	Max. qty units	№.of Rpts	Available brands
	Published	Effective				
RAVULIZUMAB						
Initial treatment						
Ravulizumab, 300 mg/3 mL IV infusion	\$6,574.12 (Public hospital)	\$ (Public hospital)	1	1	2	Ultomiris
	\$6,622.49 (Private hospital)	\$ (Private hospital)				
Ravulizumab, 1,100 mg/11 mL IV infusion	\$24,105.11 (Public hospital)	\$ (Public hospital)	1	1	2	
	\$24,153.48 (Private hospital)	\$ (Private hospital)				
Continuing treatment						
Ravulizumab, 300 mg/3 mL IV infusion	\$6,574.12 (Public hospital)	\$ (Public hospital)	1	1	2	Ultomiris
	\$6,622.49 (Private hospital)	\$ (Private hospital)				
Ravulizumab, 1,100 mg/11 mL IV infusion	\$24,105.11 (Public hospital)	\$ (Public hospital)	1	1	2	
	\$24,153.48 (Private hospital)	\$ (Private hospital)				
<b>Category/Program:</b>	Section 100 – Highly Specialised Drugs Program					
<b>Prescriber type:</b>	Medical Practitioners					
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)					
<b>Authority type:</b>	: Complex Authority Required (CAR)					
<b>Condition:</b>	Generalised myasthenia gravis (gMG)					
<b>Indication:</b>	Generalised myasthenia gravis (gMG)					
<b>Treatment Phase:</b>	Initial treatment – newly diagnosed patient population – loading doses					
<b>Clinical criteria:</b>	Patient must have a diagnosis of generalised myasthenia gravis that is not pure ocular myasthenia gravis, AND					
	Patient must have been diagnosed with MG within the past 2 years prior to starting treatment with this therapy, AND					
	Patient must have been confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (anti-AChR antibodies), AND					
	Patient must not be experiencing a myasthenic crisis, AND					
	The treatment must be added on to at least one immunosuppressive therapy, AND					
	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 prior to initiation of ravulizumab, AND					
	Patient must have failed to achieve adequate response despite treatment with either (i) stable dose of oral steroids for a minimum of 1 month; or (ii) stable doses of non-steroidal immunosuppressive therapies for a minimum of 3 months, AND					
	Patient must have failed to achieve adequate response despite treatment with either at least one of (i) plasma exchange therapy for a minimum of 1 month; or (ii) intravenous immunoglobulins for a minimum of 4 months, if patient was able to receive and is tolerant to these therapies					
<b>Treatment criteria:</b>	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					
<b>Population criteria:</b>	Patients must be aged 18 years or older					

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<b>Prescribing Instructions:</b>	<p>Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application.</p> <p>Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application.</p> <p>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).</p> <p>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.</p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</p> <p>Two authority prescription forms will be required to cover for the 12 weeks of initial therapy with ravulizumab, one for the loading dose and one for the 10 weeks balance which can be sought under the Balance of Supply.</p> <p>The authority application must be in writing and must include all the following:                      (1) A completed authority prescription form(s).                      (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).                      (3) The baseline MG-ADL profile score</p>
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised
<b>Note:</b>	The MG-ADL profile score is available at: <a href="https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx">https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx</a>
<b>Caution:</b>	WARNING: This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Consult the approved PI for information about vaccination against meningococcal infection.
<b>Category/Program:</b>	<b>Section 100 – Highly Specialised Drugs Program</b>
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Balance of supply–maintenance doses - newly diagnosed patient population
<b>Clinical criteria:</b>	<p>Patient must have received PBS-subsidised loading dose of ravulizumab for this condition, AND</p> <p>The treatment must provide no more than the balance of up to 10 weeks treatment under this restriction</p>
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	<p>At the time of the authority application, medical practitioners should request the appropriate number of vials to cover 2 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).</p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</p> <p>The authority application must be in writing and must include:                      (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</p>

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<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Continuing treatment – newly diagnosed population
<b>Clinical criteria:</b>	Patient must have previously received PBS subsidised treatment with this drug for this condition, AND Patient must have demonstrated a clinical improvement based on a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 3 points from baseline, AND Patients must not receive more than 92 weeks of treatment in total under this restriction
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing instructions:</b>	The authority application must be in writing and must include all the following: (1) A completed authority prescription form(s); (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice); (3) The current MG-ADL profile score
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.
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<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Transition from non-PBS subsidised to PBS subsidised treatment (grandfather) – newly diagnosed patient population
<b>Clinical criteria:</b>	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to date of PBS listing AND Patient must have a diagnosis of generalised myasthenia gravis that is not pure ocular myasthenia gravis AND Patient must have been diagnosed with MG within the past 2 years prior to starting treatment with ravulizumab, AND Patient must have confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (AChR antibodies), AND The treatment must be added on to at least one immunosuppressive therapy, AND

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	<p>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</p> <p>Patient must have failed to achieve adequate response despite treatment with either (i) stable dose of oral steroids for a minimum of 1 month; or (ii) stable doses of non-steroidal immunosuppressive therapies for a minimum of 3 months, AND</p> <p>Patient must have failed to achieve adequate response despite treatment with either at least one of (i) plasma exchange therapy for a minimum of 1 month; or (ii) intravenous immunoglobulins for a minimum of 4 months, if patient was able to receive and is tolerant to these therapies OR</p> <p>Patient must have demonstrated a clinical improvement consistent with a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 3 points from baseline after 12 weeks of treatment, AND</p> <p>Patient must not receive more than 104 weeks supply with ravulizumab under the newly diagnosed patient restrictions</p>
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing instructions:</b>	<p>Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application.</p> <p>Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application.</p> <p>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).</p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</p> <p>The authority application must be in writing and must include all the following:</p> <ol style="list-style-type: none"> <li>(1) A completed authority prescription form(s)</li> <li>(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)</li> <li>(3) The baseline MG-ADL profile score</li> <li>(4) The current MG-ADL profile score</li> </ol>
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.
<b>Note:</b>	The MG-ADL profile score is available at: <a href="https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx">https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx</a>
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<b>Category/Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Initial treatment – refractory patient population – loading doses
<b>Clinical criteria:</b>	<p>Patient must have a diagnosis of generalised myasthenia gravis that is not pure ocular myasthenia gravis, AND</p> <p>Patient must have been confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (anti-AChR antibodies), AND</p>

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	Patient must not be experiencing a myasthenic crisis, AND
	The treatment must be added on to at least one immunosuppressive therapy, AND
	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 existing therapies prior to initiation of ravulizumab, AND
	Patient must have failed to achieve adequate response despite treatment with at least 2 immunosuppressive therapies for at least 24 months, either in combination or as monotherapy, AND
	Patient must have failed to achieve adequate response despite at least 1 month of plasma exchange (PE) or at least 4 months of intravenous immunoglobulin (IVIg), if patient was able to receive and is tolerant to these therapies, AND
<b>Treatment criteria:</b>	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.
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	<p>Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application.</p> <p>Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application.</p> <p>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).</p> <p>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.</p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</p> <p>Two authority prescription forms will be required to cover for the 12 weeks of initial therapy with ravulizumab, one for the loading dose and one for the 10 weeks balance which can be sought under the Balance of Supply.</p> <p>The authority application must be in writing and must include all of the following:</p> <ol style="list-style-type: none"> <li>(1) A completed authority prescription form(s);</li> <li>(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);</li> <li>(3) The baseline MG-ADL profile score</li> </ol>
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.
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<b>Category/Program:</b>	Section 100 – Highly Specialised Drugs Program CAR
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Balance of supply – maintenance doses - refractory patient population
<b>Clinical criteria:</b>	Patient must have received PBS-subsidised loading dose of ravulizumab for this condition, AND The treatment must provide no more than the balance of up to 10 weeks treatment under this restriction
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	At the time of the authority application, medical practitioners should request the appropriate number of vials to cover 2 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.  The authority application must be in writing and must include all the following: (1) A completed authority prescription form(s) (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). (3) The baseline MG-ADL profile score
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<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Continuing treatment – refractory patient population
<b>Clinical criteria:</b>	Patient must have previously received PBS subsidised treatment with this drug for this condition, AND Patient must have demonstrated a clinical improvement based on a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 3 points from baseline. AND Patients must not receive more than 24 weeks of treatment in total under this restriction.
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing instructions:</b>	The authority application must be in writing and must include all the following: (1) A completed authority prescription form(s) (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice) (3) The current MG-ADL profile score

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<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.
<b>Note:</b>	The MG-ADL profile score is available at: <a href="https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx">https://ultomiris.com/-/media/Ultomiris_gMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx</a>
<b>Caution:</b>	WARNING: This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Consult the approved PI for information about vaccination against meningococcal infection.
<b>Category/Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Recommencement of therapy – loading doses - refractory patient population
<b>Clinical criteria:</b>	<p>Patient must have received prior PBS-subsidised ravulizumab for this condition, AND</p> <p>Patient must not have experienced treatment failure with ravulizumab for this condition in the most recent treatment phase, AND</p> <p>Patient must not be experiencing a myasthenic crisis, AND</p> <p>The treatment must be added on to at least one immunosuppressive therapy, AND</p> <p>Patient must be experiencing symptoms consistent with a Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 6 points, AND</p> <p>Patient must have failed to achieve adequate response despite treatment with at least 2 immunosuppressive therapies for at least 24 months, either in combination or as monotherapy, AND</p> <p>Patient must have failed to achieve adequate response despite at least 1 month of plasma exchange (PE) or at least 4 months of intravenous immunoglobulin (IVIg), if patient was able to receive and is tolerant to these therapies</p>
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	<p>Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application.</p> <p>Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application.</p> <p>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).</p> <p>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.</p> <p>Applications for treatment with this drug where the dose and dosing frequency exceeds that specified in the approved PI will not be approved.</p> <p>Two authority prescription forms will be required to cover for the 12 weeks of initial therapy with ravulizumab, one for the loading dose and one for the 10 weeks balance which can be sought under the Balance of Supply.</p> <p>The authority application must be in writing and must include all the following:</p> <ol style="list-style-type: none"> <li>(1) A completed authority prescription form(s).</li> <li>(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).</li> <li>(3) The baseline MG-ADL profile score</li> </ol>
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.

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<b>Note:</b>	The MG-ADL profile score is available at: <a href="https://ultomiris.com/-/media/Ultomiris_qMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx">https://ultomiris.com/-/media/Ultomiris_qMG/pdf/gMG-ULTOMIRIS-ADL-Tool.ashx</a>
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<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Recommencement of therapy - Balance of supply – maintenance doses - refractory patient population
<b>Clinical criteria:</b>	Patient must have received PBS-subsidised loading dose of ravulizumab for this condition, AND The treatment must provide no more than the balance of up to 10 weeks treatment under this restriction
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application. Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application. At the time of the authority application, medical practitioners should request the appropriate number of vials to cover 2 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. The authority application must be in writing and must include all the following: (1) A completed authority prescription form(s). (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). (3) The baseline MG-ADL profile score
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<b>Category/Program:</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	Medical Practitioners
<b>Restriction Type:</b>	Authority Required (in writing only via post/HPOS upload)
<b>Condition:</b>	Generalised myasthenia gravis (gMG)
<b>Indication:</b>	Generalised myasthenia gravis (gMG)
<b>Treatment Phase:</b>	Transition from non-PBS subsidised to PBS subsidised treatment (grandfather) – refractory patient population
<b>Clinical criteria:</b>	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to date of PBS listing, AND Patient must have a diagnosis of generalised myasthenia gravis that is not pure ocular myasthenia gravis AND

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	Patient must have confirmed positive by serologic testing for anti-acetylcholine receptor antibodies (AChR antibodies), AND
	The treatment must be added on to at least one immunosuppressive therapy, AND
	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 existing therapies prior to initiation of ravulizumab, AND
	Patient must have failed to achieve adequate response despite treatment with at least 2 immunosuppressive therapies for at least 24 months, either in combination or as monotherapy, AND
	Patient must have failed to achieve adequate response despite at least 1 month of plasma exchange (PE) or at least 4 months of intravenous immunoglobulin (IVIg), if patient was able to receive and is tolerant to these therapies OR
	Patient must have demonstrated a clinical improvement consistent with a decrease in Myasthenia Gravis-Activities of Daily Living (MG-ADL) profile of at least 3 points from baseline after 12 weeks of treatment
<b>Treatment criteria:</b>	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
<b>Population criteria:</b>	Patients must be aged 18 years or older
<b>Prescribing Instructions:</b>	Where treatment with plasma exchange or intravenous immunoglobulin is not possible, details must be provided at the time of application. Where intolerance to treatment with oral steroids, plasma exchange or intravenous immunoglobulin develops during the relevant treatment period (of severity to necessitate treatment withdrawal), details must be provided at the time of application. 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. The authority application must be in writing and must include all the following: (1) A completed authority prescription form(s). (2) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice). (3) The baseline MG-ADL profile score (4) The current MG-ADL profile score
<b>Administrative Advice:</b>	No increase in the maximum number of repeats may be authorised.
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<b>Caution:</b>	WARNING: This drug increases the risk of meningococcal infections (sepsis and/or meningitis). Consult the approved PI for information about vaccination against meningococcal infection.

3.1 The resubmission proposed a special pricing arrangement for ravulizumab consisting of a 1% rebate on the published AEMP per vial (the March 2024 submission proposed a 1% rebate). This represented a 1% reduction in the proposed effective price of ravulizumab compared to the previous submission. The proposed published prices were unchanged.

Newly diagnosed/bridging setting

3.2 The proposed PBS restrictions for newly diagnosed patients limit treatment to patients within 2 years of diagnosis on the basis that this period is the most difficult for patients as most standard therapies require time for treatment optimisation. The evaluation

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considered that the appropriateness of this criteria was unclear as it may be reasonable to allow ravulizumab to be used in any patient meeting the other clinical criteria who initiate therapy with slower acting NS-ISTs and require bridging therapies for symptom control. In the key CHAMPION-MG trial, the average time to ravulizumab treatment in the newly diagnosed subgroup was 1.4 years (median 1.5 years) and these patients were not required to have prior intravenous immunoglobulin (IVIg) / plasma exchange (PLEX) treatment failure as proposed in the requested restriction.

- 3.3 The proposed newly diagnosed restriction requires patients to have received prior immunosuppressive therapy with a stable dose of oral corticosteroids for at least 1 month or a stable dose of NS-ISTs for at least 3 months. The evaluation considered that these requirements were not adequately justified in the resubmission but were consistent with expert advice provided with the resubmission which suggested that clinicians would not wait an extensive time to optimise therapy if ravulizumab were available. The expert advice summary noted that there was some debate about the prior therapy timeframes as some clinicians would prefer no specified dose or duration. The experts noted that NS-ISTs would not be expected to be effective within the nominated timeframes. Additionally, there was some discussion about the inclusion of a minimum dose requirement for prior corticosteroid therapy (prednisolone  $\geq$  10 mg/day).
- 3.4 As outlined in Section 7, the ESC considered that any PBS restriction for bridging therapy should require the patient to have trialled at least three months of combination therapy with all three of: an NS-IST; plus an anti-cholinesterase; plus a corticosteroid. The restriction should require these therapies to have been used at optimised dosing (though specific doses should not be outlined in the PBS restriction, to enable clinician judgement), unless contraindicated or severely intolerant. As such, the ESC considered that the timing of initiation of the new therapy should be based on a minimum of three months having elapsed since initiation of the NS-IST. Further, the ESC considered that the intention would be for the NS-IST to be continued concurrently with the new gMG therapy (unless contraindicated or severely intolerant).
- 3.5 The resubmission proposed a maximum treatment duration of 2 years for patients with newly diagnosed disease on the basis that this was a sufficient timeframe to optimise background immunosuppressive therapies. However, as outlined in Section 7, the ESC considered that, overall, the primary literature suggests that most patients generally respond to NS-ISTs within 12 months, with many patients responding within the first one to six months. The ESC considered that any PBS restriction for bridging therapy should require the patient to cease the new therapy after around six months of treatment. After three months of therapy cessation (i.e. a total of at least 12 months since NS-IST initiation), patients whose condition remains uncontrolled may recommence under the refractory listing. Overall, the maximum treatment duration in the bridging setting would be around six months.

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- 3.6 The pre-PBAC response reiterated the submission's requested treatment duration of 2 years, stating NS-ISTs need 18-24 months to optimise and achieve symptom control.

Refractory setting

- 3.7 The proposed treatment refractory restriction requires patients to have received prior immunosuppressive therapy with at least 2 immunosuppressive agents for at least 24 months, either in combination or as monotherapy. The resubmission claimed this requirement was consistent with the definition of treatment refractory disease in international guidelines (Sanders 2016). However, this definition was not consistent with the international guidelines which suggest prior therapy with corticosteroids and at least 2 other immunosuppressive therapies used at adequate doses for adequate durations. The 2-year timeframe was not adequately justified in the resubmission but appears to be related to the duration of time required for NS-ISTs to be optimised. The evaluation and the ESC considered that this duration was not consistent with the proposed disease management algorithms provided by the sponsor to the clinical experts which proposed a 12-month prior treatment duration and was not consistent with the definition of treatment refractory disease used in the post hoc analysis of the key clinical trial (which used a 12-month prior treatment duration).
- 3.8 As outlined in Section 7, the ESC considered any PBS restriction for the refractory setting should require the patient to have prior treatment for at least one year. The ESC considered that further work would be required to determine the specific therapies and durations.
- 3.9 The resubmission did not propose a maximum treatment duration for patients with treatment refractory disease. This was not consistent with the economic model which assumed a maximum treatment duration of 8 years.

Both settings

- 3.10 As outlined in Section 7, the ESC noted that the National Blood Authority (NBA) qualifying criteria for IVIg<sup>1</sup> specifies that the patient has a Myasthenic Gravis Composite (MGC) of at least 4 points; and at least 2 other treatments are ineffective, contraindicated, unavailable or caused intolerable side effects. The ESC considered this was broad as the other treatments could comprise two of: an anti-cholinesterase; a corticosteroid; or thymectomy (i.e. there is no requirement for the patient to have trialled an NS-IST) and no time periods or doses are specified.
- 3.11 Both the newly diagnosed and treatment refractory proposed restrictions require patients to be unable to access IVIg/PLEX or have an intolerance or inadequate response to these therapies. The expert advice provided with the resubmission indicated that IVIg is widely available in Australia. The resubmission did not provide any clinical data for ravulizumab in patients who are intolerant or experience an inadequate response to chronic IVIg/PLEX. Overall, the ESC considered that a key

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<sup>1</sup> Criteria for Clinical Use of Immunoglobulin in Australia, accessed at: <https://www.criteria.blood.gov.au/MedicalCondition/View/2681>

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benefit of the new gMG therapies would be to reduce IVIg use, and as such, there should be no requirement for the patient to have trialled (and have had an intolerance or inadequate response to) prior IVIg or PLEX. Further, the ESC considered that: the submission's proposed criteria could encourage earlier use of IVIg/PLEX; and the criteria around 'able to receive' IVIg/PLEX were subjective. The pre-PBAC response stated this requirement was to target patients with the highest clinical need, however the PBAC agreed with ESC that there should be no requirement for the patient to have trialled (and have had an intolerance or inadequate response to) prior IVIg or PLEX.

- 3.12 Further, the ESC considered that the PBS restriction should state that ravulizumab should not be used in combination with maintenance IVIg. The ESC considered that in both settings, the new gMG therapies should substitute for intravenous immunoglobulin (IVIg) and plasma exchange (PLEX) rather than be added on to or used in combination with these modalities.
- 3.13 The resubmission proposed changing the continuation criterion from at least a 2-point reduction in MG-ADL score at 6 months in the March 2024 PBAC submission to at least a 3-point reduction in MG-ADL score at 12 weeks in the current resubmission. The resubmission noted that this change was consistent with expert advice from treating physicians and the May 2024 Myasthenia Gravis stakeholder meeting<sup>2</sup>. The resubmission noted that this change should also address PBAC's concerns regarding the large placebo effects observed using a 2-point threshold. The evaluation noted that while the change in threshold and timing of the assessment may individually appear reasonable their combined effect in the key trial resulted in relatively small incremental differences in response rates between treatment arms (ravulizumab responders 52.3% versus placebo responders 46.5%) comparable to the original estimates raised as a concern by PBAC (ravulizumab responders 63.9% versus placebo responders 53.0%).

*For more detail on PBAC's view, see section 8 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.
- 4.2 The disease 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

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<sup>2</sup> Myasthenia Gravis Stakeholder Meeting (May 2024) Outcome Statement, Available at: <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/stakeholder-meetings>

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double vision, shortness of breath, difficulty chewing and swallowing, impaired speech, fatigue, pain, muscle spasms and general muscle weakness. 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 resulting in respiratory failure requiring mechanical ventilation.

- 4.3 Patient perspectives included in the resubmission indicate that the fluctuating and unpredictable nature of 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 resubmission 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.
- 4.4 The symptoms of myasthenia gravis can develop at any age (including childhood) but more commonly impacts young adult women and older men. The intensity of muscle weakness can fluctuate from day to day and can be worsened due to fatigue, stress, current illness and other factors. Based on its natural history, the disease reaches maximum, or near maximum, severity in the first 2 years after onset of symptoms and most patients with ocular myasthenia gravis will develop generalised symptoms over time. The resubmission noted that the mortality of patients with myasthenia gravis has decreased over the years and most patients have a normal lifespan.
- 4.5 A recent systematic review and meta-analysis of myasthenia gravis epidemiology studies (Sciancalepore 2024) noted that the global incidence has more than doubled from 8.7 cases per million person-years in the period 1967-2007 to 22.9 cases per million person-years in the period 2008-2022; and prevalence has increased from 97.5 cases per million person-years in the period 1952-2007 to 220.1 cases per million person-years in the period 2008-2021.
- 4.6 Current treatment guidelines recommend the use of anti-cholinesterases in most patients with AChR positive generalised myasthenia gravis. However, the guidelines note that the majority of patients will also require immunosuppressive therapy, with corticosteroids used as the main first-line treatment option. The guidelines state that other immunosuppressive agents 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 guidelines note that chronic IVIg/PLEX can be used as bridging therapies while patients adjust to other slower-acting immunosuppressive agents. Patients with treatment-refractory disease (variable definitions in the literature) can receive treatment with chronic IVIg/PLEX, eculizumab (not registered

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in Australia for myasthenia gravis), cyclophosphamide or rituximab. Acute management of exacerbations typically involves the use of high dose corticosteroids, IVIg or PLEX in the community or hospital setting depending on severity.

- 4.7 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.
- 4.8 The clinical management algorithm presented in the resubmission appeared to position ravulizumab as a new 'second-line' bridging therapy in newly diagnosed patients with prior treatment failure (unable to access, intolerant or inadequate response) to IVIg/PLEX. The resubmission also appeared to position ravulizumab as a last-line therapy in patients with treatment refractory disease (after prior use of standard therapies, IVIg/PLEX, rituximab and cyclophosphamide).
- 4.9 However, the ESC considered the requirement for patients to have previously tried IVIg/PLEX was inappropriate (refer to paragraph 3.11).
- 4.10 The evaluation considered that the clinical place in therapy for ravulizumab was unclear, particularly as the use of ravulizumab and other similar agents for the treatment of myasthenia gravis are yet to be incorporated into most treatment guidelines.

*For more detail on PBAC's view, see section 8 PBAC outcome.*

## **5 Comparator**

- 5.1 The resubmission nominated placebo as the main comparator for newly diagnosed patients. The main argument provided in support of this nomination was that ravulizumab would be used as an add-on to standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, cyclosporin) in patients with prior treatment failure to IVIg/PLEX (unable to access, intolerant or inadequate response) and would not directly substitute for other therapies. This was inconsistent with the proposed treatment algorithm and economic model which indicated that use of ravulizumab as a new line of therapy in this population would displace the use of rituximab, cyclophosphamide and high dose corticosteroids. The evaluation considered that the appropriate comparator in this population was unclear as, in the absence of ravulizumab (which requires prior failure of IVIg/PLEX), it was unclear whether patients would initiate IVIg/PLEX as early in the treatment pathway.
- 5.2 The resubmission nominated placebo as the main comparator for treatment refractory patients. The main argument provided in support of this nomination was that ravulizumab would be used as a last-line therapy in this population. This was

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consistent with the proposed treatment algorithm but was inconsistent with the economic analysis which positioned ravulizumab as a new line of therapy immediately prior to using rituximab and cyclophosphamide. Overall, the evaluation considered that placebo would be an appropriate comparator in patients who have failed all other treatment options (including rituximab and cyclophosphamide), but for treatment-refractory patients who have only failed prior IVIg/PLEX the appropriate comparators would be rituximab and cyclophosphamide.

- 5.3 At its July 2024 meeting, 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” (paragraph 7.10, ravulizumab Public Summary Document (PSD), July 2024 PBAC meeting).
- 5.4 As outlined in Section 7, the ESC reiterated the PBAC’s previous advice that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost per patient of the newer gMG therapies in the refractory setting.
- 5.5 The resubmission identified zilucoplan (a complement inhibitor), and efgartigimod and rozanolixizumab (medicines that target the neonatal Fc receptor (FcRn)) as near-market comparators. This evaluation and the ESC considered this was appropriate. Submissions for PBS listing of these additional therapies were also considered at the March 2025 PBAC meeting.

*For more detail on PBAC’s view, see section 8 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the high clinical need for new treatments for gMG and the impact the condition has on patient quality of life including the impact on employment and the adverse effects of corticosteroids. The clinician outlined that while IVIg is effective in some patients (though many patients do not respond or respond sub-optimally), particularly if high doses are used (higher doses than those generally used in Australian practice), the long infusion times are not compatible with returning to work. The new therapies (both complement inhibitors and FcRn blockers) are more practical from an administration perspective.
- 6.2 The clinician stated that neurologists would like both classes (complement inhibitors and FcRn blockers) to be available, with the choice as to which drug class to use in a particular circumstance to be left to clinician discretion, taking into account individual

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patient circumstances (e.g. mode of administration). The clinician stated the eligible population for the new therapies should be based on the clinical trials in terms of disease severity. While acknowledging the trials recruited a largely refractory cohort, the clinician also outlined the value of the new therapies in the bridging setting, particularly in patients receiving a corticosteroid and NS-IST, and who have not responded to IVIg.

**Consumer comments**

- 6.3 The PBAC noted and welcomed the input from individuals (16), health care professionals (1 individual clinician, plus a group of 11 neurologists) and an organisation (Myasthenia Alliance Australia (MAA)) via the Consumer Comments facility on the PBS website. The comments described the high unmet need for new therapies to treat gMG. The comments outlined 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. The comments also described the impact on family, along with the financial burden associated with the condition. The comments also described the limitations of currently available treatment options including adverse events and lengthy administration times. The comments outlined a hope that the new therapies will reduce gMG symptoms, reduce the need for other medications and associated side-effects, and reduce hospital visits, contributing to an overall improved quality of life.
- 6.4 The comments noted the efficacy associated with ravulizumab and the rapid onset of action. The input outlined the risk of infection associated with ravulizumab including the risk of meningococcal infection. However, the majority of contributors expressed an enthusiasm to try ravulizumab regardless of potential adverse events due to its reported efficacy. An individual currently accessing ravulizumab outlined the substantial improvement in their quality of life since commencing the drug.
- 6.5 Advice from MAA stated its aim is for each patient to have equitable and timely access to the best available treatment that most benefits them. MAA supported access to the new therapies across the disease severities and settings including early, upfront access and also in patients with refractory disease, noting that refractory patients have a higher unmet need. MAA strongly supported access to a broad range of treatment options. The input received from MAA, and from individual consumers, indicated that the mode of administration is important to consumers, with 63% of participants in a recent survey indicating they are seeking a more manageable or flexible treatment option. MAA outlined that the new therapies represent a substantial improvement in administration time compared with IVIg, and also shorter travel distances for patients outside metropolitan areas. MAA highlighted that continuous and reliable treatments are important for patients and that a meaningful response would comprise well-controlled symptoms within a reasonably quick timeframe. The comments outlined that even a small improvement in the MG-ADL score can be meaningful for patients

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e.g. it may represent a capacity to perform a daily activity the patient was previously unable to perform.

- 6.6 Advice from a group of 11 neurologists highlighted the significant unmet need for patients with moderate to severe gMG, including the need for more modes of rapid onset treatments. The neurologists outlined that “combination therapy right from the start of treatment of a moderate to severe gMG patient is the norm including the use of quick onset pathogenic antibody treatments, currently principally IVIg. Whether in an individual patient one would use IVIG, PLEX; or an FcRn or a complement inhibitor if all were equally available would probably depend on individual benefit first, and ease, tolerance and accessibility a significant second.” The neurologists acknowledged that the trials largely included patients with long-standing gMG and significant use of prior treatments, but stated this should not be the only group able to access these new treatments. In terms of value optimisation, the neurologists proposed the following:
- a) These therapies should be restricted to gMG patients with AChR antibodies;
  - b) The severity of MG at commencement should be similar to the trial populations (MG-ADL of 5-6), which is more severe than the NBA criteria for IVIg. There should be a clinician-reported component to assessing the need for therapy and response. The clinician letter stated “this means also using MGC [Myasthenia Gravis Composite score]. Corresponding values MG-ADL 5-6 are MGC 10-12” noting the 95% confidence intervals for MGC values in patients entering the pivotal RCTs could help improve accuracy of the correlation.
  - c) The therapy should be co-administered with two other therapies with remission induction intent, including corticosteroids and NS-ISTs. This does include therapeutic thymectomy which should be treated as equivalent to an NS-IST. This does not include pyridostigmine or other cholinesterase inhibitors.
  - d) Patients should either have had an adequate dose AND duration of these two other therapies, perhaps one year; OR be taking an adequate dose of these two other therapies without requiring a set duration AND have failed a loading course of IVIg or plasma exchange.
  - e) Response to therapy should be assessed and the therapy only continued if there is a clear response, at least minimal clinically important differences (MCID) values of MG-ADL improvement by  $\geq 2$  points, MGC by  $\geq 3$  points. The timing of the test of response to therapy should be early (at 2-16 weeks).
  - f) “FcRn inhibitors are naturally stopped after 4 (efgartigimod) to 6 (rozanolixizumab) weeks of therapy. These therapies can be restarted if the severity of MG worsens to the minimum commencement threshold. Note on second or subsequent cycles the starting severity score while at or above threshold might be better, the same or worse than the first cycle – the underlying MG severity can worsen over time in some patients. Over the course

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of 6 months therapy these gaps in treatment can be considered intermittent trials of suspension of therapy.”

- g) Complement inhibitors should be temporarily suspended to see if they are still needed after a suitable period of therapy, perhaps one year in the first instance and perhaps two years if a patient deteriorates on the initial suspension. “Complement inhibitors should not in our view be continued if they are not needed. There is no good reason to suppose the risks of temporarily stopping complement inhibitors are any greater than the risks of temporarily stopping IVIg, PLEX or FcRn inhibitors all of which routinely stopped. There is little published data on stopping complement inhibitors for MG but we are aware that international colleagues have stopped complement inhibitors in MG patients without ill effects”.
- h) Final restriction discussions should include input from a broader range of neurologists and also the patient association.

***Clinical studies***

- 6.7 Compared to the March 2024 submission, the clinical evidence in the current resubmission was updated with new analyses of study outcomes at 12 weeks, additional post hoc subgroup analyses of newly diagnosed and treatment refractory subgroups in the CHAMPION-MG trial as well as longer term data from the final analysis of the open-label extension study and the most recent Periodic Benefit Risk Evaluation Report.
- 6.8 The resubmission was based on one head-to-head randomised trial comparing ravulizumab to placebo in patients with generalised myasthenia gravis (CHAMPION-MG).
- 6.9 Details of the included studies are provided in Table 3.

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**Table 3: Studies and associated reports presented in the resubmission**

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
	Alexion (2023). 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. End of study clinical study report addendum.	Internal study report
	Howard et al (2024). Efficacy of ravulizumab in patients with generalized myasthenia gravis by time from diagnosis: a post hoc subgroup analysis of the CHAMPION MG study.	Muscle & Nerve 69: 556-565.
	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
	Vu et al (2023). Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis.	Journal of Neurology 270: 3129-3137
	Vu et al (2022). Terminal complement inhibitor ravulizumab in generalized myasthenia gravis.	New England Journal of Medicine Evidence 1(5)

Source: Table 2A-3, p70 of the resubmission

Note: Abstracts of studies with full publications are not presented

6.10 The key features of the CHAMPION-MG trial are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Ravulizumab vs. placebo</b>						
CHAMPION-MG	175	MC, R, DB, PC, 26 weeks duration with open-label extension to 4 years (mean exposure 2.33 years)	Low <sup>a</sup>	AChR+ generalised myasthenia gravis with functional impairment (MG-ADL ≥ 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: Table 2A-4, p74; Section 2A.4, pp80-85 of the resubmission

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.

<sup>a</sup> The CHAMPION-MG trial had a low risk of bias. However, the extension study, in which all patients received ravulizumab treatment, was at high risk of bias given the observational study design.

### Comparative effectiveness

6.11 The mean change in MG-ADL score from baseline with ravulizumab and placebo in the CHAMPION-MG trial is summarised in Table 5.

**Table 5: Mean change in MG-ADL scores from baseline with ravulizumab and placebo**

Treatment arm	Baseline, Mean (SD)	Final, Mean (SD)	LS mean change (95% CI)	Treatment difference (95% CI)
<b>Change from baseline to Week 12</b>				
Ravulizumab N = 83	9.2 (2.65)	5.8 (3.87)	-3.3 (-3.9, -2.6)	-1.0 (-1.9, -0.2)
Placebo N = 84	8.9 (2.23)	6.6 (3.49)	-2.2 (-2.9, -1.5)	
<b>Change from baseline to Week 26</b>				
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)	

Source: Table 2A-21, p102 of the resubmission; Table 14.2.1.1.2.1, pp701-702, Table 14.2.1.1.15.1, pp719-721 of the CHAMPION-MG trial report

Abbreviations: CI, confidence interval; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; MMRM, mixed model for repeated measures; SD, standard deviation

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

Note: Results based on the MMRM full analysis set that includes treatment group, stratification factor region and MG-ADL total score at baseline, study visit, and study visit by treatment group interaction.

- 6.12 Treatment with ravulizumab was associated with a small but nominally significant improvement in MG-ADL scores compared to placebo over 12 weeks (difference of 1.0 point on a 25-point scale). The difference between treatment arms improved slightly at 26 weeks (difference of 1.6 points) primarily due to a smaller reduction in MG-ADL scores from baseline in the placebo arm.
- 6.13 Differences between treatment arms in mean MG-ADL scores were observed by Week 1 and were maintained over the 26-week randomised treatment period. Data from the final analysis of the extension study suggest that the improvement in MG-ADL scores observed with ravulizumab treatment may be sustained over the longer term, with follow-up data indicating no loss of effect for up to 164 weeks (least squares mean change at Week 164: -4.0, 95% CI -5.3, -2.8).
- 6.14 A similar pattern of results was also observed using other functional measures (QMG and MGC instruments).
- 6.15 The proportion of patients achieving different MG-ADL response thresholds is summarised in Table 6.

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**Table 6: Responder analysis of MG-ADL scores from baseline with ravulizumab and placebo**

Treatment arm	Adjusted % (95% CI)	Odds Ratio (95% CI)
<b>Proportion of patients with ≥ 3-point reduction on MG-ADL score at Week 12</b>		
Ravulizumab N = 83	52.3 (40.2, 64.1)	1.259 (0.679, 2.335)
Placebo N = 84	46.5 (34.9, 58.5)	
<b>Proportion of patients with ≥ 3-point reduction on MG-ADL score at Week 26</b>		
Ravulizumab N = 78	56.7 (44.3, 68.3)	2.526 (1.330, 4.799)
Placebo N = 82	34.1 (23.8, 46.1)	
<b>Proportion of patients with ≥ 2-point reduction on MG-ADL score at Week 26</b>		
Ravulizumab N = 78	63.9 (51.7, 74.6)	1.569 (0.833, 2.955)
Placebo N = 82	53.0 (41.1, 64.6)	

Source: Table 14.2.2.5.1.1.1, p955; Table 14.2.2.5.1.2.1, p958 of the CHAMPION-MG trial report

Abbreviations: CI, confidence interval; GLMM, generalised linear mixed model; MG-ADL, Myasthenia Gravis Activities of Daily Living

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

Note: Estimates are based on a GLMM that includes treatment group, stratification factor region and MG-ADL total score at baseline, study visit, and study visit by treatment group interaction. An unstructured covariance structure was used.

- 6.16 There was no statistically significant difference in the proportion of treatment responders between arms based on a 2-point difference at 26 weeks or 3-point difference in MG-ADL score at 12 weeks. However, treatment with ravulizumab was associated with a nominally significant increase in the proportion of treatment responders based on a 3-point difference in MG-ADL score at 26 weeks (OR 2.526, 95% CI 1.330, 4.799).
- 6.17 There was no statistically significant difference in quality-of-life outcomes or clinical deterioration events between treatment arms although results numerically favoured ravulizumab.
- 6.18 The resubmission presented additional post hoc subgroup analyses of newly diagnosed and treatment refractory populations based on the following definitions:
- Newly diagnosed population: Patients who were diagnosed with myasthenia gravis (ocular or generalised) in the previous 2 years AND have functional impairment (MG-ADL ≥ 6) despite no therapy or stable immunosuppressive therapy.
  - Treatment refractory population: Patients who have a prior history of using at least 2 immunosuppressant therapies as monotherapy or in combination for at least 12 months OR patients with a prior history of using at least 1 immunosuppressant therapy and chronic IVIG/PLEX for at least 12 months AND have functional impairment (MG-ADL ≥ 6) despite current stable treatment with at least 1 immunosuppressant therapy.
- 6.19 There was overlap between the treatment refractory and newly diagnosed subgroup definitions, however the extent of the overlap could not be determined.
- 6.20 The definitions were not consistent with the target PBS populations as the resubmission’s proposed PBS restriction would require a more extensive history of prior treatment use for both subgroup populations (newly diagnosed patients need to have trialled at least 1 immunosuppressive therapy and failed prior IVIg/PLEX while

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treatment refractory patients need to have trialled immunosuppressive therapies for at least 2 years and failed prior IVIg/PLEX).

- 6.21 The newly diagnosed subgroup population had a higher proportion of male patients with an older average age at diagnosis compared to the complement subgroup. Patients also had a shorter average disease duration but were more likely to have received treatment with corticosteroids only and less likely to have received combination immunosuppressive therapy compared to other patients. Additionally, due to the small patient numbers included in the newly diagnosed subgroup there were imbalances in patient characteristics between treatment arms particularly in regard to severity of muscle weakness, prior history of exacerbations and baseline immunosuppressive therapy.
- 6.22 The Pre-Sub-Committee Response (PSCR) acknowledged the limitations of the subgroup analyses, but stated that the resubmission “provided the best available evidence for this rare disease to support informed decision-making”.
- 6.23 Table 7 summarises the change in MG-ADL score with ravulizumab and placebo in the subgroup populations of the CHAMPION-MG trial.

**Table 7: Mean change in MG-ADL scores from baseline with ravulizumab and placebo in post hoc subgroup populations**

Population	Ravulizumab	Placebo	Treatment difference	Treatment interaction p-value
<b>Least squares mean change (95% CI) in MG-ADL score from baseline to Week 12</b>				
Overall population	-3.3 (-3.9, -2.6) N = 83	-2.2 (-2.9, -1.5) N = 84	-1.0 (-1.9, -0.2)	-
Newly diagnosed subgroup	-4.3 (-5.7, -2.8) N = 19	-1.7 (-3.2, -0.1) N = 14	-2.6 (-4.6, -0.6)	0.0793
Complement established disease subgroup	-3.0 (-3.7, -2.2) N = 64	-2.4 (-3.1, -1.6) N = 70	-0.6 (-1.6, 0.4)	
Treatment refractory subgroup	-3.1 (-4.1, -2.2) N = 38	-2.1 (-2.9, -1.2) N = 47	-1.1 (-2.3, 0.2)	0.8262
Complement non-refractory subgroup	-3.3 (-4.2, -2.4) N = 45	-2.5 (-3.4, -1.5) N = 37	-0.9 (-2.1, 0.4)	
<b>Least squares mean change (95% CI) in MG-ADL score from baseline to Week 26</b>				
Overall population	-3.1 (-3.8, -2.3) N = 78	-1.4 (-2.1, -0.7) N = 82	-1.6 (-2.6, -0.7)	-
Newly diagnosed subgroup	-4.3 (-5.8, -2.7) N = 17	-1.4 (-3.1, 0.3) N = 13	-2.9 (-5.1, -0.7)	0.1994
Complement established disease subgroup	-2.7 (-3.5, -1.9) N = 61	-1.4 (-2.2, -0.7) N = 69	-1.3 (-2.3, -0.2)	
Treatment refractory subgroup	-3.0 (-4.1, -1.9) N = 34	-1.3 (-2.2, -0.3) N = 46	-1.7 (-3.1, -0.4)	0.7858
Complement non-refractory subgroup	-3.1 (-4.1, -2.1) N = 44	-1.6 (-2.7, -0.6) N = 36	-1.5 (-2.8, -0.1)	

Source: Table 2A-21, p102; Table 2A-22, p103 of the resubmission; Table 14.2.1.1.2.1, pp701-702, Table 14.2.1.1.15.1, pp719-721; Table 2B-13, p175; Table 2B-14, p176 of the resubmission; Table 14.2.1.1.2.1, pp701-702, Table 14.2.1.1.15.1, pp719-721 of CHAMPION-MG trial report.

Abbreviations: CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living score; MMRM, mixed model for repeated measures

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6.24 There was no statistically significant treatment interaction by time since diagnosis or treatment refractory status although the treatment difference between ravulizumab and placebo was numerically larger in the newly diagnosed patient subgroup.

6.25 The proportion of patients achieving a 3-point reduction in MG-ADL scores from baseline in the subgroup populations are summarised in Table 8.

**Table 8: Responder analysis with ravulizumab and placebo in post hoc subgroup populations**

Population	Ravulizumab	Placebo	Treatment difference	Treatment interaction p-value
<b>Proportion of patients with ≥ 3-point reduction on MG-ADL score at Week 12</b>				
Overall population	52.3% (40.2, 64.1) N = 83	46.5% (34.9, 58.5) N = 84	OR 1.259 (0.679, 2.335)	-
Newly diagnosed subgroup	73.7% N = 19	35.7% N = 14	38.0% (6.0, 69.9)	NR
Complement established disease subgroup	50.0% N = 64	51.4% N = 70	-1.4% (-18.4, 15.5)	
Treatment refractory subgroup	55.2% (36.9, 72.1) N = 38	46.8% (30.9, 63.4) N = 47	OR 1.397 (0.569, 3.432)	NR
Complement non-refractory subgroup	50.6% (34.3, 66.9) N = 46	47.3% (30.2, 65.2) N = 37	OR 1.142 (0.464, 2.813)	
<b>Proportion of patients with ≥ 3-point reduction on MG-ADL score at Week 26</b>				
Overall population	56.7% N = 86	34.1% N = 89	OR 2.526 (1.330, 4.799)	-
Newly diagnosed subgroup	70.6% N = 17	38.5% N = 13	32.1% (-2.1, 66.3)	NR
Complement established disease subgroup	57.4% N = 61	36.2% N = 69	21.1% (4.3, 38.0)	
Treatment refractory subgroup	61.5 % (42.3, 77.7) N = 34	38.8% (24.0, 56.1) N = 46	OR 2.519 (0.984, 6.447)	NR
Complement non-refractory subgroup	53.9% (37.1, 69.9) N = 44	29.2% (15.9, 47.4) N = 36	OR 2.835 (1.105, 7.271)	

Source: Table 2A-26, p117; Table 2B-17, Table 2B-18, p186 of the resubmission; Table 14.2.2.5.1.1.1, p955; Table 14.2.2.5.1.2.1, p958 of CHAMPION-MG trial report

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; NR, not reported; OR, odds ratio

Note: The CHAMPION-MG study report used adjusted percentage for the overall population and treatment-refractory subgroups, based on a generalised linear mixed model that included treatment group, stratification factor region and MG-ADL total score at baseline, study visit, and study visit by treatment group interaction. The resubmission did not report adjustment of the newly diagnosed subgroup and complement subgroup proportions. Confidence interval of difference in proportions for subgroups was based on the Wald method.

6.26 The proportions of patients in the newly diagnosed subgroup with an improvement of at least 3 points in MG-ADL at Week 12 and Week 26 were numerically greater in the ravulizumab arm compared to the placebo arm. This difference appeared numerically larger than observed in the overall population or the complement established disease subgroup.

6.27 The proportion of patients in the treatment refractory subgroup with an improvement of at least 3 points in MG-ADL was similar between arms at Week 12 but was numerically greater in the ravulizumab arm compared to the placebo arm at Week 26. The results in the treatment refractory subgroup were similar to the estimates from both the overall population and complement non-refractory subgroup. The PSCR outlined that, in the newly diagnosed subgroup there was a statistically significant

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greater proportion of responders in the ravulizumab group than in the placebo group at 12 weeks (73.7% vs 35.7%; p=0.0397). However, the ESC noted the imbalances in patient characteristics between treatment arms in this subgroup (refer to paragraph 6.21).

- 6.28 During the evaluation, summary details were presented of 5 published network meta-analyses (NMAs) that compared ravulizumab and near market comparators efgartigimod, zilucoplan, and rozanolixizumab (Chen 2023, Gu 2024, Sacca 2023, Smith 2024, Zhong 2024) and one published matching adjusted indirect comparison that compared efgartigimod and ravulizumab (van Steen 2024).
- 6.29 The evaluation noted that results of the indirect treatment comparisons suggest that FcRn blockers (e.g. efgartigimod, rozanolixizumab) may provide improved outcomes for patients with generalised myasthenia gravis, compared to complement inhibitors (e.g. ravulizumab, zilucoplan). However, the published analyses acknowledge the difficulties in comparing the different therapies due to differences between treatments administered with fixed dosing intervals compared to treatments administered as on/off treatment cycles, which does not account for the treatment effects waning over time during the off-treatment period. The publications also noted other limitations, including differences between trials in patient characteristics and prior and concomitant therapies, and the lack of direct evidence resulting in reliance on indirect estimates. The PSCR further outlined that complement inhibitors “achieve stable and prolonged improvements on both the MG-ADL and QMG scales during the randomised controlled period and extension phase of their trials”. In contrast, FcRn blockers “are administered cyclically with treatment effects 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”.
- 6.30 None of the indirect treatment comparisons included IVIg or PLEX trials.

**Comparative harms**

- 6.31 An overall summary of the adverse events reported in the CHAMPION-MG trial is presented in Table 9.

**Table 9: 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%)
<b>Adverse events of special interest</b>		
Meningococcal infection	0 (0.0%)	0 (0.0%)
Infusion-related reactions	28 (32.6%)	28 (31.5%)

Source: Table 2A-33, p126 of the resubmission

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- 6.32 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.
- 6.33 Treatment with ravulizumab was associated with a higher incidence of serious adverse events compared to the placebo arm (including a higher incidence of infections and infestations). Two serious adverse events were considered related to ravulizumab including one case each of dysphagia and tendonitis. No treatment-related deaths were reported in either treatment arm.
- 6.34 The final analysis of the extension study (25 May 2023 cut-off; 342 patient years of therapy) did not identify any additional safety concerns with ravulizumab treatment.
- 6.35 The current Periodic Benefit Risk Evaluation Report (January 2023 to December 2023) for ravulizumab noted that during this period, regulators required enhancements to the risk evaluation and mitigation strategy to manage the risk of meningococcal infection. The current TGA-approved product information for ravulizumab now indicates that there is a potential role for the ongoing use of preventative antibacterials to reduce the risk of meningococcal infection.

**Benefits/harms**

- 6.36 On the basis of direct evidence presented in the submission, for every 100 patients treated with ravulizumab in comparison with placebo for 26 weeks in the overall trial population:
- 23 additional patients would experience a clinically important improvement in functional outcomes ( $\geq$  3-point reduction on MG-ADL score, refer to Table 6).
  - Approximately 8 additional patients would experience a serious adverse event.
- 6.37 During the evaluation, the post hoc subgroup analyses presented in the submission were not considered sufficiently robust to assess the benefits/harm in these populations. Additionally, the resubmission did not present an assessment of safety outcomes at 12 weeks to allow a benefit/risk assessment at the earlier timepoint.

**Clinical claim**

- 6.38 The resubmission 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 in generalised myasthenia gravis patients with newly diagnosed disease or treatment refractory disease. The evaluation and the ESC considered that this claim was reasonable. The ESC reiterated the PBAC's previous advice that the incremental benefit appeared modest, noting the high placebo response rates reported in the trial.
- 6.39 The evaluation and the ESC considered that the following issues should be noted for the comparison versus standard care:

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- The resubmission claimed differences in treatment effects in the subgroup populations compared to the overall population which were not well supported by the available data. Overall, the ESC considered that the subgroup analyses remained difficult to interpret given the lack of statistically significant treatment interactions and the uncertainty associated with numerical differences due to small patient numbers, non-representative samples and imbalances in patient characteristics between treatment arms.
  - The differences between treatment arms appeared more robust using the Week 26 endpoint rather than the Week 12 endpoint due to the substantial placebo effects observed at the earlier timepoint.
- 6.40 The ESC and the PBAC acknowledged the limitations of the available evidence for chronic IVIg but considered that there was insufficient evidence to suggest superior efficacy or safety of ravulizumab versus chronic IVIg or PLEX.
- 6.41 Further, the ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod alfa and rozanolixizumab). The ESC considered that the published NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 6.42 Overall, the PBAC considered that ravulizumab has non-inferior comparative effectiveness and safety versus chronic IVIg and also against zilucoplan, efgartigimod and rozanolixizumab.

***Economic analysis***

- 6.43 The economic evaluation was extensively revised from the March 2024 submission which presented an economic analysis of ravulizumab when used as a treatment option immediately prior to the classification of patients as having treatment-refractory disease (i.e. before IVIg/PLEX). The current resubmission presented two separate economic analyses of ravulizumab as a treatment option for newly diagnosed and treatment refractory patients after prior failure of IVIg/PLEX. Key changes include structural assumptions (removal of IVIg/PLEX as a second-line treatment option, and placebo patients are now allowed to achieve a pharmacological remission in newly diagnosed patients), revised patient characteristics and circumstances of use, revised transition probabilities for response, treatment discontinuation and loss of effect, revised health state utility values and a reduced price for ravulizumab.
- 6.44 The resubmission 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 newly diagnosed and treatment refractory patients. 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.

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6.45 Key components of the economic evaluation are summarised in Table 10.

**Table 10: 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 with subsequent-line treatment using 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	6 health states defined by treatment status (treatment initiator, responder, non-responder) and lines of therapy (first-line, subsequent-line treatment) and death.
Cycle length	13-weeks (with no half-cycle correction)
Patient populations	Newly diagnosed patients, treatment refractory patients
Circumstances of use	<p>The maximum duration of ravulizumab therapy was assumed to be 2 years for newly diagnosed patients and 8 years for treatment refractory patients.</p> <p>It was assumed that all patients would remain on standard therapies for the duration of the model without any changes in use from baseline.</p> <p>It was assumed that rituximab and cyclophosphamide would be used as subsequent-line treatment options in both patient populations.</p>
Transition probability	<p>Treatment response rates for ravulizumab and placebo were based on subgroup analyses of the CHAMPION-MG trial. Response rates for rituximab were based on published literature (Zhao 2021, Li 2021). Response rates for cyclophosphamide were assumed.</p> <p>Discontinuation rates for ravulizumab responders were based on the CHAMPION-MG extension study and were assumed for rituximab and cyclophosphamide. All patients in the non-responder states were assumed to have discontinued therapy.</p> <p>In newly diagnosed patients, it was assumed that all patients (in both arms) who have maintained a treatment response for 2 years would achieve a pharmacological remission and no longer require any further treatment other than standard therapy. The loss of effect with placebo over time, as well as the loss of effect after 2 years in the ravulizumab arm were based on assumed rates.</p> <p>In treatment refractory patients, it was assumed that ravulizumab patients who have maintained a treatment response for 8 years would achieve a pharmacological remission and no longer require any further treatment other than standard therapy. The loss of effect with placebo over time as well as the loss of effect after 8 years in the ravulizumab arm were based on assumed rates.</p> <p>Patients who discontinue therapy or experience a loss of effect were assumed to initiate later lines of therapy after a 1 cycle break in therapy. Patients who discontinue subsequent-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 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 the 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.</p>

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Component	Description												
	<p>Responders/non-responders to subsequent-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>												
Utility values	<p>The health state utility value for first-line treatment initiators was estimated based on pooled baseline EQ-5D-5L values (Australian value set, Norman 2023) from both treatment arms in the newly diagnosed and treatment refractory subgroups of the CHAMPION-MG trial.</p> <p>The resubmission estimated first-line health state utility values for treatment responders and non-responders based a post hoc mixed model repeated measures analysis of the change in EQ-5D-5L health index scores from baseline separately for each treatment arm in the newly diagnosed and treatment refractory subgroups of the CHAMPION-MG trial.</p> <p>Health state utility values for treatment initiators to subsequent-line therapy were assumed to be equivalent to the non-response value of the preceding line of therapy. Utility values for responders to subsequent-line therapy were assumed to be equivalent to published estimates (Dewilde 2023) for mild myasthenia gravis while non-responders were assumed to have utility values equivalent to moderate myasthenia gravis (newly diagnosed patients) or moderate-to-severe myasthenia gravis (treatment refractory patients).</p> <p>Utility values were age-adjusted based on Australian general population EQ-5D-3L data (Clemens 2014).</p> <p>Some of the health state utility values applied in the model are outlined below.</p> <table border="1"> <thead> <tr> <th></th> <th>Newly diagnosed</th> <th>Refractory</th> </tr> </thead> <tbody> <tr> <td>Baseline:</td> <td>0.710</td> <td>0.750</td> </tr> <tr> <td>Responder</td> <td>Ravulizumab: 0.880 Placebo: 0.850 Subsequent therapy: 0.766</td> <td>Ravulizumab: 0.880 Placebo: 0.890 Subsequent therapy: 0.766</td> </tr> <tr> <td>Non-responder</td> <td>Ravulizumab: 0.750 Placebo: 0.750 Subsequent therapy 0.648</td> <td>Ravulizumab: 0.760 Placebo: 0.740 Subsequent therapy: 0.589</td> </tr> </tbody> </table> <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. The QALY decrement associated with adverse events for other therapies was assumed to be equivalent to an exacerbation.</p>		Newly diagnosed	Refractory	Baseline:	0.710	0.750	Responder	Ravulizumab: 0.880 Placebo: 0.850 Subsequent therapy: 0.766	Ravulizumab: 0.880 Placebo: 0.890 Subsequent therapy: 0.766	Non-responder	Ravulizumab: 0.750 Placebo: 0.750 Subsequent therapy 0.648	Ravulizumab: 0.760 Placebo: 0.740 Subsequent therapy: 0.589
	Newly diagnosed	Refractory											
Baseline:	0.710	0.750											
Responder	Ravulizumab: 0.880 Placebo: 0.850 Subsequent therapy: 0.766	Ravulizumab: 0.880 Placebo: 0.890 Subsequent therapy: 0.766											
Non-responder	Ravulizumab: 0.750 Placebo: 0.750 Subsequent therapy 0.648	Ravulizumab: 0.760 Placebo: 0.740 Subsequent therapy: 0.589											
Discount rate	5% for costs and outcomes												
Software package	Microsoft Excel 365												

Source: Table 3A-3, p210 of the resubmission

Abbreviations: IVIg, Intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MSAC, Medicare Services Advisory Committee; PLEX, plasma exchange

6.46 All patients begin the model in the first-line treatment initiator health state. During this period, patients may only experience adverse events associated with first-line therapy.

6.47 After the first cycle, patients are assigned to response and non-response health states. Responders may remain in this state, die due to general mortality or crisis-related mortality, prematurely discontinue therapy (active therapies only) or experience loss

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of response (with different estimates depending on whether patients had achieved a pharmacological remission). All non-responders are assumed to have discontinued therapy and may die due to general mortality or crisis-related mortality. During this period, both responders and non-responders may also experience exacerbations or myasthenic crisis events.

- 6.48 Patients in both arms who remain in the response state for 2 years (newly diagnosed patients) and patients in the ravulizumab arm who remain in the response state for 8 years (treatment refractory patients) achieve a pharmacological remission and do not require any further treatment other than standard therapy but may lose response over time.
- 6.49 After discontinuation/loss of effect, patients are assumed to enter a subsequent treatment initiator health state for one cycle before being assigned to response and non-response health states similar to first-line therapy. 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 discontinue subsequent-line therapy are assumed to remain on treatment with standard therapy alone.
- 6.50 The evaluation and the ESC considered that the resubmission did not adequately justify the modelling of rituximab and cyclophosphamide as subsequent-line therapies in the economic evaluation for the newly diagnosed population (as these therapies are typically reserved for treatment refractory disease) or the treatment refractory population (as ravulizumab is proposed as a last-line therapy in treatment refractory disease). The major impact of modelling subsequent-line therapies was the inclusion of worse utility values for treatment non-responders derived from external data sources rather than using the observed utility values from the CHAMPION-MG trial.
- 6.51 Key drivers of the economic model are summarised in Table 11.

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Table 11: Key drivers of the model

Description	Method/Value	Impact
Time horizon	<p>The resubmission nominated a 15 year time horizon for both economic analyses on the basis that this was sufficient to capture the costs and consequences of multiple lines of therapy for a long-term condition.</p> <p>The evaluation considered that a 2-year time horizon may be more appropriate in newly diagnosed patients given the proposed role of ravulizumab as a treatment to provide symptom control while non-steroidal immunosuppressive therapies are being optimised (which the resubmission claimed may take up to 2 years). The evaluation considered that there is currently no clinical evidence to support a difference in pharmacological remission rates between ravulizumab and placebo after background therapies have been optimised. However, the PSCR argued that a 2 year time horizon would not adequately capture the long term benefits for patients who achieved greater symptom control within the initial treatment phase.</p> <p>Overall, the ESC considered that a ten year time horizon (rather than 15 years) may be more appropriate in both settings given the uncertain long-term extrapolations e.g. due to the lack of long-term data around treatment/remission durations.</p>	High, favours ravulizumab
Subgroup clinical data	<p>The resubmission estimated treatment response rates and most patient characteristics (age, sex, disease duration, baseline MG-ADL score and baseline EQ-5D-5L health state index score) based on post hoc subgroup data for newly diagnosed and treatment refractory patients in the CHAMPION-MG trial.</p> <p>The definitions used to define the subgroup populations in the CHAMPION-MG trial were not consistent with the target PBS populations which require a more extensive history of prior treatment use for both subgroup populations. As a consequence, the patient characteristics reported for these subgroups may not be representative of the target PBS populations.</p> <p>The resubmission claimed differences in treatment effects in the subgroup populations compared to the overall population that were not well supported by the available data. There was no statistically significant treatment interaction by time since diagnosis or treatment refractory status in mean change in MG-ADL score from baseline. While there appeared to be numerical differences in response in the newly diagnosed population, this should be interpreted with caution given the small patient numbers, differences in patient characteristics compared to other trial participants (which were suggestive of a higher proportion of late-onset myasthenia gravis patients in this subgroup) and imbalances between treatment arms (particularly in regards to severity of muscle weakness, prior history of exacerbations and baseline immunosuppressive therapy).</p>	High, favours ravulizumab
Treatment discontinuation/ loss of effect in the newly diagnosed model	<p>All patients in the non-responder states were assumed to have discontinued add-on therapy with ravulizumab, rituximab and cyclophosphamide.</p> <p>The resubmission assumed that treatment responders to ravulizumab could discontinue therapy between the first cycle and 2-years based on the reported discontinuations in the 60-week CHAMPION-MG interim extension report. The resubmission did not adequately justify the use of overall population results to inform discontinuation rates rather than subgroup results (which were used in the treatment refractory model). Additionally, the resubmission did not justify using interim data rather than final data from the extension study. As stated above, there is currently no clinical evidence to support a difference in pharmacological remission rates between ravulizumab and placebo after background therapies have been optimised.</p> <p>The resubmission assumed that the proportion of responders in the placebo arm would decrease between the first cycle and 2 years as these patients have not had sufficient time to achieve treatment optimisation. The resubmission estimated this rate based on the assumption that 64% of patients (based on the proportion of non-responders at 12 weeks) would lose response by 2 years which resulted in a loss of response rate of</p>	High, favours ravulizumab

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Description	Method/Value	Impact
	<p>12.1% per cycle. The calculation of this estimate was poorly justified and did not appear to be a valid method to estimate loss of response in placebo patients.</p> <p>The resubmission assumed that patients in both treatment arms who achieved a pharmacological remission at 2 years and stopped their first-line therapy would gradually lose that response over time. The resubmission estimated this rate based on the assumption that 15% of patients (based on expert advice that 10% to 20% of generalised myasthenia gravis patients are treatment refractory) would lose response over 12 years (the remaining time after 2 years of first-line therapy and 1 year of subsequent-line therapy) which resulted in a loss of response rate of 0.34% per cycle. The expert advice related to all generalised myasthenia gravis patients rather than the proportion of newly diagnosed patients who respond to second-line bridging therapy and then become non-responders. Based on the information presented in the resubmission, there appears to be insufficient data to reliably estimate loss of response over time in patients who have achieved a pharmacological remission.</p> <p>The resubmission assumed that treatment responders to cyclophosphamide and rituximab would have a maximum treatment duration of 1 year. The maximum treatment duration of these therapies in clinical practice is currently unclear.</p>	
<p>Treatment discontinuation/ loss of effect in the treatment refractory model</p>	<p>All patients in the non-responder states were assumed to have discontinued add-on therapy with ravulizumab, rituximab and cyclophosphamide.</p> <p>The resubmission assumed that treatment responders to ravulizumab could discontinue therapy between the first cycle and 8-years years based on the reported discontinuations in the treatment refractory subgroup using data from the CHAMPION-MG extension report. This estimate was inadequately documented and could not be validated during the evaluation.</p> <p>The resubmission assumed that patients would only receive treatment for half of the model duration (based on expert advice from treating physicians who stated that they would be willing to consider stopping ravulizumab treatment to assess the impact of concomitant immunosuppressive therapy). Patients who completed 8-years of ravulizumab treatment were assumed to have achieved a pharmacological remission and no longer require any further treatment with ravulizumab. The assumption that patients would receive treatment for half of the model duration was arbitrary and not well justified. The resubmission described the 8-year duration as an average duration however it was implemented in the model as a maximum treatment duration using the exact same approach as the 2-year cap applied to newly diagnosed patients. The average treatment duration of ravulizumab responders in the treatment refractory model was 6.41 years; when the maximum treatment cap was removed the average treatment duration increased to 9.83 years.</p> <p>For treatment refractory patients, the proportion of responders in the placebo arm was assumed to decrease over the 15-year duration of the model as these patients had demonstrated inadequate response to standard therapies. The resubmission also assumed this same rate would apply to ravulizumab patients who achieved pharmacological remission at 8 years. The resubmission estimated this rate based on the assumption that 55% of patients (based on the proportion of non-responders at 12 weeks) would lose response by 2 years which resulted in a loss of response rate of 9.6% per cycle. The calculation of this estimate was poorly justified and did not appear to be a valid method to estimate loss of response in placebo patients.</p> <p>The resubmission assumed that treatment responders to cyclophosphamide and rituximab would have a maximum treatment duration of 1 year. The maximum treatment duration of these therapies in clinical practice is currently unclear.</p>	<p>High, favours ravulizumab</p>

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Description	Method/Value	Impact
Utility values for subsequent-line therapies.	The resubmission assumed that newly diagnosed patients who responded to subsequent-line therapies would have the same utility as patients with mild myasthenia gravis (MGFA Class II) while non-responders would have the same utility value as patients with moderate myasthenia gravis (MGFA Class III) using reported EQ-5D-5L estimates (UK value set) from the MyRealWorld-MG patient registry.	High, favours ravulizumab
	The resubmission assumed that treatment refractory patients who responded to subsequent-line therapies would have the same utility as patients with mild myasthenia gravis (MGFA Class II) while non-responders would have the same utility value as patients with moderate-to-severe myasthenia gravis (MGFA Class III/IV) using reported EQ-5D-5L estimates (UK value set) from the MyRealWorld-MG patient registry.	
	The resubmission did not adequately justify the use of different utility values for subsequent-line treatments compared to the estimated values for first-line therapies given that the disease does not typically progress with treatment failure. The ESC noted that the model was highly sensitive to this assumption.	
	The ESC noted that the resubmission applied treatment-specific values for responder/non-responder health states in each arm (e.g. in newly diagnosed patients, responders were assigned utility values of 0.88 and 0.85 in the ravulizumab and placebo arms, respectively). The ESC considered it would have been more appropriate to use pooled values for responders and non-responders from both treatment arms as there was no apparent difference in quality of life outcomes between treatment arms by responder status.	

Source: Constructed during the evaluation

6.52 The results of the stepped economic evaluation for newly diagnosed patients are summarised in Table 12.

**Table 12: Stepped economic evaluation of ravulizumab compared to placebo in newly diagnosed patients**

Type of resource item	Ravulizumab	Placebo	Increment
<b>Step 1: Modelled estimate based on the first 12 weeks of treatment</b>			
Costs		\$1,025	
Patients with response	0.7368	0.3571	0.3797
<b>Incremental cost per additional patient with response</b>			<sup>1</sup>
<b>Step 2: Modelled estimate extrapolated to 15 years</b>			
Costs		\$241,713	
Responder years	8.9682	2.4134	6.5549
<b>Incremental cost per additional year in response</b>			<sup>2</sup>
<b>Step 3: Modelled estimate extrapolated to 15 years with utility weights applied</b>			
Costs		\$241,713	
QALYs	10.6191	9.2732	1.3459
<b>Incremental cost per QALY gained</b>			<sup>3</sup>
<b>Step 4: Modelled estimate extrapolated to 15 years with utility weights and discounting applied</b>			
Costs		\$172,890	
QALYs	7.7063	6.7342	0.9721
<b>Incremental cost per QALY gained</b>			<sup>1</sup>

Source: Table 3A-32, p249 of the resubmission

Abbreviations: QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$155,000 to < \$255,000

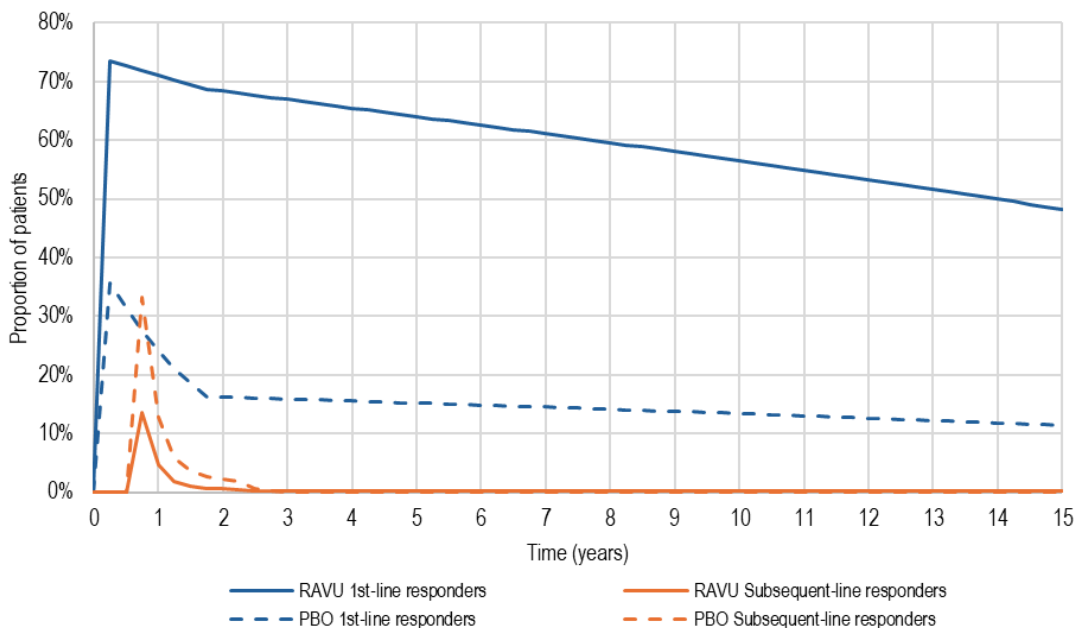
<sup>2</sup> \$25,000 to < \$35,000

<sup>3</sup> \$115,000 to < \$135,000

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- 6.53 Based on the economic model, treatment with ravulizumab in combination with standard therapy was associated with an incremental cost per QALY gained of \$155,000 to < \$255,000 compared to placebo in combination with standard therapy in newly diagnosed myasthenia gravis patients.
- 6.54 During the evaluation, it was noted that 83% of incremental QALYs in the model are accrued after the maximum duration of ravulizumab treatment (2 years) while the difference in incremental costs between treatment arms decreased over time after ravulizumab discontinuation.
- 6.55 Figure 1 presents a model trace of the proportion of responders over time in newly diagnosed patients.

**Figure 1: Model trace of responders by line of therapy in newly diagnosed patients**



Source: Constructed during the evaluation based on 'Section 3A Newly Diagnosed Workbook' Excel Spreadsheet  
 Abbreviations: AE, adverse event; PBO, placebo; RAVU, ravulizumab.

- 6.56 The model trace indicates a clear separation in the proportion of responders at 12 weeks which favours ravulizumab treatment and is consistent with the clinical data from the newly diagnosed subgroup of the CHAMPION-MG trial. The curves continue to diverge between Week 12 and Year 2 due to different assumptions regarding treatment discontinuation/loss of response over time between the treatment arms. After two years, first-line therapy is discontinued in both arms, with the proportion of responders slowly declining over time based on assumed disease relapse rates. The trace also demonstrates that patients who do not achieve response in the first 12 weeks of treatment will never achieve a treatment response. This is not consistent with timeframes required to optimise NS-ISTs.
- 6.57 For every 100 newly diagnosed patients treated with ravulizumab versus placebo and followed up for 15 years, the economic evaluation (based on undiscounted values) estimated that there would be:

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- An increase in the time spent with higher functional capacity (with an average of 5.467 additional years in response per patient).
- A reduction in clinical events (151 fewer exacerbation events; 9 fewer myasthenic crisis events).
- Additional ravulizumab drug acquisition costs of \$1 million.

6.58 The results of the stepped economic evaluation for treatment refractory patients are summarised in Table 13.

**Table 13: Stepped economic evaluation of ravulizumab compared to placebo in treatment refractory patients**

Type of resource item	Ravulizumab	Placebo	Increment
<b>Step 1: Modelled estimate based on the first 12 weeks of treatment</b>			
Costs	\$1	\$1,025	\$1
Patients with response	0.5526	0.4468	0.1058
<b>Incremental cost per additional patient with response</b>			<b>\$1</b>
<b>Step 2: Modelled estimate extrapolated to 15 years</b>			
Costs	\$1	\$237,695	\$1
Responder years	4.3287	1.3369	2.9918
<b>Incremental cost per additional year in response</b>			<b>\$2</b>
<b>Step 3: Modelled estimate extrapolated to 15 years with utility weights applied</b>			
Costs	\$1	\$237,695	\$1
QALYs	9.6685	8.7919	0.8766
<b>Incremental cost per QALY gained</b>			<b>\$3</b>
<b>Step 4: Modelled estimate extrapolated to 15 years with utility weights and discounting applied</b>			
Costs	\$1	\$168,533	\$1
QALYs	7.0780	6.4155	0.6624
<b>Incremental cost per QALY gained</b>			<b>\$3</b>

Source: Table 3B-11 of the resubmission

Abbreviations: QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$555,000 to < \$655,000

<sup>2</sup> \$155,000 to < \$255,000

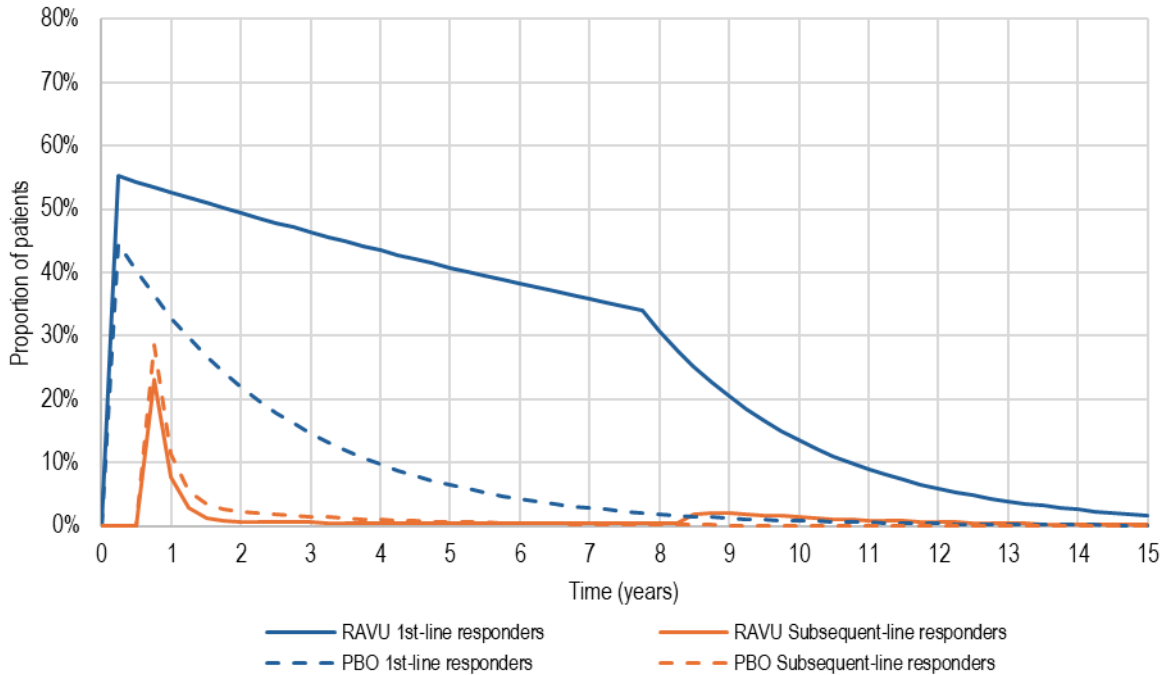
<sup>3</sup> \$655,000 to < \$755,000

6.59 Based on the economic model, treatment with ravulizumab in combination with standard therapy was associated with an incremental cost per QALY gained of \$655,000 to < \$755,000 compared to placebo in combination with standard therapy in treatment refractory myasthenia gravis patients.

6.60 During the evaluation, it was noted that 22% of incremental QALYs in the model are accrued after the maximum duration of ravulizumab treatment (8 years) while the difference in incremental costs between treatment arms remained relatively stable over time after ravulizumab discontinuation.

6.61 Figure 2 presents a model trace of the proportion of responders over time in treatment refractory patients.

Figure 2: Model trace of responders by line of therapy in treatment refractory patients



Source: Constructed during the evaluation based on 'Section 3B Optimised Refractory Workbook' Excel Spreadsheet  
 Abbreviations: PBO, placebo; RAVU, ravulizumab.

- 6.62 The model trace indicates that similar proportions of patients in both treatment arms achieve response at 12 weeks, consistent with the clinical data from the treatment refractory subgroup of the CHAMPION-MG trial. However, the curves begin to substantially diverge between Week 12 and Year 8 due to different assumptions regarding treatment discontinuation/loss of response over time between treatment arms. After 8 years, ravulizumab treatment is discontinued and both curves use the same loss of response rates however the ravulizumab arm begins this period with a much higher proportion of responders compared to placebo.
- 6.63 As with the trace in newly diagnosed patients, the model trace in treatment refractory patients indicates that patients who do not demonstrate a response within 3 months of treatment will never achieve a response and also shows that patients using subsequent-line therapies cannot achieve a sustained treatment response. The evaluation and the ESC considered that neither of these patterns appeared to be plausible.
- 6.64 For every 100 treatment refractory patients treated with ravulizumab versus placebo and followed up for 15 years, the economic evaluation (based on undiscounted values) estimated that there would be:
- An increase in the time spent with higher functional capacity (with an average of 2.620 additional years in response per patient).
  - A reduction in clinical events (51 fewer exacerbation events; 4 fewer myasthenic crisis events).

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- Additional ravulizumab drug acquisition costs of \$1 million.

6.65 The estimated weighted incremental cost-effectiveness ratio of ravulizumab compared to placebo across both requested populations is summarised in Table 14.

**Table 14: Weighted cost effectiveness estimates across both requested myasthenia gravis populations**

Population	Incremental cost (\$)	Incremental QALY	Weighting	Incremental cost per QALY
Newly diagnosed		0.9721	85%	<sup>1</sup>
Treatment refractory		0.6624	15%	<sup>2</sup>
<b>Overall</b>		0.9256	100%	<sup>1</sup>
Immediately prior to treatment refractory (March 2024 submission)		1.032	-	<sup>3</sup>

Source: Resubmission

Abbreviations: QALY, quality-adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$155,000 to < \$255,000

<sup>2</sup> \$655,000 to < \$755,000

<sup>3</sup> \$255,000 to < \$355,000

6.66 The resubmission estimated a weighted incremental cost per QALY gained of \$155,000 to < \$255,000 with ravulizumab compared to placebo across both requested myasthenia gravis populations.

6.67 In comparison, the March 2024 submission estimated an incremental cost per QALY gained of \$255,000 to < \$355,000 with ravulizumab compared to placebo when used as a new line of therapy immediately prior to the classification of patients as having treatment-refractory disease.

6.68 The proposed weights were based on expert advice on the proportion of myasthenia gravis patients who were likely to be treatment refractory. However, this approach inappropriately assumed that all non-refractory patients are newly diagnosed (≤ 2 years from diagnosis) and does not account for the large pool of patients with established myasthenia gravis (> 2 years from diagnosis). Further, the approach does not account for the higher number of prescriptions likely to be used per patient in the refractory setting. Overall, the evaluation and the ESC considered that this analysis should be more heavily weighted towards the treatment refractory population. The ESC noted this was supported by the IVIg utilisation data (refer to Section 7).

6.69 The results of key sensitivity analyses for the newly diagnosed population are summarised in Table 15.

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Table 15: Results of key sensitivity analyses for newly diagnosed patients

Analyses	Incremental cost (\$)	Incremental QALYs	ICER	Change from base case ICER
<b>Base case</b>		<b>0.9721</b>	<b>1</b>	<b>-</b>
<b>Discount rate (base case: 5% for benefits and costs)</b>				
3.5% discount rate		1.0654	1	- %
0% discount rate		1.3459	2	- %
<b>Time horizon (base case: 15 years)</b>				
20 years		1.1137	1	- %
10 years		0.7505	3	+ %
5 years		0.4283	4	+ %
2 years (consistent with role as bridging therapy)		0.1678	5	+ %
<b>Response rates (base case: ravulizumab and placebo response rates based on proportion of patients with a 3-point reduction in MG-ADL scores at 12-weeks in the newly diagnosed subgroup from the CHAMPION-MG trial; response rates for other therapies based on published data using MGFA-PIS outcomes)</b>				
Ravulizumab and placebo response rates based on the overall population at 12 weeks in the CHAMPION-MG trial		0.4957	3	+ %
<b>Loss of response (base case: 12.08% per cycle in the placebo arm [assumption] in first 2 years and 0.34% per cycle in both arms for patients who achieved a pharmacological remission at 2 years)</b>				
Double placebo loss of response in first 2 years		1.1381	1	- %
Halve placebo loss of response in first 2 years		0.8374	1	+ %
<b>Events (base case: exacerbation and myasthenic crisis risk based on post hoc analysis of CHAMPION-MG trial and extension; adverse event risk for ravulizumab and placebo based on the CHAMPION-MG trial adverse events; risk for other therapies based on published sources)</b>				
Increase exacerbation risk by 50%		0.9729	1	- %
Decrease exacerbation risk by 50%		0.9715	1	+ %
<b>Utility values (base case: first-line treatment initiator utility values based on baseline EQ-5D-5L scores from the newly diagnosed subgroup in the CHAMPION-MG trial, first-line treatment responder and non-responder utility values for each treatment arm based on change in EQ-5D-5L at Week 12 using an MMRM analysis in the newly diagnosed subgroup in the CHAMPION-MG trial; subsequent-line responder utility values assumed to be the same as mild disease and subsequent-line non-responder utility values assumed to be the same as moderate disease)</b>				
Treatment initiator utility increased by 5% (0.746)		1.1337	1	- %
Treatment initiator utility decreased by 5% (0.676)		0.8182	1	+ %
Assume subsequent-line response and non-response utility values are the same as pooled first-line estimates (MMRM analysis)		0.5097	6	+ %
Assume subsequent-line response and non-response utility values are the same as pooled first-line estimates (regression panel analysis)		0.6626	3	+ %

Source: Table 3A-92 of the resubmission; Section 3A Newly Diagnosed Excel Workbook

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:

<sup>1</sup> \$155,000 to < \$255,000

<sup>2</sup> \$135,000 to < \$155,000

<sup>3</sup> \$255,000 to < \$355,000

<sup>4</sup> \$455,000 to < \$555,000

<sup>5</sup> > \$1,055,000

<sup>6</sup> \$355,000 to < \$455,000

6.70 The results of the sensitivity analyses in newly diagnosed patients indicate that the model is most sensitive to time horizon.

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- 6.71 The economic model was also sensitive to the discount rate, baseline patient characteristics (primarily baseline EQ-5D-5L scores), treatment response, placebo loss of response rates, exacerbation risk (primarily due to the costs of hospitalised treatment) and utility values for subsequent-line treatment.
- 6.72 The results of key sensitivity analyses for the treatment refractory population are summarised in Table 16.

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Table 16: Results of key sensitivity analyses for treatment refractory patients

Analyses	Incremental cost (\$)	Incremental QALYs	ICER	Change from base case ICER
<b>Base case</b>		<b>0.6624</b>	<b>1</b>	<b>-</b>
<b>Discount rate (base case: 5% for benefits and costs)</b>				
3.5% discount rate		0.7178	1	-%
0% discount rate		0.8766	2	-%
<b>Circumstances of use (base case: ravulizumab dose intensity 91.7%; the discontinuation rate for responders in the ravulizumab arm was 1.46% per cycle [based on subgroup analysis of the CHAMPION-MG extension study] with a maximum duration of 8 years [assumption]; the discontinuation rate for responders to subsequent therapy was 68.38% per cycle based on an assumed maximum duration 1 year).</b>				
Double ravulizumab discontinuation rate in first 8 years		0.4684	3	+%
Halve ravulizumab discontinuation rate in first 8 years		0.7810	1	-%
<b>Loss of response (base case: loss of response was assumed to be 9.58% per cycle for all placebo patients and patients in the ravulizumab arm who achieved a pharmacological remission at 8 years)</b>				
Double probability of loss of response		0.7383	2	-%
Halve probability of loss of response		0.5187	4	+%
<b>Utility values (base case: first-line treatment initiator utility values based on baseline EQ-5D-5L scores from the treatment refractory subgroup in the CHAMPION-MG trial, first-line treatment responder and non-responder utility values for each treatment arm based on change in EQ-5D-5L at Week 12 using an MMRM analysis in the treatment refractory subgroup in the CHAMPION-MG trial; subsequent-line responder utility values assumed to be the same as mild disease and subsequent-line non-responder utility values assumed to be the same as moderate-to-severe disease)</b>				
Treatment initiator utility increased by 5% (0.788)		0.7472	2	-%
Treatment initiator utility decreased by 5% (0.714)		0.5817	3	+%
Use first-line responder (0.880) and non-responder (0.749) values based on pooled estimates from both treatment arms (MMRM analysis)		0.6638	1	-%
Use first-line responder (0.841) and non-responder (0.754) values based on pooled estimates from both treatment arms (regression panel analysis)		0.5745	3	+%
Use first-line responder (ravulizumab: 0.850; placebo 0.832) and non-responder (ravulizumab: 0.759; placebo 0.749) values separately for each treatment arm (regression panel analysis)		0.6086	3	+%
Assume subsequent-line response and non-response utility values are the same as pooled first-line estimates (MMRM analysis)		0.3032	5	+%
Assume subsequent-line response and non-response utility values are the same as pooled first-line estimates (regression panel analysis)		0.2930	5	+%

Source: Table 3B-16, of the resubmission; Section 3B Optimised Refractory Excel Workbook

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:

<sup>1</sup> \$655,000 to < \$755,000

<sup>2</sup> \$555,000 to < \$655,000

<sup>3</sup> \$755,000 to < \$855,000

<sup>4</sup> \$855,000 to < \$955,000

<sup>5</sup> > \$1,055,000

6.73 The results of the sensitivity analyses in treatment refractory patients indicate that the model is most sensitive to the assumed utility values for subsequent-line responders and non-responders. The economic model was also sensitive to

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ravulizumab discontinuation rates, loss of response rates, baseline utility scores and the calculation method for first-line responder and non-responder utility values.

- 6.74 The ESC considered the economic model was limited due to the lack of long-term data available and the complex nature of the condition. Specifically, the ESC considered:
- there was a lack of data to inform treatment discontinuations/loss of response over time which resulted in the economic evaluation being highly dependent on numerous assumptions to model these effects.
  - impacts on the treatment algorithm were unclear, such as whether it was appropriate to model rituximab and cyclophosphamide as subsequent-line therapies for the newly diagnosed population (as these therapies are typically reserved for treatment refractory disease) or the treatment refractory population (as ravulizumab is proposed as a last-line therapy in treatment refractory disease).
  - the subgroup data (which were used to inform treatment response estimates and patient characteristics) may not be sufficiently reliable.

***Drug cost/patient/year***

- 6.75 The estimation of ravulizumab drug costs was broadly consistent between the economic model and budget impact estimates, the only difference was the assumption of perfect persistence in newly diagnosed patients treated with ravulizumab in the first two years of financial estimates while the economic model allowed for a small number of patients to discontinue therapy each cycle.
- 6.76 The commentary stated that the estimated drug cost for ravulizumab in the first year of treatment was \$| (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 \$| for the 300 mg vial, with additional fees and markups for use in the private hospital setting). The estimated drug cost for ravulizumab in the second year of treatment was \$| (based on patients receiving 6 maintenance doses with the same assumptions as the first-year calculations). The estimated drug cost for ravulizumab in the third year of treatment was \$| (based on patients receiving 7 maintenance doses with the same assumptions as the first-year calculations). The cost in subsequent years then alternates between second year and third year costs depending on the timing of doses.
- 6.77 The estimated drug costs per year decreased in the current resubmission compared to the March 2024 submission due to the proposed lower effective price of ravulizumab (effective AEMP reduced from \$| to \$| per 300 mg vial).
- 6.78 The estimated annual drug cost for standard therapy (anticholinesterases, corticosteroids and other immunosuppressive agents) was \$2,261 per year. The estimated annual cost for rituximab was \$877 per year and for cyclophosphamide was \$1,071 per year.

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Cost-comparison

6.79 The resubmission noted previous PBAC advice that the cost of chronic IVIg/PLEX should be considered as a frame of reference for the cost of ravulizumab in the refractory setting (para 7.10, ravulizumab Public Summary Document, July 2024 PBAC meeting). Therefore, the resubmission presented a comparison of the average annual cost for maintenance therapy (excluding loading doses) with ravulizumab and IVIg (summarised in Table 17).

**Table 17: Comparison of the annual dose and/or drug cost of ravulizumab and IVIg**

Treatment	Annual cost or dose	Source			
Ravulizumab (not accounting for the loading dose)	21,951 mg per year	Assuming the same weight distribution as patients in the trial (average dose of 3,377 mg per maintenance dose, see row below) with 6.5 administrations per year (total ravulizumab dose of 21,951 mg per year). The ESC noted this did not account for the loading dose or dose intensity/compliance. - With 95% compliance, this would be 20,854 mg per year (21,951 mg x 95%)			
Ravulizumab (accounting for the loading dose)	23,340 mg per year for the first 2 years	Based on the dose in the Product Information comprising one loading dose (at Week 0, average of 2,777 mg) and 13 maintenance doses (from Week 2 to Week 104, average of 3,377 mg per maintenance dose) over the first two years, at 100% dose intensity (46,680 mg over the first two years, or 23,340 mg per year over the first two years). Assuming the same weight distribution as patients in the trial (i.e. 10.3% of patents weigh <60kg, 53.7% weigh ≥ 60 kg to < 100 kg; and 36% weigh ≥ 100 kg). This was based on the doses outlined in the Product Information and does not account for dose intensity/compliance or response rates.			
		<b>Loading and maintenance doses by patient weight (100% dose intensity)</b>			
		Weight category for dosing	≥ 40 kg to < 60 kg	≥ 60 kg to < 100 kg	≥ 100 kg
		Loading (Dose 1 only)	2,400 mg	2,700 mg	3,000 mg
		Maintenance (Week 2 then every 8 weeks)	3,000 mg	3,300 mg	3,600 mg
		Proportion of patients in each weight range in trial	10.3%	53.7%	36.0%
<b>Average loading dose (mg)</b>	<b>2,777 mg (one dose at Week 0)</b>				
<b>Average maintenance dose (mg)</b>	<b>3,377 mg (13 doses from Week 2 to 104)</b>				
<b>IVIg costing scenarios</b>					
Submission: IVIg (weight based on NBA data or CHAMPION-MG data)	\$█ to \$█	Based on an estimated cost of \$█ per gram for IVIg <sup>a</sup> and the assumption that all patients would be treated at the maximum recommended dose (1 g/kg every 4 weeks) and have an average weight based on either: <ul style="list-style-type: none"> <li>the distribution on adult patients accessing IVIg under the NBA for all indications (79.6 kg). Total estimated dose: 1,035 grams per year</li> <li>the CHAMPION-MG trial (91.2 kg). Total estimated dose: 1,186 grams per year</li> </ul>			
ESC: IVIg (average IVIg dose per NBA data)	\$█	Based on an estimated cost of \$█ per gram for IVIg and average dose of 541 grams per patient per year based on data received from the NBA for 2023-24 (refer to Section 7). <sup>b</sup> This excludes patients who commenced in 2023-24, as this may represent a part year of treatment for some patients, and may include non-responders.			
pre-PBAC response: IVIg	\$█ to \$█	Based on IVIg cost of \$█ per gram, loading dose of 2 g/kg; maintenance dose of 0.8 g/kg Q4W (lower value) or 1 g/kg Q4W (upper value); and patient weight of 84kg.			

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Treatment	Annual cost or dose	Source
<b>IVIg costing scenarios: sensitivity analyses</b>		
Average IVIg dose per NBA data plus IVIg price based on MSAC review	\$32,688	The MSAC review of 'Immunoglobulin therapy for Myasthenia Gravis' from April 2020 <sup>c</sup> used a price of \$60.41 per gram in the base case based on NBA data from 2017-18 i.e. this was the cost at which the cost-effectiveness of IVIg was assessed. Average IVIg dose of 541 grams per patient per year based on data received from the NBA for 2023-24
Pre-PBAC response dose of IVIg plus IVIg price based on MSAC review	\$70,788	As above for the price of IVIg. IVIg dose based on a loading dose of 2 g/kg; maintenance dose of 1 g/kg Q4W (upper value from pre-PBAC response) for a total of 1,172 g per year

Source: Table 4-16, p292 of the resubmission; Section 3A Newly Diagnosed Excel Workbook

Abbreviations: IVIg, intravenous immunoglobulin; NBA, National Blood Authority

<sup>a</sup> The cost per gram was estimated based on total expenditure / total grams dispensed by the NBA reported in 2021-2022 annual report which accounted for the costs of plasma fractionation as well as domestic and imported products; inflated to 2024 values using the AIHW health inflation index

<sup>b</sup> Actual IVIg dose used in the calculations was 541.0625 g

<sup>c</sup> Based on MSAC Public Summary Document, Application No. 1566 – Review of immunoglobulin use for Myasthenia Gravis, 3 April 2020. Available at: [https://www.msac.gov.au/sites/default/files/documents/1566%2520Final%2520PSD\\_Apr2020.pdf](https://www.msac.gov.au/sites/default/files/documents/1566%2520Final%2520PSD_Apr2020.pdf)

- 6.80 The evaluation and the ESC considered that costing scenarios based on the maximum recommended dose of IVIg were not plausible as these estimates substantially exceeded the quantities of IVIg dispensed by the NBA. Based on the average amount of IVIg dispensed per patient as maintenance therapy for myasthenia gravis, the cost of IVIg was approximately \$█████ per year, which the ESC considered was more plausible. The ESC noted the proposed effective cost of ravulizumab was |||||.
- 6.81 The PBAC noted that the average dose of ravulizumab would be 46,680 mg over the first two years (or 23,340 mg per year over the first two years) based on the dose recommended in the Product Information, with 100% dose intensity and compliance, and assuming the same weight distribution as patients in the trial (refer to Table 17). Alternatively, excluding the loading dose, and assuming 6.5 maintenance doses per year (7 doses one year and 6 doses the next), the average annual dose of ravulizumab would be 21,951 mg per year (assuming the same weight distribution as patients in the trial).
- 6.82 The economic model assumed 91.7% compliance from the 5th administration onwards because the clinical study report stated that 91.7% of patients who received ravulizumab had 100% compliance over 60 weeks (i.e. the patient received the dose at the scheduled visit). However, the clinical study report stated half of the patients who had missed a ravulizumab infusion at the protocol-specified time point, received the infusion at an unscheduled visit (and one of the most common reasons for missing a scheduled dose was due to COVID-19). Overall, the PBAC considered it was likely that the compliance in the trial would have been greater than 91.7%, potentially around 95%.

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- 6.83 Additional costs associated with ravulizumab include:
- meningococcal vaccines (meningococcal B and ACWY boosters), and for patients who initiate ravulizumab less than 2 weeks after receiving a meningococcal vaccine, prophylactic antibiotics are required until 2 weeks after vaccination; and
  - administration costs, with the Product Information stating ravulizumab is to be administered as an intravenous infusion over 25 to 55 minutes depending on body weight. Over the first 2 years, 14 infusions would be required (1 loading dose at Week 0, and 13 maintenance doses commencing in Week 2) and the submission's economic model assumed MBS item 105 would be required for each administration, with a fee of \$49.75.
- 6.84 The pre-PBAC response argued that the NBA criteria for IVIg are less stringent than the proposed PBS restriction for ravulizumab, and as such allow access in patients with moderate disease activity who may receive lower doses of IVIg. The pre-PBAC response stated that according to Australian neurologists, patients with an MG-ADL score  $\geq 6$  require higher IVIg doses, consistent with the maximum recommended dose of 1 g/kg as outlined in various guidelines, Bril 2024 and the Product Information. The pre-PBAC response argued the average annual dose of 541.1 grams underestimated the dose used in the proposed population.
- 6.85 Further, the pre-PBAC response argued that the average IVIg dose in the NBA data may include patients who are unresponsive to IVIg and includes all patients irrespective of treatment duration. However, the PBAC noted the average dose of IVIg excluded patients who commenced treatment in 2023-24 (the most recent year of data), as this may represent a part year of treatment and may include non-responders.
- 6.86 The pre-PBAC response stated that the following should be captured in a cost-comparison: 1) the IVIg dose used in patients with an MG-ADL  $\geq 6$ ; (2) calculation based on responding patients only; (3) inclusion of any administration costs and additional costs such as vaccinations; (4) the cost of IVIg inclusive of locally manufactured or globally imported product. Further, the pre-PBAC response requested a price premium given the: lengthy administration of IVIg and the impact this has on patient employment and hospital resources; and the potential for adverse events with IVIg.

Cost-per-responder

- 6.87 The PBAC noted that, at the price proposed by the sponsor, the incremental cost-per-responder versus placebo would be \$755,000 to < \$855,000 (based on 10.9% difference in the proportion of patients with  $\geq 2$  point reduction in MG-ADL at 26 weeks, and a cost of \$| for 26 weeks of therapy). The PBAC advised that this was unacceptably high in the context of previous cost-per-responder analyses.
- 6.88 The PBAC noted that, at a cost per patient per year of \$

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6.89 [REDACTED], and assuming the average of the incremental difference in response rates across the four gMG trials (24% at 12 weeks, based on a simple mean of the proportion of patients with  $\geq 2$  point reduction in MG-ADL in the four key trials), the incremental cost-per-responder versus placebo would be around \$55,000 to < \$75,000.

**Estimated PBS usage & financial implications**

6.90 The financial estimates presented in the resubmission were extensively revised from the March 2024 submission. The March 2024 submission requested a broad listing in patients with functional impairment while the current resubmission proposed more narrow listings for newly diagnosed and treatment refractory patients.

6.91 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impacts of listing ravulizumab as a therapy for newly diagnosed patients and treatment refractory patients with generalised myasthenia gravis.

6.92 The key inputs used to derive the financial implications are presented in Table 18.

**Table 18: Key inputs for financial estimates presented in the resubmission**

Data	Value applied and source	Comment
Incidence and prevalence of myasthenia gravis	<p>Incidence: 47 per 1,000,000 persons in 2022 with an average annual increase of 3%.</p> <p>Prevalence: 20.3 per 100,000 persons in 2022 with an average annual increase of 5%.</p> <p>Based on a sponsor-commissioned analysis of PBS data for the cholinesterase inhibitor pyridostigmine, based on the methodology reported in Gattellari 2012 (IQVIA analysis provided with the resubmission).</p>	<p>This was the same data source used in the March 2024 submission. DUSC previously considered that pyridostigmine prescriptions may not be an appropriate method to identify myasthenia gravis patients (particularly given that a substantial proportion of prevalent patients may not be using this treatment, and pyridostigmine may also be used for other indications) (Table 13, ravulizumab PSD, July 2024 PBAC meeting).</p> <p>Additionally, the ratio of incidence to prevalence using this methodology is not plausible, with prevalence estimates approximately 5 times higher than incidence which is not consistent with the life expectancy of patients with myasthenia gravis.</p> <p>The previous submission assumed no change in prevalence over time which DUSC considered to be inconsistent with the available data. The current resubmission includes annual growth rates for incidence and prevalence based on the sponsor-commissioned study.</p> <p>A recent systematic review and meta-analysis of myasthenia gravis epidemiology studies (Sciancalepore 2024) noted that that the global incidence and prevalence of myasthenia gravis has been growing over time with an incidence of 22.9 cases per 1,000,000 persons and a prevalence of 22 cases per 1,000,000 cases between 2008-2022 (prevalence is approximately 10-20 times higher than incidence in most published studies).</p>
% with AChR+	77%. The submission stated this was based on the midpoint of multiple studies reporting the	The previous evaluation noted the majority of included estimates were based on all myasthenia gravis

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Data	Value applied and source	Comment
	<p>proportion of MG which is AChR+, with estimates ranging from 68.5% to 88%; (Anil et al. 2020; Oh et al. 2009; Hendricks et al. 2019; Tomschik et al. 2020), consistent with MGBase registry of Australian patients (subgroup of interest).</p>	<p>patients, with only one estimate based on a gMG population (Hendricks 2019; 88% of patients with generalised myasthenia gravis were AChR +). Where reported, a higher proportion of patients with gMG were AChR positive compared to all, or ocular, myasthenia gravis patients (e.g. Hendricks 2019, Pallaver 2011). The previous evaluation stated that the midpoint value is consistent with data from the Australian MGBase cohort indicating that 79.4% of generalised myasthenia gravis patients were AChR positive. Refer to paragraph 8.25 for PBAC advice on this parameter.</p>
<p>Proportion with MG-ADL score <math>\geq 6</math></p>	<p>17%. Based on the proportion of patients with MG-ADL <math>\geq 6</math>, with <math>\geq 1</math> point from non-ocular items from Petersson 2021, a Swedish cross-sectional cohort study of 1,077 patients with myasthenia gravis (2018-2019). The estimate appears to have been extracted from Figure 3B which showed 17% of patients with early-onset, 18% with late-onset, and 4% with thymoma-associated myasthenia gravis had MG-ADL <math>\geq 6</math> and <math>\geq 1</math> point from non-ocular items, weighted by the proportion of patients from each subgroup (47% early-onset; 49% late-onset; 4% thymoma-associated myasthenia gravis).</p> <p>The resubmission also noted that only 11.53% of AChR+ myasthenia gravis patients with a recorded visit in the last 2 years in the MGBase registry reported an MG-ADL score <math>\geq 8</math> as their worst ever recorded score (July 2024 analysis MGBase analysis provided with the resubmission).</p> <p>Expert advice from treating physicians (provided in the resubmission) indicated that the proportion of generalised myasthenia patients expressing an MG-ADL score of 6 or more ranges between 10% and 20%.</p>	<p>DUSC previously considered that the estimate from the Petersson (2021) publication may be an underestimate of the proportion of patients meeting this criterion in clinical practice given the subjective nature of the MG-ADL instrument (Table 13, ravulizumab PSD, July 2024 PBAC meeting).</p> <p>Estimates from the MGBase registry should be interpreted with caution given that a further 10.9% of patients reported MG-ADL scores between 5-7 and the patient cohort included patients with ocular myasthenia gravis which presumably would have lower functional impairment on average compared to generalised myasthenia gravis.</p> <p>Using the more commonly reported MGC scale, a substantial proportion of patients reported a MGC score <math>&gt; 10</math> as the worst ever recorded score (43.81%) in the MGBase registry suggesting a relatively large pool of patients with functional impairment.</p>
<p>Patients with treatment refractory disease</p>	<p>15%. The resubmission noted that depending on the definition of treatment refractory disease, the prevalence typically ranges between 10% and 20% based on a published literature review (Schneider-Gold 2019).</p> <p>Expert advice from treating physicians (provided in the resubmission) indicated that 10-20% of generalised myasthenia gravis patients would be considered treatment refractory in clinical practice.</p>	<p>Based on the treatment refractory definition used in the post hoc analyses presented in the resubmission approximately 50% of the CHAMPION-MG trial population had treatment refractory disease.</p> <p>Expert advice from the May 2024 Myasthenia Gravis stakeholder meeting indicated that approximately 30% of generalised myasthenia gravis patients would be considered treatment refractory in clinical practice.</p>
<p>Proportion who cannot access IVIg/PLEX</p>	<p>Assumed to be 10%. The resubmission noted the PBAC previously raised concerns regarding access to IVIg/PLEX in regional/remote areas.</p>	<p>The estimate used in the resubmission was inconsistent with expert advice (provided in the resubmission) from treating physicians that indicated <math>&lt; 5\%</math> have difficulty accessing these treatments. Additionally, it is unclear whether patients having</p>

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Data	Value applied and source	Comment
		difficulty accessing IVIg/PLEX would also have similar difficulty accessing ravulizumab.
Proportion with intolerance to IVIg/PLEX	11.97%. Calculated by assuming 90% of patients can access IVIg/PLEX and 13.3% would experience a serious adverse event based on a randomised controlled trial of IVIg and placebo (Bril 2024).	Patients using IVIg in the Bril 2024 trial had a numerically lower risk of serious adverse events compared to placebo (13.3% vs 20.0%).  The dosing regimen used in the Bril 2024 trial is unlikely to reflect Australian clinical practice as it is inconsistent with the approved product information for IVIg, exceeds the maximum subsidised dose under the NBA and is substantially higher than supported by the available Australian IVIg utilisation data.
Proportion with inadequate response to IVIg/PLEX	47.7%. Calculated by assuming 90% of patients can access IVIg/PLEX and 53% would not respond to treatment based on the midpoint of published estimates from randomised controlled trials of IVIg versus placebo (Bril 2024; Zinman 2007) as well as IVIg versus PLEX (Barth 2011; Liu 2010). The resubmission acknowledged there was little consistency across the trials in terms of patient populations, treatment regimens, endpoints, or timing of response assessment.	Expert advice from treating physicians (provided in the resubmission) indicated that the majority of patients treated with IVIg would respond to treatment, but clinicians also stated that 40-50% of patients would fail to respond to IVIg treatment.  The ESC considered that the resubmission's proposed requirement for patients to have previously tried IVIg/PLEX was inappropriate. The PBAC noted there was little consistency across the trials in terms of therapy regimens, endpoints, or timing of response assessment.
Ravulizumab uptake rate	Assumed rates of █████% in Year 1 increasing to █████% in Years 4-6. The resubmission noted that the PBAC previously recognised the high clinical need for effective therapies for generalised myasthenia gravis, particularly in patients who are not responding to or are unable to use existing therapies, and for those with refractory disease (paragraph 7.1, ravulizumab PSD, July 2024 PBAC meeting).  The resubmission assumed the same uptake rate in newly diagnosed and treatment refractory patients.	DUSC previously raised concerns that the uptake rates in the March 2024 submission were potentially underestimated (increasing from █████% to █████%). However, while the estimates in the current resubmission are higher, they remain highly uncertain.  The resubmission did not adequately justify the use of the same uptake rates in both requested populations.
Treatment response at 12 weeks	Newly diagnosed: 73.68% Treatment refractory: 55.30% Based on post hoc analyses of the proportion of newly diagnosed and treatment refractory patients achieving a ≥ 3-point reduction in MG-ADL score at 12 weeks in the CHAMPION-MG trial.	DUSC previously considered that the proportion of treatment responders in clinical practice is likely to be lower than trial-based estimates (Table 13, ravulizumab PSD, July 2024 PBAC meeting).
Treatment persistence in newly diagnose patients	Assumed to be 100%	This assumption was not justified in the resubmission and was inconsistent with the economic model which included a discontinuation rate of 0.96% every 13 weeks.
Treatment persistence in treatment refractory patients	94.3% in all years. Based on a post hoc subgroup analysis of treatment refractory patients in the CHAMPION-MG extension study	This estimate was inadequately documented and could not be validated during the evaluation.

Source: Section 4.2.1, pp281-289; Table 4-14, p290; Table 4-15, p291 of the resubmission

Abbreviations: DUSC, Drug Utilisation Sub-Committee; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living Scale; MGC, Myasthenia Gravis Composite; PBAC, Pharmaceutical Benefits Advisory Committee; PLEX, plasma exchange; RPBS, Repatriation Pharmaceutical Benefits Scheme

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6.93 Table 19 summarises the submission’s estimated number of patients treated, scripts dispensed and net cost to the PBS of listing ravulizumab for newly diagnosed and treatment refractory disease.

**Table 19: Estimated net cost to the PBS/RPBS of listing ravulizumab in newly diagnosed and treatment refractory patients (as estimated in the submission)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Incident patients	1	1	1	1	1	1
Eligible newly diagnosed patients	2	2	2	2	2	2
Prevalent patients	3	3	3	3	3	3
Eligible treatment refractory patients	2	2	2	2	2	2
Total ravulizumab scripts	1	1	1	1		
<b>Total PBS/RPBS cost less copay</b>	4	5	6	6	7	8
<b>Total PBS/RPBS cost (March 2024 submission)</b>	5	9	10	10	10	10
Cost to the MBS for administration	11	11	11	11	11	11
<b>Net cost to PBS/RPBS/MBS</b>	4	5	6	6	7	8

Source: Table 4-3, p281; Table 4-4, p282; Table 4-8, p285; Table 4-9, p286; Table 4-10, p287; Table 4-11, p287; Table 4-12, p288; Table 4-15, p291; Source: 4-20, p295 of the resubmission

Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

- <sup>1</sup> 500 to < 5,000
- <sup>2</sup> < 500
- <sup>3</sup> 5,000 to < 10,000
- <sup>4</sup> \$20 million to < \$30 million
- <sup>5</sup> \$40 million to < \$50 million
- <sup>6</sup> \$50 million to < \$60 million
- <sup>7</sup> \$60 million to < \$70 million
- <sup>8</sup> \$70 million to < \$80 million
- <sup>9</sup> \$90 million to < \$100 million
- <sup>10</sup> \$100 million to < \$200 million
- <sup>11</sup> \$0 to < \$10 million

6.94 The submission estimated the net cost to the PBS/RPBS of listing ravulizumab for both proposed populations would be \$20 million to < \$30 million in Year 1, increasing to \$70 million to < \$80 million in Year 6, a total cost of \$300 million to < \$400 million over the first 6 years of listing.

6.95 The estimated PBS/RPBS cost in the current resubmission was substantially lower than in the March 2024 submission (previously \$600 million to < \$700 million over 6 years) primarily due a smaller treated population (as ravulizumab treatment was restricted to a subsequent line of therapy following IVIg/PLEX) as well as a lower effective price for ravulizumab (proposed AEMP per 300 mg vial decreased from \$| to \$|).

6.96 The evaluation considered that the submission’s estimated cost to the PBS/RPBS was uncertain due to the following reasons:

- The ratio of incidence (47 per 1,000,000 persons) to prevalence (20.3 per 100,000 persons) of myasthenia gravis in 2022 estimated in the sponsor-commissioned analysis (prevalence approximately 5 times higher than incidence) was implausible given the life expectancy of patients with myasthenia gravis. Most published

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epidemiology studies for myasthenia gravis estimate that prevalence is approximately 10-20 times higher than incidence (Sciancalepore 2024). DUSC previously noted that the methodology used in the sponsor-commissioned analysis which estimated patient numbers based on pyridostigmine scripts dispensed under the PBS may underestimate prevalence as not all myasthenia gravis patients will require active treatment with pyridostigmine, but may also overestimate prevalence as pyridostigmine may also be used for other indications (Table 13, ravulizumab PSD, July 2024 PBAC meeting). Overall, the prevalence estimate used in the resubmission appeared to broadly align with other published values but the incidence estimate was substantially higher than most other values (Sciancalepore 2024).

- The prevalent population used to calculate treatment refractory utilisation should exclude the incident population in the current year and the previous year as these patients would not be eligible for treatment under the proposed treatment refractory PBS restriction (minimum 24 months prior treatment duration).
  - The evidence supporting the estimated proportion of patients with an MG-ADL  $\geq 6$  and the proportion of patients with treatment refractory disease was limited and both estimates may be highly variable in clinical practice (as MG-ADL is a subjective patient-reported instrument and the intensity of prior treatment may affect determination of treatment refractory status).
  - The estimated treatment failure rate for IVIg/PLEX (10% unable to access, 11.97% intolerant and 47.7% inadequately responsive to treatment; total failure rate: 69.67%) appeared to be very high for these treatments and may not be representative of clinical practice. Expert advice from treating physicians indicated that IVIg is widely available, and a majority of patients would respond and remain on therapy (based on the clinical consultation minutes provided with the resubmission).
  - The estimated uptake rate for ravulizumab was based on assumptions and its likely use in clinical practice remains unclear.
- 6.97 The evaluation considered there were also additional areas of uncertainty regarding response rate, treatment persistence, application of ravulizumab dose intensity estimates and calculation of non-responder scripts.
- 6.98 The PBAC noted the financial estimates included a ravulizumab compliance rate of 91.7% based on CHAMPION-MG where 91.7% of patients who received ravulizumab had 100% compliance over 60 weeks. However, the evaluation considered the calculation of dose intensity/compliance was incorrect as it assumed that all patients without perfect adherence had no use of ravulizumab treatment. The PBAC agreed with the evaluation that the dose intensity/compliance in the trial would have been greater than 91.7% (refer to paragraph 6.82).

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- 6.99 The ESC noted that the costs to the National Immunisation Program for increased use of meningococcal vaccines were not included in the financial estimates.
- 6.100 The ESC noted the financial estimates were based on the resubmission’s proposed place in therapy of patients who have previously tried IVIg/PLEX, but considered this requirement was inappropriate (refer to paragraph 3.11) and would affect the patient estimates.
- 6.101 The ESC noted the uncertainties regarding the epidemiological approach used in the submission, including estimating: the ratio of incidence to prevalence, the proportion of patients with an MG-ADL  $\geq 6$ ; and the proportion of patients with treatment refractory disease. Overall, as outlined in Section 7, the ESC considered that the use of IVIg as maintenance therapy, from the NBA data, may be a more appropriate starting point to estimate the use of new gMG therapies.
- 6.102 The PBAC agreed with the ESC and advised the parameters outlined in Table 20 may be reasonable for determining the estimated use and financial implications of the new therapies for gMG.

**Table 20: PBAC advised inputs for the financial estimates**

Input	Value and rationale (estimated patient numbers are indicative only)
Total number of patients accessing IVIg as gMG maintenance therapy	1,324 in 2023-24 (refer to Table 21: Data received from the NBA on the use of IVIg for maintenance treatment of gMG Table 21)
Market growth	3.96% per year based on the last five years of IVIg data (i.e. 1,431 patients in Year 1 and 1,738 patients in Year 6)
% with AChR+	85.57% based on the totality of the evidence presented across all the submissions, and similar to the estimate of 88% provided in Hendricks et al. 2019 (i.e. 1,224 patients in Year 1 and 1,487 patients in Year 6)
Uptake across all new gMG therapies that are listed	Uptake from new patients and existing IVIg users with ongoing functional impairment: The PBAC, in its expert opinion, considered this could be up to █%, and this could represent around one-third of current IVIg users based on: █% of IVIg pts commenced within the most recent year, plus of the remaining █% around █% may be using IVIg but experiencing ongoing functional impairment (i.e. █% + (█% * █%) = █% of the market). Total uptake of █% in █% of the market. Uptake from prevalent patients already established on IVIg: The PBAC, in its expert opinion, considered this could be up to █%, and this could represent around two-thirds of current IVIg users based on: of the █% of IVIg users who commenced more than a year ago, around █% are responding (i.e. █% * █% = █%). Total uptake of █% in █% of the market. Total market uptake of █% in Year 1 (i.e. █ <sup>1</sup> patients in Year 1)
Increase in uptake over time	5 percentage points each year for the first six years of listing (i.e. █ <sup>2</sup> patients in Year 6)

Source: Compiled during preparation of the PBAC Minutes

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> 500 to < 5,000

- 6.103 The PBAC considered that uptake rates would be the largest source of uncertainty in the financial estimates, particularly given the range of patients currently taking IVIg (with new patients and existing IVIg users with ongoing functional impairment expected to have substantially higher uptake than those prevalent patients already

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established on IVIg) and also given that the uptake rates would need to account for: any additional eligible patients (e.g. patients who are not responding to, or who are unable to be treated with IVIg); the PBS restriction being narrower than the current IVIg criteria; and the stopping rules (as these would generally mirror how IVIg is used in practice).

**Quality Use of Medicines**

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

**Financial Management – Risk Sharing Arrangements**

6.105 The sponsor proposed a risk sharing arrangement (RSA) (market cap) based on the financial estimates presented in the resubmission. No further details were provided.

6.106 As outlined in Section 7, the ESC considered that a single RSA that includes all of the new PBS listed treatments would be required to mitigate the risk of use outside the intended restriction.

*For more detail on PBAC's view, see section 8 PBAC outcome.*

**7 ESC Advice relevant across the four gMG submissions*****ESC's view on the appropriate restriction and place for the new therapies***

7.1 The Economics Sub-Committee (ESC) noted that there are two key, distinct places in therapy which may be feasible for PBS-listing of the new therapies for gMG (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab):

- early in the treatment algorithm, in combination with standard therapy to provide symptom relief whilst remission induction occurs, often referred to as 'bridging therapy'; and
- later in the disease course in refractory patients.

The ESC considered that separate PBS restrictions would be required in each of these settings.

7.2 The ESC recalled advice from the clinicians present at the gMG stakeholder meeting (May 2024)<sup>3</sup> that the complement inhibitors should be available in both these settings.

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<sup>3</sup> Myasthenia Gravis Stakeholder Meeting (May 2024) Outcome Statement, Available at: <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/stakeholder-meetings>

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- 7.3 The ESC considered that in both settings, the new gMG therapies should substitute for IVIg and plasma exchange (PLEX) rather than be added on to or used in combination with these modalities.

Bridging setting

- 7.4 In terms of bridging therapy, the ESC recalled that the stakeholder meeting had discussed that specific patient criteria should 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 ESC considered that any PBS restriction for bridging therapy should require the patient to have trialed at least three months of combination therapy with all three of: an NS-IST; plus an anti-cholinesterase; plus a corticosteroid. The restriction should require these therapies to have been used at optimised dosing (though specific doses should not be outlined in the PBS restriction, to enable clinician judgement), unless contraindicated or severely intolerant. As such, the ESC considered that the timing of initiation of the new therapy should be based on a minimum of three months having elapsed since initiation of the NS-IST. Further, the ESC considered that the intention would be for the NS-IST to be continued concurrently with the new gMG therapy (unless contraindicated or severely intolerant). Refer to paragraphs 8.6 to 8.13 for the PBAC's advice regarding the restriction criteria.
- 7.5 The ESC considered that a key issue in the bridging setting would be the potential for ongoing use of the new therapies in patients who would have responded to standard therapy, or whose condition would have improved over time (given the potential for recovery of receptors in gMG). As such, the ESC reiterated the advice from the stakeholder meeting that there should be robust stopping rules to prevent ongoing use.
- 7.6 The ESC considered that, overall, the primary literature suggests that most patients generally respond to NS-ISTs within 12 months, with many patients responding within the first one to six months.<sup>4,5</sup> The ESC considered that any PBS restriction for bridging therapy should require the patient to cease the new therapy after around six months of treatment (acknowledging that variations in treatment duration between therapies may be required to align with treatment courses). After three months of therapy cessation (i.e. a total of at least 12 months since NS-IST initiation), patients whose condition remains uncontrolled may recommence under the refractory listing. Overall, the maximum treatment duration in the bridging setting would be around six months.

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<sup>4</sup> Hehir, M.K., Burns, T.M., Alpers, J., Conaway, M.R., Sawa, M. and Sanders, D.B. (2010), Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: Outcomes in 102 patients†. *Muscle Nerve*, 41: 593-598. <https://doi.org/10.1002/mus.21640>, Accessed at <https://pubmed.ncbi.nlm.nih.gov/20405499/>

<sup>5</sup> Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Myasthenia Gravis Study Group. Neurology*. 1998 Jun;50(6):1778-83. doi: 10.1212/wnl.50.6.1778. PMID: 9633727.

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- 7.7 The ESC considered that another key issue in the bridging setting was the lower level of certainty in the incremental benefit versus optimisation of existing therapies given the availability of therapies that are effective for many patients, and that this would impact on the cost-effectiveness of the new therapies. The ESC considered that it was unclear whether these concerns would be adequately addressed by limiting use in this setting to a maximum duration of six months, along with a combined risk sharing arrangement (RSA) for any recommended drugs across both setting.

Refractory setting

- 7.8 In terms of the treatment refractory setting, the ESC considered any PBS restriction should require the patient to have prior treatment for at least one year. The ESC considered that further work would be required to determine the specific therapies and durations.

Both settings

- 7.9 The ESC considered that restrictions should be consistent across any new gMG therapies recommended for listing.
- 7.10 Across both settings, the following aspects of the restrictions would need to be determined:
- functional impairment criteria;
  - response criteria;
  - requirements around prior and concomitant treatments; and
  - restriction structure around: balance of supply; grandfather arrangements (where applicable); a transition pathway between the bridging and refractory settings; any allowance for switching between the newer therapies; and recommencement in the refractory setting (if ceased for reasons other than loss of response or exceeding the six month duration in the bridging setting).
- 7.11 The ESC noted that the NBA qualifying criteria for IVIg<sup>6</sup> specifies that the patient has a Myasthenic Gravis Composite (MGC) of at least 4 points; and at least 2 other treatments are ineffective, contraindicated, unavailable or caused intolerable side effects. The ESC considered this was broad as the other treatments could comprise two of: an anti-cholinesterase; a corticosteroid; or thymectomy (i.e. there is no requirement for the patient to have trialled an NS-IST) and no time periods are specified, nor is there a requirement for the doses to have been optimised.
- 7.12 The ESC noted that the IVIg criteria are referred to as a ‘maintenance’ indication (i.e. “as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects”), but that the criteria also stated “IVIg should be regarded as a stopgap treatment while using short-term drugs such as

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<sup>6</sup> Criteria for Clinical Use of Immunoglobulin in Australia, accessed at: <https://www.criteria.blood.gov.au/MedicalCondition/View/2681>

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pyridostigmine and while introducing effective immunotherapy”. The ESC considered that it was likely that IVIg is being used in both the bridging and refractory settings.

7.13 In both settings, the ESC considered that the new gMG therapies should substitute for IVIg and PLEX rather than be added on or used in combination, and that a reduction in IVIg use would be expected. The ESC considered that:

- the PBS restriction should state that the new therapy should not be used in combination with maintenance use of IVIg (although use of IVIg prior to surgery or in a myasthenic crisis should be permitted);
- there should be no requirement for the patient to have trialed prior IVIg (or PLEX); and
- amendments to the prescribing criteria for IVIg may be required, along with systems to ensure that the anticipated reductions in IVIg use are realised.

***ESC’s view on the comparator***

7.14 At its July 2024 meeting, 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” (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).

7.15 As such, the ESC reiterated the PBAC’s previous advice that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost per patient of the newer gMG therapies in the refractory setting.

7.16 The ESC considered that the four gMG therapies considered at the March 2025 meeting (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.

***ESC’s view on the comparative effectiveness and safety***

7.17 The ESC noted the PBAC’s previous advice that “for the non-refractory group, the comparator should be optimisation of existing therapies”, but that none of the trials for the new therapies required baseline therapies to have been optimised.

7.18 The ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab). The ESC considered that the published NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.

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- 7.19 Further, the ESC acknowledged the limitations of the available evidence for chronic IVIg but considered that there was no evidence to suggest superior efficacy of any of the four new gMG therapies versus chronic IVIg or PLEX.

***ESC's view on the economic analysis***

- 7.20 The ESC considered that any cost-utility analyses for the new therapies would be limited by the lack of available information to reliably inform the model.
- 7.21 The ESC considered a cost-comparison approach versus IVIg may provide an appropriate frame of reference for interpreting the cost of each of the four new therapies in the refractory setting. The ESC was less certain as to whether this approach would be appropriate in the bridging setting.
- 7.22 Table 21 summarises data received from the NBA on the utilisation of IVIg as maintenance therapy for myasthenia gravis in 2023-24.

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**Table 21: Data received from the NBA on the use of IVIg for maintenance treatment of gMG**

Average cost per gram of IVIg (across all indications on the NBA)	\$ [REDACTED]
<b>Data below is specific to the myasthenia gravis maintenance setting</b>	
Average number of 'dispensing events' per patient in 2023-24	15.7 per patient per year
Average total annual dose in 2023-24 <sup>a</sup>	541.0625 grams
Average grams per 'dispensing event'	34.4 grams
Average cost per patient per year of IVIg for maintenance <sup>a</sup>	\$ [REDACTED]
Total number of patients treated with IVIg for maintenance in 2023-24	1,324 patients
Annual growth in the number of patients using IVIg for maintenance (from 2019-20 to 2023-24) <sup>d</sup>	3.3%
Of the patients who were treated with IVIg for maintenance in 2023-24, the percent who:	
commenced more than 7 years ago	28.5%
commenced 7 years ago	4.1%
commenced 6 years ago	5.2%
commenced 5 years ago	6.9%
commenced 4 years ago	7.6%
commenced 3 years ago	8.2%
commenced 2 years ago	10.9%
commenced 1 years ago	12.1%
commenced within the last full year of data (2023-24)	16.6%
<b>Context of IVIg use for gMG <sup>b</sup></b>	
Proportion of all IVIg use in Australia that is for myasthenia gravis maintenance (2022-23)	7.3%
Total spend on IVIg for gMG maintenance in 2023-24	\$ [REDACTED]
% of IVIg use in gMG that is in the maintenance setting (2023-24) <sup>c</sup>	91%

Overall notes:

- Patients' commencement year was the first year they received IVIg for any condition or indication in BloodSTAR, therefore patients have not necessarily been on continuous treatment since commencement.
- Nearly half of the patients currently on gMG for maintenance commenced in 2020-21 or earlier.
- Total number of patients supplied IVIg for 'maintenance' therapy 2019-20: 1,167; 2020-21: 1,135; 2021-22: 1,239; 2022-23: 1,276; 2023-24: 1,324.

<sup>a</sup> Excluding patients who commenced in 2023-24, as this may represent a part year of treatment and may include non-responders.

<sup>b</sup> Some of this data is from <https://www.blood.gov.au/report-issue-and-use-immunoglobulin> data from 2022-23.

<sup>c</sup> Remainder is in patients with myasthenia gravis prior to surgery/thymectomy or in myasthenic crisis.

<sup>d</sup> Result is similar (3.4%) using the most recent two years of data

7.23 The ESC noted that these data showed that the average drug cost per patient in 2023-24 for IVIg was \$ [REDACTED] based on an average cost per gram of \$ [REDACTED] (which is an average across all IVIg use in Australia) and an average of 541.1 grams per patient per year (specific to the myasthenia gravis maintenance setting). This excluded patients who commenced in 2023-24, as this may represent a part year of treatment and may include non-responders. The IVIg doses used in clinical practice were lower than the maximum recommended dose in the Product Information. As such, the ESC noted that applying NBA utilisation data produced substantially lower costs per patient when compared to applying maximum recommended doses for IVIg.

7.24 The ESC advised that, for the new therapies, the average amount of drug per patient would need to be determined and should appropriately account for any loading doses and, for the FcRn blockers, the likely decreasing treatment-free intervals over time seen in the extension trials. The ESC requested that sponsors provide information to

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inform the equi-effective doses and cost-comparison approach in their pre-PBAC responses.

***ESC's view on the estimated PBS usage and financial implications***

- 7.25 The ESC considered that the use of IVIg as maintenance therapy, from the NBA data, may be an appropriate starting point to estimate the use of new gMG therapies.
- 7.26 The ESC considered that the following would also need to be considered: the proportion of patients who are AChR antibody positive; uptake rates; treatment response rates; and annual growth rates. Consideration would be required as to whether there would be: additional eligible patients (e.g. patients who are unable or unwilling to be treated with IVIg); and/or, on the other hand, patients who still require IVIg in this setting (e.g. patients who do not respond to the new therapies, patients at high risk of infections). Overall, the ESC considered that the total number of patients on the newer therapies is likely to be less than the number of patients who access IVIg.
- 7.27 Should the PBS restrictions for the new therapies be more restrictive than the existing IVIg criteria (e.g. in terms of functional impairment criteria and number of prior therapies), there may be patients who qualify for IVIg but not the newer therapies.
- 7.28 The ESC noted that the vast majority of patients accessing IVIg (under the NBA maintenance listing) commenced two or more years ago (71%). This indicated that most patients are using IVIg for refractory disease, with those accessing it for bridging therapy likely to be a proportion of the 29% of patients who commenced within the past two years.
- 7.29 The ESC considered that any listing of the new therapies should be approximately cost-neutral to government across the NBA and PBS.
- 7.30 The ESC considered that a single RSA that includes all of the new PBS listed treatments would be required to mitigate the risk of use outside the intended restriction. The ESC considered that for efgartigimod and rozanolixizumab the RSA would also need to mitigate the risk of an increase in the frequency of cycles received over time.

*For more detail on PBAC's view, see section 8 PBAC outcome.*

**8 PBAC Outcome**

- 8.1 The PBAC recommended the listing of ravulizumab for the treatment of generalised myasthenia gravis (gMG), on the basis that it should be available only under special arrangements under the Section 100 Highly Specialised Drugs Program. The PBAC recognised the high clinical need for new therapies to treat this condition, which has substantial impacts on patient quality of life. The recommendation was made on the basis of a cost-comparison versus intravenous immunoglobulin (IVIg), supported by a cost-per-responder analysis versus placebo. The PBAC acknowledged the limitations of the available evidence for chronic IVIg, however the PBAC considered that there was no evidence to suggest superior efficacy or safety of ravulizumab versus chronic

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IVIg or PLEX. Further, the PBAC considered that there was no reliable evidence to suggest that ravulizumab was superior in terms of efficacy or safety compared with the other three therapies considered at the March 2025 meeting for the treatment of gMG (zilucoplan, efgartigimod and rozanolixizumab). Overall, the PBAC advised that the four treatments should be considered as non-inferior with each other and with IVIg.

- 8.2 The recommendation was made on the basis of the totality of the evidence presented across all four of the submissions for new gMG therapies.
- 8.3 The PBAC noted the strong consumer and clinician support for the new gMG therapies received via the Consumer Comments facility on the PBS website. The PBAC appreciated the input provided by patients, carers and clinicians and found the comments very informative for understanding the high and unmet clinical need for new effective treatments and the potential use of the new therapies in practice. The comments outlined the significant impact that gMG can have on quality of life, including the impact on patients' families. The comments also described the limitations of currently available treatment options including adverse events and lengthy administration times. Consumers outlined that the new therapies represent a substantial improvement in administration time compared with IVIg, and also shorter travel distances for patients outside metropolitan areas. The comments described a hope that the new therapies will reduce gMG symptoms quickly, reduce the need for other medications and associated side-effects, and reduce hospital visits, contributing to an overall improved quality of life. The PBAC noted the strong support for access to both complement inhibitors (ravulizumab and zilucoplan) and FcRn blockers (efgartigimod and rozanolixizumab) across both the bridging and refractory settings.
- 8.4 The PBAC advised that the restrictions were complex and further work would be required to finalise the restrictions including further consultation with expert neurologists and immunologists before listing can proceed.
- 8.5 The PBAC acknowledged the key trials of the new therapies were not designed to specifically assess efficacy in the bridging setting, but considered the new gMG therapies (both complement inhibitors and FcRn blockers) should be listed in both the bridging and refractory settings given the high unmet need, clinical rationale and strong clinician support (both through the stakeholder meeting and the consumer comments) for broad listings that allow clinician discretion in the choice as to which agent to use in a particular patient.
- 8.6 As such, the PBAC considered the four new therapies for gMG should be listed in three settings, consistent with the advice provided by clinicians at the stakeholder meeting and in the consumer comments:

Immediate access for patients whose condition is acute and severe, and who are at high risk of rapid deterioration. The PBAC advised that the restriction in this setting should require patients to be treated with concomitant corticosteroid and NS-IST therapy with the flexibility that NS-IST can be

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commenced within two weeks of initiation of the new therapy. A maximum time on treatment of 3-months would apply for this setting.

- Bridging: early in the treatment algorithm, in combination with standard therapy to provide bridging immunosuppression whilst immunosuppression with NS-IST/thymectomy takes effect. A maximum time on treatment of 6-months would apply for this setting.
- Refractory: later in the disease course where other treatments have failed.

- 8.7 The PBAC considered the restriction in the bridging setting should provide access for patients whose condition is moderate-to-severe, and who have trialled at least three months of therapy with remission-inducing intent. The PBAC advised this should be defined as two of the following three: NS-IST; a corticosteroid; thymectomy. The NS-IST and/or corticosteroid should have been administered at optimised dosing (definition of optimised doses not specified and will be up to the treating physician to determine). The PBAC advised the initiation criteria in this setting should require patients to meet a disease severity threshold similar to most of the key trials, e.g. around MG-ADL  $\geq 6$  (consistent with two of the four trials of the new therapies for gMG). The PBAC agreed with the clinician correspondence which expressed a preference for also including a clinician-reported component i.e. using the MGC instrument (with a threshold to be determined based on consultation with expert neurologists and immunologists) in addition to the MG-ADL (paragraph 6.6c).
- 8.8 The PBAC considered the restrictions in the refractory setting should require patients to have trialled at least 12 months of two of the following three treatments: a NS-IST; a corticosteroid; thymectomy. This would allow patients to transition from the bridging setting (with a 3-month treatment break) as the NS-IST and/or corticosteroid should have been co-administered in the previous bridging setting. The PBAC advised the disease severity thresholds for initiation in the refractory setting should be the same as those for the bridging setting.
- 8.9 The PBAC considered that, in the acute and bridging settings, there should be a maximum time on treatment of 3 months and 6 months respectively, to prevent ongoing use given the potential for the condition to respond to NS-IST therapy or improve over time. The PBAC considered that the initial restriction for the treatment refractory setting should require the patient to have trialled cessation of the new therapy for three months to be eligible for further treatment with new therapy for this setting (consistent with the ESC advice in paragraph 7.6).
- 8.10 In terms of response criteria in the refractory setting, the PBAC considered that response should be based on an MG-ADL  $\geq 2$  (plus a corresponding MGC level to be determined based on consultation with expert neurologists and immunologists), achieved at 2 to 16 weeks, per the clinician correspondence (paragraph 6.6e).
- 8.11 The PBAC considered it would be appropriate to list the required number of doses with repeats to enable the approximate full treatment time of 3-months for the acute

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- severe setting, and 6-months for the bridging setting. The PBAC also advised it would be appropriate to list the number of doses with repeats for each 6-months of treatment in the refractory setting. The PBAC acknowledged there will be some variability in the number of doses and treatment when taking into account the specific dosing regimens of each drug.
- 8.12 The PBAC considered that the patient must be treated by (or in consultation with) a neurologist or clinical immunologist with experience in the management of gMG. The PBAC advised that there should be no age criteria in the restrictions.
- 8.13 Due to the short timeframe of 3-months and 6-months of acute severe treatment and bridging therapy respectively, the PBAC considered switching between the new therapies would not be appropriate within these settings, however a patient may switch when moving from one phase of treatment to the next. Within the refractory setting, patients may switch as needed on the basis that any unused repeat prescriptions for the previous therapy be cancelled.
- 8.14 The PBAC considered that the new gMG therapies should substitute for IVIg and PLEX rather than be added on to or used in combination with these modalities. The PBAC advised that:
- the PBS restriction should state that the new therapy should not be used in combination with IVIg;
  - there should be no requirement for the patient to have trialed prior IVIg (or PLEX) given the limitations of the available evidence for chronic IVIg; and
  - the prescribing criteria for IVIg should be revised to ensure use remains appropriate in the context of the availability of the new therapies.
- 8.15 The PBAC considered that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost-per-patient of the newer gMG therapies across both the refractory and bridging settings. The PBAC acknowledged the ESC's concerns that, in the bridging setting, there is a lower level of certainty in the incremental benefit versus optimisation of existing therapies but considered these concerns would be adequately addressed by having a maximum duration of use in this setting, along with a combined RSA across both settings.
- 8.16 The PBAC also considered that the four new gMG therapies (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.
- 8.17 The PBAC considered there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab). The PBAC further considered that the published network meta-analyses had substantial limitations, in particular the lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.

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- 8.18 The PBAC noted the ravulizumab submission did not include a clinical comparison versus IVIg, but noted that at least one of the submissions for a new gMG therapy claimed non-inferior efficacy and safety versus IVIg based on an indirect comparison versus NCT02473952 (later published as Brill 2024) which found no statistically significant differences in functional outcomes or serious adverse events between the new therapy and IVIg. The PBAC acknowledged the limitations of the available evidence for chronic IVIg however, based on the totality of the evidence presented across the four submissions, the PBAC considered that there was insufficient evidence to support superior efficacy or safety of any of the four new gMG therapies versus chronic IVIg or PLEX.
- 8.19 Overall, the PBAC considered that ravulizumab has non-inferior comparative effectiveness and safety versus chronic IVIg and also against zilucoplan, efgartigimod and rozanolixizumab.
- 8.20 The PBAC noted the economic model was based on a treatment setting in which patients had an inadequate prior response to IVIg/PLEX (or were intolerant or unable to access these treatments), which was inconsistent with the recommended place in therapy. Further, the PBAC agreed with ESC that the cost-utility analysis submitted was limited by the lack of long-term data available and the complex nature of the condition. As such, the PBAC considered the uncertainty in the ICER was unlikely to be adequately resolved with further revisions to the model structure and reiterated that the cost-per-patient of IVIg could provide a frame of reference for the newer gMG therapies in a cost-comparison approach.
- 8.21 To determine the average IVIg dose per patient per year, the PBAC considered it would not be practical to use the dose recommended in the Product Information (induction dose: 1-2g/kg and maintenance dose: 0.4-1 g/kg every 4 to 6 weeks)<sup>7</sup> given the wide dose range specified which could result in annual doses of 352g to 1,172g per patient (using an average patient weight of 83.7 kg per Brill 2024). Further, in Brill 2024 (one of the key studies of chronic IVIg in gMG), IVIg was administered every 3 weeks which does not align with the Product Information (dosing every 4 to 6 weeks).
- 8.22 The PBAC acknowledged the NBA data was based on the average dose across all severity levels and thus included patients with less severe disease than the threshold for initiation of the new therapies. Further, use of the 2023-24 NBA data would not account for the varying cost per gram of IVIg (which depends on the proportion of imported IVIg, with the cost in 2023-24 being higher than previous years). Notwithstanding this, the PBAC considered the IVIg utilisation data from the NBA was the most appropriate data available for determining the average annual dose of IVIg being used in Australian patients.

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<sup>7</sup> Australian Product Information for Privigen and Intragam  
<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2020-PI-01935-1&d=20250321172310101>;  
<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2014-PI-03087-1>

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- 8.23 The PBAC considered that a cost-comparison versus IVIg would need to be based on the drug cost per patient per year accounting for:
- the total average annual dose of IVIg per patient observed in the NBA data (for maintenance gMG) of 541.1 grams per year (shown in Table 21).
  - the ravulizumab dose recommended in the product information assuming the same weight distribution as patients in the trial (outlined in Table 17), not accounting for response rates. The PBAC considered it would be reasonable to exclude the ravulizumab loading dose from the cost-comparison (i.e. account for 6.5 ravulizumab maintenance doses per year) given the IVIg dose was akin to a steady state dose. Compliance assumptions of around 95% may be appropriate for the complement inhibitors (administered on a chronic basis) given the cost-comparison approach being applied. Based on these assumptions the average annual dose of ravulizumab would be: 20,854 mg per year (i.e. 21,951 x 0.95 compliance).
  - a small premium to account for the administration benefits associated with the newer therapies compared with IVIg, noting the extensive administration requirements associated with IVIg, with an infusion time of around 2 to 4 hours and up to 8 hours, which have resource implications and a direct impact on patients and carers.
  - meningococcal vaccination for the complement inhibitors.
- 8.24 The PBAC noted the results of a cost-per-responder analysis versus placebo which assumed the same drug cost per patient as IVIg (based on the NBA data), along with the average incremental response rate across the four gMG trials (refer to paragraph 6.88). The PBAC considered cost-per-responder analysis supported that the new therapies would be cost effective if priced based on the IVIg cost as outlined above.
- 8.25 The PBAC advised that the financial estimates should take the total number of patients accessing IVIg as gMG maintenance therapy as a starting point, which was 1,324 in 2023-24 (refer to Table 20). The PBAC considered the following should then be applied: market growth (of around 4% per year, based on the last five years of IVIg data); and the proportion of patients whose gMG is AChR+ (of around 86%, based on the pooled estimates provided in one of the submissions, noting this is similar to the estimate of 88% provided in Hendricks et al. 2019, which was the only estimate included in the ravulizumab submission that was based on a gMG population).
- 8.26 The PBAC advised that uptake should be based on the new therapies as a group, and should be from two key groups within existing IVIg users:
- uptake from new patients and existing IVIg users with ongoing functional impairment (i.e. % of the AChR+ patient cohort, Table 20). This group would likely have relatively high uptake of the new therapies (potentially up to %).

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- uptake from prevalent patients (i.e. the remaining  $\frac{1}{2}$ % of the AChR+ patient cohort) already established on IVIg (uptake of around  $\frac{1}{2}$ %).
- 8.27 The PBAC advised that the aforementioned uptake rates were intended to account for: any additional eligible patients (e.g. patients who are not responding to, or who are unable to be treated with IVIg); the PBS restriction being narrower than the current IVIg criteria; and the stopping rules (as these would generally mirror how IVIg is used in practice). The aforementioned rates would equate to an overall uptake rate of around  $\frac{1}{2}$ % in Year 1 (i.e.  $\frac{1}{2}$ % of all patients on IVIg for AChR+ gMG would commence a new gMG therapy in Year 1 of listing, refer to Table 20). The PBAC considered this was at the higher end of plausibility given the proportion of patients on IVIg who would be eligible for the new therapies could potentially be quite low.
- 8.28 The PBAC advised that uptake was likely to increase over time, and that this may be gradual given the large prevalent pool with a long history of IVIg use. As such, the PBAC advised that it would be reasonable for the estimated uptake rates to increase by 5 percentage points each year for the first six years of listing.
- 8.29 The PBAC advised that the dose assumptions (e.g. number of doses per patient per year) in the financial estimates should be the same as those applied in the cost-comparison (refer to paragraph 8.23) although the ravulizumab loading dose should be accounted for.
- 8.30 The PBAC considered that any listing of the new gMG therapies would be associated with a substantial reduction in the utilisation of IVIg for gMG maintenance, given the lack of other treatment options but also acknowledging that a small proportion of patients cannot tolerate or access IVIg, or have ceased IVIg due to lack of response.
- 8.31 The PBAC noted that more complex approaches to estimating the financial impacts could be used (e.g. calculating utilisation in the bridging and refractory settings separately, taking stopping rules into account) but considered the simplified approach outlined above was likely to provide more accurate forecasts given the: lack of robust data to inform a more complex approach and the intent of the restrictions to mimic the current use of IVIg in clinical practice (in terms of use across both the bridging and refractory settings, with clinicians regularly assessing the on-going need for continuing IVIg therapy including through treatment breaks).
- 8.32 The PBAC advised that a single RSA that includes all of the new therapies (in all settings) would be required to mitigate the risk of use outside the intended restriction. For the FcRn blockers, the RSA would also need to mitigate the risk of an increase in the frequency of cycles received over time. The PBAC advised that the risk of higher dosing frequency is less relevant for the complement inhibitors and thus these sponsors should not be adversely affected by more frequent FcRn blocker dosing. The PBAC advised that the Department and each sponsor should work to ensure the cost per patient does not exceed the estimates in the cost-comparison and the financials.

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- 8.33 The PBAC acknowledged the financial estimates as outlined in paragraphs 8.25 to 8.29 were associated with some uncertainty and considered that it may be reasonable for the risk of use outside the intended restriction to be managed through a | RSA – with the || based on the financial estimates outlined by the PBAC (e.g. with the AChR+ proportion and uptake rates applied as outlined in paragraphs 8.25 to 8.29 and Table 20) with a rebate of less than |%, then a || based on the total number of patients using IVIg for maintenance gMG with a rebate of |%.
- 8.34 The PBAC advised that a utilisation review by DUSC should be conducted two years after listing of any new therapies, which should also assess whether the newer therapies have resulted in a reduction in IVIg use (noting this would require data from the NBA).
- 8.35 The PBAC noted the Product Information for ravulizumab stated “vaccines against serogroups A, C, Y, W135 and B where available, are recommended to reduce the risk of infection with the commonly pathogenic meningococcal serogroups. Patients must be vaccinated or revaccinated according to current medical guidelines for vaccination use.” The PBAC advised it would be appropriate to extend access on the National Immunisation Program for the vaccinations recommended in the Product Information.
- 8.36 The PBAC advised that ravulizumab should not be treated as interchangeable with any other drugs.
- 8.37 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for ravulizumab:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over IVIg;
  - The treatment is not expected to address a high and urgent unmet clinical need because an alternative therapy (IVIg) is available;
  - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 8.38 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 9 Recommended listing

This restriction is in the process of being finalised (see paragraph 8.4). The sponsor will be notified of the final restriction.

**10 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.

**11 Sponsor's Comment**

The sponsor had no comment.