

7.11 ZILUCOPLAN,

**Solution for injection 16.6 mg in 0.416 mL (as tetrasodium)
pre-filled syringe,**

**Solution for injection 23 mg in 0.574 mL (as tetrasodium)
pre-filled syringe,**

**Solution for injection 32.4 mg in 0.810 mL (as tetrasodium)
pre-filled syringe,**

Zilbrysq[®],

UCB AUSTRALIA PTY LTD

1 Purpose of submission

- 1.1 The standard re-entry submission requested a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for treatment with zilucoplan in adult patients with anti-acetylcholine receptor antibody (AChR) positive generalised myasthenia gravis who are refractory to conventional immunotherapies.
- 1.2 The resubmission claimed that there is an unmet clinical need for patients with treatment refractory generalised myasthenia gravis as access to chronic intravenous immunoglobulin (IVIg) and chronic plasma exchange (PLEX) can be difficult for those who would otherwise be treated with these therapies.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus placebo.

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

Component	Description
Population	Adult patients with symptomatic generalised myasthenia gravis who are AChR-positive <u>and refractory to conventional immunotherapies^a</u> .
Intervention	Zilucoplan subcutaneous injection daily (weight-based dosing 16.6-32.4 mg); in combination with standard therapy (including anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, ciclosporin).
Comparator	Placebo as add on therapy to standard therapy.
Outcomes	Reduction in functional impairments, reduction in clinical exacerbations and myasthenic crisis events, improvements in quality of life.
Clinical claim	Zilucoplan in combination with standard therapy is superior in terms of efficacy and non-inferior in terms of safety compared to placebo in combination with standard therapy.

Source: Table 1.1-1, p4 of the resubmission

Abbreviations: AChR, anti-acetylcholine receptor

^a The criteria for patients who were considered to be refractory to conventional immunotherapies are as follows: (1) treatment for at least 1 year with 2 or more of the following therapies: prednisone, azathioprine, mycophenolate, ciclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids for generalised myasthenia gravis, other immunosuppressant therapy, or (2) the history of treatment with at least 1 of these therapies for 1 year or more and required chronic plasma exchange, intravenous immunoglobulin, or subcutaneous immunoglobulin at least every 3 months for the 12 months prior to enrolment.

2 Background

Registration status

- 2.1 Zilucoplan was approved by the TGA and registered on the ARTG on 20 August 2024. The approved TGA indication is:
- For the treatment of generalised myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
- 2.2 The product information includes a black box warning on the risks of serious meningococcal infection associated with zilucoplan treatment and physicians should provide patients with an alert card that explains the symptoms of meningococcal infection and when to seek immediate medical care. The product information states that all patients must be vaccinated against meningococcal infection at least 2 weeks prior to receiving zilucoplan. However, the product information notes that vaccination may not be sufficient to prevent meningococcal infection and the ongoing use of prophylactic antibacterials may also have a potential role.
- 2.3 Zilucoplan is subject to additional monitoring in Australia under the Black Triangle Scheme.

Previous PBAC consideration

- 2.4 The sponsor presented a Category 1 submission to the July 2024 PBAC meeting requesting a Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for treatment initiation and a Section 85 Authority Required (Written) listing for treatment continuation with zilucoplan in adult patients with AChR-positive generalised myasthenia gravis.
- 2.5 The PBAC did not recommend zilucoplan for the requested listing with the primary reason being the limitations of the economic evaluation.
- 2.6 The key matters of concern from the July 2024 PBAC meeting are summarised in Table 2.

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Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Restriction	
<p>The PBAC expressed a preference for listing the new therapies in a broad patient population.</p> <p>The PBAC considered that a resubmission should identify how treatment criteria may differ for refractory and non-refractory patients; and that a resubmission should give further consideration to the place in therapy, as it was noted that access to chronic IVIg/PLEX can be difficult and there is a higher clinical need to effective therapies in patients who would otherwise be treated with IVIg/PLEX (para 7.8).</p>	<p>The resubmission restricted use of zilucoplan to treatment refractory AChR-positive generalised myasthenia gravis patients who would otherwise be treated with IVIg/PLEX.</p>
<p>The PBAC noted that the restriction was broad given it did not: require the corticosteroid/immunosuppressive therapy to have been optimised; require combination corticosteroid plus non-steroid immunosuppressive therapy to have been trialled; nor specify a timeframe for assessing response prior to commencing zilucoplan (para 7.4).</p>	<p>The proposed restriction includes criteria specifying the type and timeframe of prior therapies but did require treatment optimisation, prior use of combination therapies or a timeframe for assessing response prior to initiating zilucoplan.</p>
<p>The PBAC considered that the continuation criterion proposed in the pre-PBAC response (a 3-point reduction in MG-ADL from baseline) required further consideration as it would mean that almost half of the treated population would be continuing based on the placebo effect alone (46.1% of patients in the placebo arm achieved this response level in the RAISE trial).</p>	<p>This issue was not addressed. The same continuation criterion was proposed in the resubmission.</p>
<p>The PBAC noted that the submission did not include a stopping rule in the proposed restriction. The PBAC agreed with the clinicians present at the stakeholder meeting that there should be robust stopping rules to prevent ongoing use, noting that it would be harder to cease treatment in patients whose condition is refractory (para 7.6).</p>	<p>The resubmission did not propose any stopping rules, consistent with advice from the stakeholder meeting which did not suggest a stopping rule in treatment refractory populations.</p>
Comparator	
<p>The PBAC noted that the submission nominated placebo (standard therapy alone) as the main comparator and chronic IVIg and PLEX as secondary comparators. 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 zilucoplan in the refractory setting (para 7.9, 7.21).</p>	<p>Placebo was the nominated comparator in the resubmission.</p> <p>The resubmission did not use the cost of IVIg/PLEX as a frame of reference for the cost per patient of zilucoplan. A comparison of costs per patient per year is presented in Drug cost/patient/year.</p>
Clinical evaluation	
<p>The PBAC considered that the outcomes for the refractory and non-refractory subgroups were difficult to interpret based on the information provided, but the high placebo response rates presented in the responder analyses indicated that standard therapies are effective for many patients, particularly those in the non-refractory group (para 7.13).</p>	<p>There were no substantial updates to the clinical data presented in the previous submission.</p>

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Matter of concern	How the resubmission addresses it
The PBAC considered that the claim of non-inferior comparative safety versus placebo was not adequately supported given the limited safety data and the requirement for patients to receive meningococcal vaccinations (para 7.14).	The resubmission presented an updated PSUR which did not identify any new safety concerns. The resubmission maintained a safety claim of non-inferiority versus placebo.
Economic evaluation	
Responders in the zilucoplan arm have larger improvements in MG-ADL scores than responders in the placebo arm which was inconsistent with the clinical trial data (para 7.15).	Assumptions regarding changes in MG-ADL scores for treatment responders were revised resulting in minor differences between treatment arms up to Week 12, and no differences between treatment arms beyond Week 12.
Non-responders in the treatment refractory setting switch to chronic IVIg/PLEX and escalated standard therapies and remain fully adherent for the remainder of the model, despite gaining no improvement in clinical outcomes with treatment (para 7.15).	The proportion of zilucoplan and placebo non-responders who receive IVIg/PLEX was revised (from 100% to 20%; with IVIg/PLEX patients receiving concomitant standard therapy), and a treatment effect associated with IVIg/PLEX therapy included (70%; previously 0%); with patients able to discontinue therapy due to non-response, non-persistence, following a clinical event, or death.
Patients experiencing an exacerbation or myasthenic crisis discontinue therapy with zilucoplan and placebo despite no clear clinical rationale for this assumption. The calculation of event rates was poorly justified and was likely to have substantially overestimated the risk of events (para 7.15).	Clinical event rates were revised, based on hospitalised events in a retrospective analysis of a US claims database (Parthan 2024). The revised event rates were generally higher than those used in the July 2024 submission. Risks of treatment discontinuation following an exacerbation event were revised.
The assumption that corticosteroid users who respond to treatment no longer require high-dose corticosteroids, while corticosteroid users who fail to achieve a response require high-dose corticosteroids was not adequately supported by the available clinical data. Additionally, the disutility applied for high-dose corticosteroids was likely to have substantially overestimated the disutility attributable to corticosteroid use (para 7.15).	The proportion of treatment responders receiving high-dose corticosteroids was revised from 0% to 6.9% (derived from baseline use in the RAISE trial). The proportion of non-responders receiving escalated standard therapy who receive high-dose corticosteroids was also increased from 63.8% to 100%. A smaller disutility associated with high-dose corticosteroids was used.
The PBAC noted that the proposed price was very high and was a driver of the ICER/QALY gained, and thus a substantial price reduction would be required to achieve an acceptable ICER (para 7.20).	The resubmission proposed an AEMP per mg of \$ [redacted] for zilucoplan, an [redacted]% increase on the proposed AEMP per mg of \$ [redacted] in the July 2024 submission. The estimated ICER of \$ [redacted] ¹ per QALY gained, was a [redacted]% increase on the ICER estimated in the July 2024 submission (\$ [redacted] ² per QALY gained).
Utilisation and financial impact of listing	
The prevalence of myasthenia gravis was likely underestimated (para 7.19).	The prevalence of myasthenia gravis was increased from 11.77 to 22.4 per 100,000 persons.
The expected uptake of zilucoplan was potentially overestimated (para 7.19).	Uptake rates were unchanged.
There was uncertainty regarding the likely duration of zilucoplan treatment (as the impact of a stopping rule needs to be accounted for) (para 7.19).	A stopping rule was not proposed for the treatment refractory population.
The PBAC advised the estimated patient numbers should be substantially lower to reflect the requirement for patients to have an MG-ADL score ≥ 6 prior to initiation (para 7.19, 7.20).	The proportion of patients eligible for treatment was revised to account for the treatment refractory population (20.78%; compared to 70.13% treated with a corticosteroid and/or immunosuppressive therapy in the July 2024 submission). However, a criterion to identify the proportion of patients with MG-ADL ≥ 6 was not included in the resubmission.

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Matter of concern	How the resubmission addresses it
The potential reduction in utilisation of existing therapies such as chronic IVIg and PLEX was likely overestimated (para 7.19).	Multiple inputs informing cost offsets associated with substituted use of IVIg/PLEX were updated.
The PBAC considered that any proposal to list zilucoplan in a narrower population would need to include an RSA proposal to manage the risk of use outside the intended listing (para 7.21).	The sponsor proposed an RSA based on the financial estimates of the resubmission, with no further details provided.

Source: Zilucoplan PBAC PSD, July 2024 PBAC meeting; Sections 1-4 of the resubmission.

Abbreviations: AChR, anti-acetylcholine receptor; AEMP, approved ex-manufacturer price; ICER, incremental cost-effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living score; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PLEX, plasma exchange; PSUR, Periodic Safety Update Report ;QALY, quality adjusted life year; RSA, risk sharing arrangement.

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² \$255,000 to < \$355,000

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty		Max. qty packs	Max. qty units	No. of Rpts	Available brands
	Published	Effective				
ZILUCOPLAN						
Initial treatment, balance of supply, grandfather						
Zilucoplan 40 mg/mL 0.416 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	3	Zilbrysq
Zilucoplan 40 mg/mL 0.574 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	3	
Zilucoplan 40 mg/mL 0.810 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	3	
Zilucoplan 40 mg/mL 0.416 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	3	
Zilucoplan 40 mg/mL 0.574 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	3	
Zilucoplan 40 mg/mL 0.810 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	3	
Continuing treatment (or alternative initial treatment, balance of supply, grandfather)						
Zilucoplan 40 mg/mL 0.416 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	5	Zilbrysq

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MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty		Max. qty packs	Max. qty units	No. of Rpts	Available brands
	Published	Effective				
Zilucoplan 40 mg/mL 0.574 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	5	
Zilucoplan 40 mg/mL 0.810 mL injection, 28 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	1	28	5	
Zilucoplan 40 mg/mL 0.416 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	5	
Zilucoplan 40 mg/mL 0.574 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	5	
Zilucoplan 40 mg/mL 0.810 mL injection, 7 pre-filled syringes	\$ (Public hospital) \$ (Private hospital)	\$ (Public hospital) \$ (Private hospital)	4	28	5	

Category/Program: Section 100 – Highly Specialised Drugs Program

Prescriber type: Medical Practitioners

Restriction type: Authority Required (in writing only via post/HPOS upload)

Authority type: Complex Authority Required (CAR)

Caution: C5 inhibitors increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.

Condition: Generalised myasthenia gravis (gMG)

Indication: Generalised myasthenia gravis (gMG)

Treatment Phase: Initial treatment

Clinical criteria:

Patient must be ≥ 18 years of age

AND

Clinical criteria:

Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies

AND

Clinical criteria:

Patient must have a diagnosis of Myasthenia Gravis Foundation of America (MGFA) Disease Class II to IV

AND

Clinical criteria:

Patient must have an MG-ADL score ≥ 6

AND

Clinical criteria:

Patient must be receiving concomitant treatment with-at least one of the following: (i) corticosteroid (ii) immunosuppressive therapy

AND

Clinical criteria:

Patient must have been treated for at least 1 year with at least two of the following: (i) corticosteroids (ii) azathioprine, (iii) mycophenolate, (iv) ciclosporin (v) cyclophosphamide (vi) methotrexate OR

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Patient must have a history of treatment over the past 1 year of plasma exchange or intravenous immunoglobulin (IVIg) at least every 3 months
AND
Clinical criteria:
Treatment must not be in combination with another complement inhibitor
AND
Treatment criteria:
Must be treated by a neurologist
Note:
The myasthenia gravis activities of daily living (MG-ADL) referenced in this restriction is described in the following literature publication: Wolfe, G.I, Herbelin, L., Nations, S.P, Foster, B., Bryan, W.W. & Barohn, R.J. 1999. Myasthenia gravis activities of daily living profile. Neurology, 52, 1487-9.
Administrative Advice:
The authority application must be made in writing and must include: (1) a completed authority prescription form; and (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); and (3) At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: Baseline MG-ADL score.
Category/Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Caution: C5 inhibitors increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Condition: Generalised myasthenia gravis (gMG)
Indication: Generalised myasthenia gravis (gMG)
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must have demonstrated or sustained an adequate response to treatment, defined as at least a 3-point reduction in MG-ADL score from baseline
AND
Clinical criteria:
Treatment must not be in combination with another complement inhibitor
AND
Treatment criteria:
Must be treated by a neurologist
Note:
The myasthenia gravis activities of daily living (MG-ADL) referenced in this restriction is described in the following literature publication: Wolfe, G.I, Herbelin, L., Nations, S.P, Foster, B., Bryan, W.W. & Barohn, R.J. 1999. Myasthenia gravis activities of daily living profile. Neurology, 52, 1487-9.
Prescribing instructions:
Patients are eligible to receive continuing treatment with this drug in courses of up to 24 weeks providing they continue to maintain a response.

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Administrative Advice:
The authority application must be made in writing and must include: An assessment of response, defined as at least a 3-point reduction in MG-ADL from baseline, following a minimum of 12 weeks and up to 16 weeks of treatment with this drug.
Category/Program: Section 100 – Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Caution: C5 inhibitors increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Condition: Generalised myasthenia gravis (gMG)
Indication: Generalised myasthenia gravis (gMG)
Treatment Phase: Balance of supply
Clinical criteria:
Patient must have a previously received this drug for this condition
AND
Clinical criteria:
Patient must have temporarily ceased treatment for reasons other than lack of response (e.g. family planning, vaccination, adverse-effect investigation), thereby being unable to achieve/maintain an adequate response immediately prior to this authority application
AND
Clinical criteria:
Patient must have received insufficient therapy with this drug under the initial treatment restriction to receive 16 weeks of continuous treatment
AND
Clinical criteria:
Treatment must not be in combination with another complement inhibitor
Treatment criteria:
Must be treated by a neurologist
Note:
The myasthenia gravis activities of daily living (MG-ADL) referenced in this restriction is described in the following literature publication: Wolfe, G.I, Herbelin, L., Nations, S.P, Foster, B., Bryan, W.W. & Barohn, R.J. 1999. Myasthenia gravis activities of daily living profile. Neurology, 52, 1487-9.
Administrative Advice:
The authority application must be made in writing and must include: (1) a completed authority prescription form; and (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); and (3) At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: Reason for temporarily ceasing treatment
Category: Program: Section 100 - Highly Specialised Drugs Program
Prescriber type: Medical Practitioners
Restriction type: Authority Required (in writing only via post/HPOS upload)
Caution: C5 inhibitors increases the risk of meningococcal infections (septicaemia and/or meningitis). Please consult the approved PI for information about vaccination against meningococcal infection.
Condition: Generalised myasthenia gravis (gMG)
Indication: Generalised myasthenia gravis (gMG)

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Treatment Phase: Grandfather
Clinical criteria:
Patient must have previously received non-PBS subsidised drug for this condition prior to [list date]
AND
Clinical criteria:
Patient must be at least 18 years of age
AND
Clinical criteria:
Patient must have a diagnosis of Myasthenia Gravis Foundation of America (MGFA) Disease Class II to IV at treatment initiation
AND
Clinical criteria:
Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies
AND
Clinical criteria:
Patient must have an MG-ADL score \geq 6 at treatment initiation
AND
Clinical criteria:
Patient must be receiving concomitant treatment with at least one of the following: (i) corticosteroid (ii) immunosuppressive therapy
AND
Clinical criteria:
Patient must have been treated for at least 1 year with at least two of the following: (i) corticosteroids (ii) azathioprine, (iii) mycophenolate, (iv) ciclosporin (v) cyclophosphamide (vi) methotrexate at treatment initiation OR
Patient must have a history of treatment over the past 1 year of plasma exchange or intravenous immunoglobulin (IVIg) at least every 3 months at treatment initiation
AND
Clinical criteria:
Must not be in combination with another complement inhibitor
Treatment criteria:
Must be treated by a neurologist
Note:
The myasthenia gravis activities of daily living (MG-ADL) referenced in this restriction is described in the following literature publication: Wolfe, G.I, Herbelin, L., Nations, S.P, Foster, B., Bryan, W.W. & Barohn, R.J. 1999. Myasthenia gravis activities of daily living profile. Neurology, 52, 1487-9.
Administrative Advice:
The authority application must be made in writing and must include: (1) a completed authority prescription form; and (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); and (3) At the time of the authority application, details (result and date of result) of the following monitoring requirements must be provided: Baseline MG-ADL score at treatment initiation of non-PBS subsidised drug for this condition

3.1 The resubmission proposed a special pricing arrangement for zilucoplan, which represented a rebate of approximately |% of the published DPMQ per script (the pre-PBAC response proposed revised published prices, not presented in the requested restriction above). The proposed effective AEMP was \$| per mg, representing an |%

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increase compared to \$| per mg in the July 2024 submission. The PBAC previously considered that the proposed price was very high, and a substantial price reduction would be required (para 7.20, zilucoplan PBAC Public Summary Document [PSD], July 2024 PBAC meeting). The Pre-Sub-Committee Response (PSCR) outlined that a higher price was proposed due to the higher clinical need in the revised population and a smaller target population compared with the July 2024 submission.

- 3.2 The resubmission requested listing in treatment refractory patients only given this is the patient group with the highest clinical need, however, in its July 2024 consideration the PBAC had expressed a preference for listing the new gMG therapies in a broad population. The July 2024 PBAC PSD stated that any proposal to list zilucoplan in a narrower population (i.e. refractory patients): should be supported by clinical evidence; would need to include an RSA proposal to manage the risk of use outside the intended listing; and could use chronic IVIg/PLEX as a frame of reference for interpreting the cost per patient (paragraph 7.21, zilucoplan PSD, July 2024 PBAC meeting). The ESC considered that the resubmission had not adequately addressed these issues (e.g. the RSA proposal was based on likely overestimated utilisation estimates, and the frame of reference versus chronic IVIg/PLEX was not addressed) and thus the case for the narrower treatment setting proposed in the resubmission may not have been adequately justified.

Refractory population proposed in the resubmission

- 3.3 The proposed PBS restriction in the resubmission was narrower than the TGA indication due to additional clinical criteria for functional impairment, treatment refractory status, co-administered therapies and treatment response.
- 3.4 The revised restriction proposed in the resubmission was also narrower than the restriction proposed in the July 2024 submission due to additional criteria defining functional impairment and treatment refractory status. Other differences in the proposed restriction include removal of the criteria for concomitant treatment with an acetylcholinesterase inhibitor, a revised response criterion, and revised duration of treatment for balance of supply.
- 3.5 The resubmission acknowledged that there was no consensus definition of treatment refractory disease for myasthenia gravis. However, the resubmission adapted the criteria from the key clinical trial as a working definition of treatment refractory disease: treatment for at least 1 year with 2 or more of corticosteroids, azathioprine, mycophenolate, ciclosporin, cyclophosphamide, or methotrexate; or history of treatment over the past year of PLEX or IVIg at least every 3 months. However, given the fluctuating nature of symptoms in myasthenia gravis, the evaluation considered that a prior history of use does not necessarily indicate patients are refractory to therapy.
- 3.6 As outlined in Section 7, the ESC considered that any PBS restriction for the treatment refractory setting should require the patient to have prior treatment for at least one

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- year. The ESC considered that further work would be required to determine the specific therapies and durations.
- 3.7 International clinical treatment guidelines (Sanders 2016) define treatment refractory patients as having a post-intervention status that was unchanged or worse after corticosteroids and at least 2 other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning (as defined by patient and physician).
- 3.8 The PBAC previously noted that, in clinical practice, treatment refractory disease may include patients who: have disease that is unchanged or worse after corticosteroids and at least one other immunosuppressive agent (used at an adequate dose and for an adequate duration) with persistent symptoms or side effects that limit function; need ongoing rescue therapy with IVIg/PLEX or who experience frequent crises while on immunotherapy; or with intolerable adverse reactions or the presence of comorbid illnesses that preclude use of conventional immunotherapies (paragraph 4.12, zilucoplan PBAC PSD, July 2024 PBAC meeting).
- 3.9 The resubmission proposed switching the instrument used to assess functional impairment from the Myasthenia Gravis Composite score (MGC) instrument used in the July 2024 submission to the Myasthenia Gravis Activities of Daily Living (MG-ADL) instrument. The resubmission claimed that this was reasonable as responder analyses from the key clinical trial were based on MG-ADL outcomes and the ESC previously raised concerns regarding the assumed correlation between the MG-ADL and MGC instruments in the July 2024 submission (paragraph 3.9, zilucoplan PBAC PSD, July 2024 PBAC meeting). The resubmission also noted expert advice that both the MG-ADL and MGC instruments provided robust estimates of functional impairment. As noted in the July 2024 submission, the MGC instrument is the most widely used measure of functional impairment in Australian clinical practice and this instrument is used in the current National Blood Authority (NBA) listing for chronic IVIg for the treatment of myasthenia gravis. Overall, the resubmission did not adequately justify switching from the MGC to MG-ADL as both instruments appear potentially relevant to Australian clinical practice.
- 3.10 The July 2024 submission did not require any assessment of functional impairment for treatment initiation. In contrast, the current resubmission proposed a requirement for patients to have an MG-ADL score of at least 6 in the initial treatment restriction. This change was originally proposed in the pre-PBAC response for the July 2024 submission on the basis that this requirement was more closely aligned with the inclusion criteria of the key clinical trial. The evaluation considered that the proposed initiation criterion was not adequately justified in the resubmission and was inconsistent with the key trial eligibility criteria (MG-ADL ≥ 6 ; QMG ≥ 12 and 4 or more QMG items scored ≥ 2) and the current NBA listing for chronic IVIg (MGC ≥ 4). The PSCR outlined that the proposed criterion was intended as a simplification of the RAISE eligibility criteria since clinicians advised that the QMG was not used in Australian clinical practice. Refer to

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- paragraphs 8.7 and 8.8 for the PBAC's advice regarding criteria for treatment initiation.
- 3.11 The July 2024 submission required patients to achieve a 3-point reduction in MGC score after 12-16 weeks of treatment to qualify for ongoing therapy, consistent with the current NBA listing for chronic IVIg. However, the current resubmission requires patients to achieve a 3-point reduction in MG-ADL score after 12-16 weeks of treatment (with an additional alternative option for assessment at 24 weeks) on the basis that this was consistent with the reported outcomes from the key clinical trial and extension. This was consistent with the continuation criterion proposed in the July 2024 pre-PBAC response, which the PBAC considered required further consideration as it would mean that almost half of the treated population would be continuing based on the placebo effect alone (46.1% of patients in the placebo arm achieved this response level in the RAISE trial) (paragraph 7.7, zilucoplan PBAC PSD, July 2024 PBAC meeting). Refer to paragraph 8.10 for the PBAC's advice regarding response criteria.
- 3.12 The resubmission did not propose any stopping rules for the use of zilucoplan. This was consistent with advice from the myasthenia gravis stakeholder meeting which suggested a potential stopping rule (total treatment duration of 2 years) in non-refractory populations but did not suggest a stopping rule in treatment refractory populations. Refer to paragraph 8.9 for the PBAC's advice regarding stopping rules.
- 3.13 The July 2024 submission required patients to be receiving concomitant treatment with an anticholinesterase inhibitor (unless intolerant) and at least one immunosuppressive therapy (corticosteroids and/or other immunosuppressants). The revised restriction in the resubmission omits the criterion for patients to be treated with an anticholinesterase inhibitor, with the resubmission arguing that anticholinesterase inhibitors are a first line treatment, which refractory patients may have discontinued due to intolerance or lack of efficacy.
- 3.14 The evaluation considered the generalisability of key trial results to the target PBS population was unclear (refer to paragraph 6.12 for a discussion of the baseline characteristics of patients enrolled in the trial).
- 3.15 The proposed clinical criteria for zilucoplan are more restrictive than the current NBA listing for chronic IVIg, which may affect the utilisation of zilucoplan in clinical practice as patients may qualify for IVIg/PLEX before becoming eligible for zilucoplan treatment.
- 3.16 The proposed restriction specifies that zilucoplan treatment must not be in combination with another complement inhibitor, however, it does not preclude combination use with an FcRn blocker.
- 3.17 The resubmission proposed a grandfathering restriction that appears to be based on the treatment initiation criteria. It was unclear whether this population would meet the proposed criterion for treatment continuation that applies to non-grandfathered

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patients. The resubmission estimated < 500 patients in the sponsor's patient access program may be eligible for grandfathering treatment.

Bridging setting and both settings

3.18 ESC advice relevant to the bridging setting and both settings is in Section 7.

Meningococcal vaccination

3.19 The ESC noted that the Product Information states 'before starting therapy with zilucoplan, patients must be vaccinated against *Neisseria meningitidis*' and 'vaccines against serogroups A, C, Y, W, and where available, serogroup B, are recommended for preventing the commonly pathogenic meningococcal serogroups' and vaccination 'should occur according to the most current relevant guidelines'. As such, the ESC considered it would be appropriate to enable patients commencing zilucoplan (or any PBS-subsidised complement inhibitor) to access the relevant meningococcal vaccinations on the National Immunisation Program.

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 85%) having autoantibodies against AChR (Sciancalepore 2024).

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 limb, bulbar and respiratory system (generalised myasthenia gravis). The symptoms of myasthenia gravis can develop at any age (including childhood) but more commonly impacts young adult women and older men. Typical symptoms include drooping eyelids, blurred or double vision, shortness of breath, difficulty chewing and swallowing, impaired speech, fatigue, pain, muscle spasms and general muscle weakness.

4.3 The intensity of muscle weakness can fluctuate from day to day and can be worsened due to fatigue, stress, current illness and other factors. The course of disease is highly variable but 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.

4.4 During the course of the disease, patients may experience transient periods of rapid symptom worsening, commonly referred to as disease exacerbations. Of particular concern are myasthenic crises, which are severe, life-threatening exacerbations that

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are due to weakness in respiratory muscles which results in respiratory failure requiring mechanical ventilation.

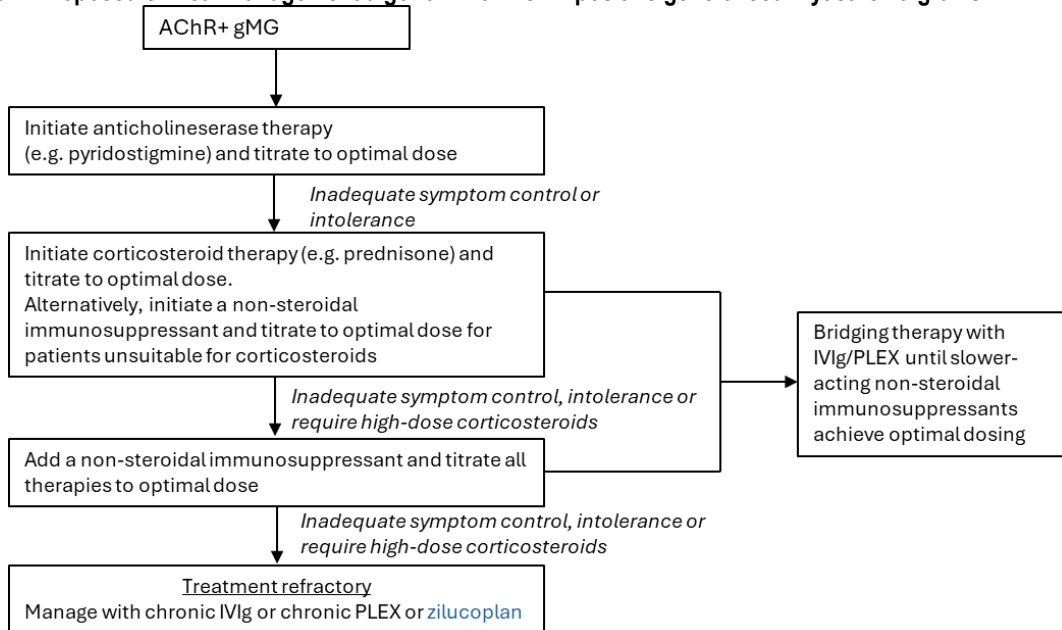
- 4.5 The resubmission noted that the fluctuating and unpredictable nature of generalised myasthenia gravis symptoms substantially impact quality of life, with increased burden associated with planning daily activities to cope with the variable symptoms (Jackson 2023, Twork 2010, Petersson 2021, Law 2021). Persistent fatigue and physical impairments are associated with reduced workforce participation and can prevent patients from performing everyday tasks, contributing to a loss of independence (Cleanthous 2021, Blum 2015). Other concerns noted during the evaluation include the social/emotional impacts of the disease (such as anxiety, depression and feeling isolated) as well as the treatment burden associated with current therapies (Nadali 2023, Sansoni 2023).
- 4.6 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 (95% CI 5.5, 11.9) cases per million person-years in the period 1967-2007 to 22.9 (95% CI 14.1, 31.7) cases per million person-years in the period 2008-2022; and prevalence has increased from 97.5 (95% CI 59.9, 141.9) cases per million person-years in the period 1952-2007 to 220.1 (95% CI 149.3, 288.1) cases per million person-years in the period 2008-2021. However, the review acknowledged that there was significant variation in frequencies of myasthenia gravis between and within countries because of methodological biases and complex heterogeneity of the disease characterised by several phenotypes and different clinical responses.
- 4.7 Current treatment guidelines (Sanders 2016 updated in Narayanaswami 2021) 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 such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus and ciclosporin 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 PLEX/IVIg¹, eculizumab (not registered

¹ IVIg is funded by the National Blood Authority (NBA) as maintenance therapy for moderate to severe myasthenia gravis when other treatments have been ineffective or caused intolerable side effects. The NBA criteria for IVIg requires (a) a patient to have a MGC score ≥ 4 points; and (b) ≥ 2 other treatments to have been ineffective, contra-indicated, unavailable or caused intolerable side effects. The NBA criteria state 'IVIg should be regarded as a stopgap treatment while using short-term drugs such as pyridostigmine and while introducing effective immunotherapy' and requires evidence of response for ongoing therapy after 4 months and then annually thereafter.

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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.
- 4.8 While these standard therapies have shown good efficacy in improving myasthenia gravis-related symptoms, they can carry a considerable burden of long-term adverse effects. Extended use of corticosteroids can result in the development of diabetes, hypertension and osteoporosis. Most non-steroidal immunosuppressive therapies (NS-ISTs) have a delayed onset of action, requiring several months of treatment before their full benefits appear. Abrupt discontinuation of NS-ISTs may result in a clinical relapse, so slow tapering and discontinuation is required. These treatments also have a risk of adverse effects in the liver and bone marrow. Immunosuppressive therapies also leave patients vulnerable to severe infections, and a small but significant long-term risk of developing malignancies and drug-related toxicity (Iorio 2024; Alhaidar 2022).
- 4.9 Zilucoplan is a PEGylated, macrocyclic peptide that binds to the C5 terminal complement protein and inhibits its cleavage into pro-inflammatory components (C5a and C5b). Additionally, because zilucoplan binds to the C5b moiety it may reduce any residual activity specifically associated with this component. It is presumed that the therapeutic effects of zilucoplan 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.
- 4.10 The clinical management algorithm proposed in the resubmission is presented in Figure 1.

Figure 1: Proposed clinical management algorithm for AChR-positive generalised myasthenia gravis



Source: Figure 1.2-2, p27 of the resubmission

Abbreviations: AChR acetylcholine receptor; gMG generalised myasthenia gravis; IVIg intravenous immunoglobulin; PLEX plasma exchange.

Note that thymectomy and IVIg for myasthenic crisis is not shown in the treatment algorithm.

Note that while maintenance/chronic treatment is permitted by the National Blood Authority criteria for IVIg maintenance therapy, the international treatment guidelines only recommend short-term treatment in non-refractory patients.

4.11 The revised clinical management algorithm positioned zilucoplan as an alternative to IVIg or PLEX for treatment refractory generalised myasthenia gravis patients. The resubmission also noted that for some patients, zilucoplan may be used after IVIg (i.e., in patients with an inadequate response to IVIg).

4.12 The ESC considered that the resubmission’s proposal to list zilucoplan in the refractory setting only may not have been adequately supported, and that the appropriate place for the new gMG therapies may also include the bridging setting.

4.13 The evaluation considered that the clinical place in therapy for zilucoplan is currently unclear, particularly as the use of newer agents such as complement inhibitors (zilucoplan, ravulizumab) and FcRn blockers (rozanolixizumab, efgartigimod) have 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 positioned zilucoplan as an alternative to chronic IVIg/PLEX in treatment refractory patients, however, it nominated placebo (standard therapy with anti-cholinesterase inhibitors, corticosteroids and other immunosuppressants such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, ciclosporin) as the main comparator based on previous advice from the PBAC:

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- 5.2 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 zilucoplan in the refractory setting (paragraph 7.9, zilucoplan PBAC PSD, July 2024 PBAC meeting).
- 5.3 Although nominated as a secondary comparator in the July 2024 submission, the resubmission did not nominate chronic IVIg/PLEX as a comparator. This was not adequately justified in the resubmission. 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.
- 5.4 In the financial impact estimates, the resubmission acknowledged that chronic IVIg/PLEX therapies are the therapies most likely to be replaced in clinical practice. However, in the economic model, zilucoplan was assumed to be primarily used as a subsequent therapy after treatment failure with chronic IVIg/PLEX.
- 5.5 The July 2024 submission also nominated ravulizumab (another complement inhibitor) as a near-market comparator, however, the resubmission did not nominate any near market comparators. The ESC considered that the four gMG therapies being considered at the March 2025 meeting (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.
- 5.6 Zilucoplan and rozanolixizumab have the same sponsor but neither submission addressed the potential use of the other medication.

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 sponsor outlined the clinical positioning of its two agents for gMG (zilucoplan and rozanolixizumab). Zilucoplan was proposed for use in the refractory setting given the PBAC's previous advice to target patients with the highest clinical need, and because the trial was not specifically designed to assess efficacy in the bridging setting. On the other hand, the sponsor targeted rozanolixizumab at the bridging setting because it is a symptom-led treatment that was designed as an IVIg replacement. The sponsor stated that a price premium should be applied in any cost-comparison versus IVIg because zilucoplan is intended for patients with a higher clinical need compared with the clinical place of IVIg.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (15), health care professionals (10 individual health care professionals 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.
- 6.3 The comments noted the efficacy associated with zilucoplan and the rapid onset of action. The comments noted the ease of administration of zilucoplan given it is a self-administered daily subcutaneous injection, which would provide flexibility for patients. The input outlined the risk of infection associated with zilucoplan including the risk of meningococcal infection. However, the majority of contributors expressed an enthusiasm to try zilucoplan regardless of potential adverse events due to its reported efficacy. One clinician stated they “believe this drug is being considered for those with refractory or severe disease only. However, its rapid onset of action gives clinicians the opportunity to gain rapid control of this condition in the acute setting, regardless of refractoriness. Rapid control in this condition is important to minimise side effects from other treatments as outlined above, reduce hospital length of stay, minimise utility of an infusion centre, and prevent disease progression.... I believe there should be a mechanism for appropriate patients to access early treatment.”
- 6.4 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.

- 6.5 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. 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 ≥ 2 points, MGC by ≥ 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 trials

- 6.6 The resubmission was based on one head-to-head randomised trial (RAISE) comparing zilucoplan to placebo in generalised myasthenia gravis patients. The resubmission also presented an interim analysis from an open-label extension study of patients previously enrolled in the RAISE trial as supportive data. This evidence was considered by the PBAC at the July 2024 meeting.
- 6.7 Additionally, the July 2024 submission presented three indirect comparisons of zilucoplan versus chronic IVIg (Bril 2024, Wolfe 2002, Zinman 2007). The July 2024 submission did not identify any trials that would allow for an indirect comparison of zilucoplan with chronic PLEX.
- 6.8 Details of the included trials are provided in Table 3.

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Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/Publication title	Publication citation
Zilucoplan studies		
RAISE NCT04115293	UCB (2022). A Phase 3, multicenter, randomized, double blind, placebo-controlled study to confirm the safety, tolerability, and efficacy of zilucoplan in subjects with generalized myasthenia gravis. Howard et al (2023). Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double blind, placebo controlled, phase 3 study.	Internal study report. <i>Lancet: Neurology</i> 22(5): 395-406.
RAISE-XT NCT04225871	UCB (2024). A Phase 3, multicenter, open-label extension study of zilucoplan in subjects with generalized myasthenia gravis. Howard et al. (2024). Long-term safety and efficacy of zilucoplan in patients with generalized myasthenia gravis: interim analysis of the RAISE-XT open-label extension study. Weiss et al (2024b). Improvement of fatigue in generalised myasthenia gravis with zilucoplan.	Internal study report. Therapeutic Advances in Neurological Disorders. 17:1-16. <i>Journal of Neurology</i> . 271(5):2758-2767.
Chronic IVIg studies		
Bril 2024 (NCT02473952)	Bril et al (2024). Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial.	<i>Muscle & Nerve</i> 71(1):43-54.
Wolfe (2002)	Wolfe et al (2002). Myasthenia Gravis-IVIg Study Group. Randomised, controlled trial of intravenous immunoglobulin in myasthenia gravis	<i>Muscle & Nerve</i> 26:549-552.
Zinman (2007)	Zinman et al (2007). IV immunoglobulin in patients with myasthenia gravis: a randomised controlled trial.	<i>Neurology</i> 68:837-841.

Source: Table 2.2-2, p48 of the resubmission; Table 2(a).2-1, p9 of Appendix 4 of the July 2024 submission.

6.9 The key features of the included trials 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
Zilucoplan vs. placebo SC						
RAISE	174	Multicentre, randomised, double-blind, placebo-controlled 12 weeks duration with an ongoing open-label extension	Low	AChR-positive generalised myasthenia gravis with functional impairment (MG-ADL ≥ 6 , QMG ≥ 12 and four or more QMG items scored ≥ 2) 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 time to rescue therapy	Baseline characteristics, treatment response, change in MG-ADL and health state utility values.

Source: Section 2.3, p49-56 of the resubmission

Abbreviations: AChR, anti-acetylcholine receptor; 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; QMG, Quantitative Myasthenia Gravis score.

6.10 Trial participants predominantly reported moderate generalised weakness at baseline including ocular, bulbar, limb and respiratory symptoms (mean baseline MGC score:

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- 20.1-21.6). The average time since diagnosis was 9.2 years and many patients had an extensive history of prior therapy use, including a substantial proportion who had previously used rescue/chronic IVIg (63.8%), rescue/chronic PLEX (33.9%) or rituximab (9.8%). At baseline, 50.6% of patients were considered treatment refractory which was defined as treatment for at least one year with two or more of the following therapies (prednisone, azathioprine, mycophenolate mofetil, ciclosporin, cyclophosphamide, methotrexate, tacrolimus, rituximab, eculizumab, other corticosteroids) OR history of treatment with at least one of the above therapies for 1 year or more and required chronic IVIg/PLEX at least every 3 months for the 12 months. The trial definition of treatment refractory did not require patients to have disease that is unchanged or worse after treatment, with persistent symptoms or side effects that limit functioning.
- 6.11 A comparison of patient characteristics between treatment refractory and non-refractory patients indicated substantial differences between these populations in terms of sex, region, time since diagnosis, history of myasthenic crisis, history of thymectomy and prior use of IVIg, PLEX and rituximab.
- 6.12 At baseline, 4.0% of the overall RAISE trial population were using no therapy, 19.5% were using anticholinesterase treatments only, 11.5% were using immunosuppressive therapies only and 64.9% were using anticholinesterase treatment in combination with immunosuppressive treatment (primarily anticholinesterase with corticosteroids; or anticholinesterase with corticosteroids and azathioprine or mycophenolate mofetil). The PSCR outlined that in the refractory subgroup at baseline: 73% (64/88) of patients were being treated with a corticosteroid; 70% (62/88) were being treated with an NS-IST; and 85% (75/88) were receiving at least one immunosuppressive therapy (corticosteroid and/or NS-IST).
- 6.13 Patients included in the trial were not allowed to have used IVIg or PLEX in the prior 4 weeks before baseline or rituximab in the prior 12 months before baseline. The trial eligibility criteria required patients to be using stable standard therapy doses but did not require patients to be using optimised therapy.
- 6.14 It is unclear whether the results from the overall RAISE trial and refractory subgroup can be generalised to the proposed PBS population given differences in eligibility criteria between the populations (the trial required patients to have MG-ADL ≥ 6 ; QMG ≥ 12 and four or more QMG items scored ≥ 2 while the restriction only requires patients to have a MG-ADL ≥ 6).
- 6.15 The primary outcome in the submission was mean change in MG-ADL scores from baseline to Week 12. The MG-ADL instrument is an 8-item assessment tool capturing patient-reported outcomes of functional disability related to different domains including ocular (2 items), bulbar (3 items), respiratory (1 item), and gross motor or limb impairment (2 items). Each item is scored on a 0-4 scale, with a total score ranging from 0 to 24, where lower scores indicate better functional outcomes. The instrument

has been externally validated and has an established minimal clinically important difference of a 2-point change in total score (Muppidi 2011).

Comparative effectiveness

6.16 The mean change in MG-ADL from baseline to Week 12 with zilucoplan and placebo in the RAISE trial and subgroups by refractory status are summarised in Table 5.

Table 5: Mean change in Myasthenia Gravis Activities of Daily Living (MG-ADL) score [primary outcome] from baseline to Week 12 by treatment refractory status

Treatment arm	Baseline, Mean (SD)	Final, Mean (SD)	LS mean change (95% CI)	Treatment difference (95% CI)
Overall population				
Zilucoplan (N = 86)	10.3 (2.5)	5.6 (4.0)	-4.39 (-5.28, -3.50)	-2.09 (-3.24, -0.95)
Placebo (N = 88)	10.9 (3.4)	8.0 (4.5)	-2.30 (-3.17, -1.43)	
Treatment refractory patients				
Zilucoplan (N = 44)	10.3 (2.6)	5.4 (4.0)	-4.72 (-5.88, -3.57)	-3.11 (-4.69, -1.52)
Placebo (N = 44)	11.0 (3.4)	8.7 (3.8)	-1.62 (-2.77, -0.47)	
Treatment non-refractory patients				
Zilucoplan (N = 42)	10.3 (2.5)	5.7 (4.1)	-3.30 (-5.05, -1.56)	-1.12 (-2.79, 0.54)
Placebo (N = 44)	10.7 (3.5)	7.4 (5.1)	-2.18 (-3.90, -0.45)	

Source: Table 2.5-1, p78; Table 2.6-2, p100 of the resubmission

Abbreviations: CI, confidence interval; LS, least squares; MG-ADL, Myasthenia Gravis Activities of Daily Living; SD, standard deviation

Note: MG-ADL scores range from 0 to 24 with lower scores indicating better functional outcomes. The nominated minimal clinically important difference was a 2-point change in total score.

Note: Bolding indicates statistically significant differences

6.17 Treatment with zilucoplan was associated with a statistically significant improvement in MG-ADL scores compared to placebo over 12 weeks, with the point estimate exceeding the nominated minimal clinically important difference (2-point reduction in MG-ADL score). Statistically significant differences favouring zilucoplan were also observed based on QMG and MGC scores. The resubmission claimed that data from the ongoing extension study suggest that scores continued to improve with zilucoplan treatment beyond the randomised period, reaching a plateau after approximately 20 weeks of treatment (least squares mean change in MG-ADL score from baseline to Week 20 in the zilucoplan/zilucoplan arm was -5.97; 95% CI -6.89, -5.05). Additional follow-up data extending to 120 weeks suggested no loss of effect with ongoing therapy.

6.18 Results by treatment refractory status suggest that the improvement in MG-ADL associated with zilucoplan treatment compared to placebo may be larger in treatment refractory patients compared to treatment non-refractory patients. A similar pattern of results was observed with QMG and MGC scores.

6.19 A *post hoc* test for treatment-effect interaction showed that refractory status was not a treatment effect modifier for the primary outcome of change in MG-ADL from baseline to Week 12 (p=0.737). The PBAC previously noted that this was a *post hoc* analysis and stated that it was unclear whether there was sufficient sample size to detect a significant difference for this interaction term (paragraph 7.13, zilucoplan PBAC PSD, July 2024 PBAC meeting).

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6.20 Table 6 summarises the proportion of patients achieving a 3-point reduction in MG-ADL scores from baseline in each treatment arm, in the overall population and subgroups by treatment refractory status.

Table 6: MG-ADL responders at Week 12 (3-point reduction in MG-ADL score) by treatment refractory status

Subgroup	Zilucoplan n/N (%)	Placebo n/N (%)	Treatment difference
Overall population	62/84 (73.1%)	40/85 (46.1%)	OR (95% CI) 3.184 (1.662, 6.101)
Treatment refractory status			
Treatment refractory patients	33/44 (75.0%)	17/42 (40.5%)	Difference: 34.5%
Treatment non-refractory patients	29/40 (72.5%)	23/43 (53.5%)	Difference: 19.0%

Source: Table 14.2.6.4, pp847-871 of the RAISE trial report

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

Note: Shading indicates a difference of +/- 10% in response between patient subgroups

6.21 Treatment with zilucoplan was associated with a statistically significant increase in the proportion of patients achieving a 3-point reduction in MG-ADL scores compared to placebo at Week 12. Subgroup analyses suggest variations in response rates across subgroups defined by treatment refractory status.

6.22 The PBAC previously considered that the outcomes for the refractory and non-refractory subgroups were difficult to interpret based on the information provided (paragraph 7.13, zilucoplan PBAC PSD, July 2024 PBAC meeting).

6.23 The resubmission did not present any additional analyses to provide further clarity on treatment outcomes in patient subgroups.

6.24 Table 7 summarises results for mean change in Revised Myasthenia Gravis Quality of Life score (MG-QoL15r) from baseline to Week 12 with zilucoplan and placebo in the RAISE trial and subgroups by refractory status.

Table 7: Mean change in Revised Myasthenia Gravis Quality of Life score (MG-QoL15r) from baseline to Week 12 with zilucoplan and placebo

Treatment arm	Baseline, Mean (SD)	Final, Mean (SD)	LS mean change (95% CI)	Treatment difference (95% CI)
Overall population				
Zilucoplan (N = 86)	18.6 (6.6)	12.5 (8.0)	-5.65 (-7.17, -4.12)	-2.49 (-4.45, -0.54)
Placebo (N = 88)	18.9 (6.8)	15.3 (8.1)	-3.16 (-4.65, -1.67)	
Treatment refractory patients				
Zilucoplan (N = 44)	18.3 (6.9)	12.3 (7.9)	-5.63 (-7.53, -3.73)	-3.28 (-5.89, -0.67)
Placebo (N = 44)	18.9 (6.9)	16.4 (7.4)	-2.36 (-4.24, -0.47)	
Treatment non-refractory patients				
Zilucoplan (N = 42)	18.9 (6.2)	12.6 (8.1)	-4.73 (-7.88, -1.58)	-1.73 (-4.66, 1.19)
Placebo (N = 44)	18.9 (6.8)	14.3 (8.8)	-3.00 (-6.11, 0.12)	

Source: Table 2.5-6, p77; Table 2.6-5, p103 of the resubmission.

Abbreviations: CI, confidence interval; LS, least squares; MG-QoL15r, revised Myasthenia Gravis Quality of Life; NR, not reported; SD, standard deviation

Note: MG-QoL15r scores range from 0 to 30 with lower scores indicating better quality of life. There was no nominated minimal clinically important difference for this outcome

Note: Bolding indicates statistically significant differences after accounting for multiplicity of testing

6.25 Treatment with zilucoplan was associated with statistically significant improvements in MG-QoL15r compared to placebo at Week 12. Zilucoplan was also associated with

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- statistically significant improvements in Quality of Life in Neurological Disorders Fatigue score compared to placebo.
- 6.26 Results by treatment refractory status suggest that the improvement in MG-QoL15r associated with zilucoplan treatment compared to placebo may be larger in treatment refractory patients compared to treatment non-refractory patients.
- 6.27 The trial report did not provide any statistical analysis of EQ-5D-5L data. However, EQ-5D-5L data from the RAISE trial were used to inform a *post hoc* analysis of the association between change in MG-ADL score and change in EQ-5D utility scores over time used in the economic model. Therefore, the data should have been available to allow a comparison of the change in EQ-5D-5L scores (visual analogue scale, health state index) between treatment arms over time.
- 6.28 The resubmission did not present a comparison of the incidence of exacerbation events between treatment arms of the RAISE trial.
- 6.29 The July 2024 submission reported that there was no statistically significant difference in use of rescue medication (with IVIg, PLEX or eculizumab) between treatment arms in the RAISE trial although results numerically favoured zilucoplan (cumulative proportion of patients receiving rescue therapy by week 12, zilucoplan 4.7% versus placebo 11.4%: HR 0.42; 95% CI 0.12, 1.20). The PBAC previously noted that this equated to a number needed to treat to avoid one patient requiring rescue therapy of 15 in the total trial population and 11 in the treatment refractory subgroup (paragraph 7.11, zilucoplan PBAC PSD, July 2024 PBAC meeting).
- 6.30 Corticosteroid doses were required to remain stable during the RAISE trial and the first 12 weeks of the extension study (total 24 weeks). After this period, corticosteroid doses were allowed to be modified based on physician discretion.
- 6.31 Based on all available data from the extension study for the zilucoplan/zilucoplan group, 50.8% (33/65) of patients using corticosteroids at baseline were able to reduce or discontinue their corticosteroid dose (mean reduction of -16.28 mg per day; from a mean baseline dose of 23.86 mg per day to 7.58 mg per day). Additionally, 6.5% (6/93) of patients either initiated or increased their corticosteroid dose during the extension study (mean increase of 11.08 mg per day; from a mean baseline dose of 14.67 mg per day to 25.75 mg per day).
- 6.32 It is unclear whether zilucoplan is steroid-sparing as there are no comparative data on steroid use without zilucoplan in the extension study. The ESC previously noted that the natural history of generalised myasthenia gravis is for its severity to wane over time and reducing of corticosteroid doses is standard practice with current treatments. Thus, the ESC previously considered it was unclear whether similar reductions in corticosteroid use would have occurred with standard therapy alone (paragraph 6.30, zilucoplan PBAC PSD, July 2024 PBAC meeting).
- 6.33 During the evaluation, summary details were presented of 5 published network meta-analyses (NMAs) that compared zilucoplan and near market comparators

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efgartigimod, ravulizumab, 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).

- 6.34 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.
- 6.35 None of the indirect treatment comparisons included IVIg or PLEX trials.
- 6.36 The resubmission did not include a clinical comparison versus chronic IVIg; however, the previous submission presented three individual indirect comparisons between zilucoplan and chronic IVIg based on the argument that the three IVIg trials were not sufficiently similar to justify a meta-analysis of results. The indirect comparison versus NCT02473952 (subsequently published as Brill 2024) found no statistically significant differences in functional outcomes (i.e. MG-ADL and QMG scores) between zilucoplan and chronic IVIg. However, the IVIg dosing regimen used in the trial was more intensive than recommended in the Australian product information. The commentary for the previous submission considered that this was the most robust comparison currently available between zilucoplan and chronic IVIg (e.g. key issues with the other two studies assessing IVIg were that: Wolfe et al 2002 was stopped prematurely due to a lack of IVIg availability; and Zinman et al 2007 only assessed the efficacy of a single loading dose of IVIg rather than ongoing chronic therapy). The previous submission considered that it was likely that zilucoplan is at least non-inferior in terms of efficacy and safety compared to chronic IVIg/PLEX, albeit noting that the limited evidence base available for chronic IVIg/PLEX precludes any robust clinical conclusion on the comparative efficacy and safety of zilucoplan versus IVIg.

Comparative harms

- 6.37 An overall summary of the adverse events reported in the RAISE trial is presented in Table 8.

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Table 8: Summary of key adverse events in the RAISE trial after 12 weeks

Patients, n (%) [number of events]	Zilucoplan N = 86	Placebo N = 88
Any adverse event	66 (76.7%) [291 events]	62 (70.5%) [222 events]
Treatment-related adverse event	28 (32.6%) [55 events]	22 (25.0%) [34 events]
Serious adverse event	11 (12.8%) [15 events]	13 (14.8%) [18 events]
Adverse events leading to treatment discontinuation	4 (4.7%) [4 events]	2 (2.3%) [2 events]
Deaths	1 (1.2%)	1 (1.1%)
Adverse events of special interest		
Infections	23 (26.7%)	16 (18.2%)
Malignancies	1 (1.2%)	1 (1.1%)
Hypersensitivity	8 (9.3%)	8 (9.1%)
Injection site reactions	23 (26.7%)	13 (14.8%)
Hepatic events	3 (3.5%)	1 (1.1%)

Source: Table 2.5-11, p91 of the submission; Table 9-2, p193; Table 14.3.14.1, pp1884-1902 of the RAISE trial report

- 6.38 All patients in the RAISE trial received a meningococcal vaccination before commencing study drug treatment and no meningococcal infections were reported during the trial.
- 6.39 The most frequently reported adverse events (> 5% of patients) in either treatment arm were injection site reactions, headache, myasthenia gravis worsening, upper respiratory tract infections, urinary tract infections, diarrhoea, nausea and vomiting, rash, skin injuries, and digestive enzyme investigations.
- 6.40 Treatment with zilucoplan was associated with a higher rate of any adverse event and treatment-related adverse events compared to placebo. This difference was primarily due to an increase in mild-to-moderate injection site reactions. In regard to adverse events of special interest, zilucoplan was associated with an increase incidence of non-serious infections and injection-site reactions.
- 6.41 Adverse events by treatment refractory status suggest that patients in the treatment refractory subgroup were more likely to experience an adverse event compared to patients in the non-refractory subgroup. In the refractory subgroup, numerically greater proportions of patients on zilucoplan compared with placebo reported any adverse event (88.6% versus 77.3%) and treatment-related adverse events (36.4% versus 29.5%). Similarly, in the non-refractory subgroup, numerically greater proportions of patients on zilucoplan compared with placebo reported any adverse event (64.3% versus 63.6%) and treatment-related adverse events (28.6% versus 20.5%).
- 6.42 The interim analysis of the RAISE open-label extension study (mean exposure 2.1 years) was suggestive of declining adverse event rates over time and did not identify any additional safety concerns with zilucoplan treatment.
- 6.43 The resubmission provided a Periodic Safety Update Report (25 September 2023 to 24 March 2024), which included the use of zilucoplan for generalised myasthenia gravis in adult patients who are AChR-positive. Important identified risks include serious hypersensitivity reactions, and pancreatitis and severe pancreatic events. Important potential risks include *Neisseria* infections (particularly meningococcal infections), and

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serious infections. Missing information includes use during pregnancy and lactation, and long-term safety.

6.44 A more detailed assessment of the safety of complement inhibitors in general would have been informative given the limited safety data available for zilucoplan.

Benefits/harms

6.45 A summary of the comparative benefits and harms for zilucoplan versus placebo is presented in Table 9.

Table 9: Summary of comparative benefits and harms for zilucoplan and placebo

Outcome	Zilucoplan	Placebo	Treatment difference
Proportion of patients with ≥2-point reduction in MG-ADL scores from baseline to Week 12	74.4%	57.9%	16.5%
Proportion of patients with ≥3-point reduction in MG-ADL scores from baseline to Week 12	73.1%	46.1%	27.0%
Proportion of patients with ≥3-point reduction in QMG scores from baseline to Week 12	72.5%	48.5%	24.0%
Proportion of patients with ≥5-point reduction in QMG scores from baseline to Week 12	58.0%	33.0%	25.0%
Proportion of patients with injection site reactions	26.7%	14.8%	11.9%
Proportion of patients with infections	26.7%	18.2%	8.5%

Source: Table 2.5-2, p79; Table 2.5-4, p81; Table 2.5-11, p97 of the resubmission; Table 9-2, p193; Table 14.2.6.11, p880; Table 14.2.7.11, p927; Table 14.3.14.1, pp1884-1902 of the RAISE trial report

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis score

Note: All changes in functional measures met or exceed the nominated minimal clinically important difference for each outcome (MCID for MG-ADL ≥2-point reduction; MCID for QMG ≥3-point reduction).

6.46 On the basis of direct evidence presented in the submission, for every 100 patients treated with zilucoplan in comparison with placebo for 12 weeks:

- Approximately 17 to 27 additional patients would experience a clinically important improvement in functional outcomes (i.e. greater than 2-point reduction in MG-ADL score or greater than 3-point reduction in QMG score).
- Approximately 9 additional patients would experience an infection.

Clinical claim

6.47 The resubmission described zilucoplan in combination with standard therapy as superior in terms of efficacy and non-inferior in terms of safety compared to placebo in combination with standard therapy.

6.48 The clinical data presented in the resubmission were largely unchanged from data presented in the July 2024 submission. The PBAC previously considered the clinical claim that zilucoplan has superior efficacy versus placebo was reasonable, although the benefit is likely modest, outcomes for the refractory and non-refractory subgroups were difficult to interpret, and the high placebo response rates presented in the responder analyses indicated that standard therapies are effective for many patients (paragraph 7.10, 7.13, zilucoplan PBAC PSD, July 2024 PBAC meeting). The ESC considered the PBAC’s previous conclusions from July 2024 remained unchanged.

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- 6.49 In July 2024, the PBAC considered that, while zilucoplan appeared well-tolerated, the claim of non-inferior comparative safety versus placebo was not adequately supported given the limited safety data and the requirement for patients to receive meningococcal vaccinations (paragraph 7.14, zilucoplan PBAC PSD, July 2024 PBAC meeting). This was unchanged in the resubmission.
- 6.50 The ESC noted that results by refractory status suggest that the improvement in MG-ADL associated with zilucoplan compared to placebo may be larger in refractory patients compared to non-refractory patients, but considered that the subgroup analyses remained difficult to interpret (e.g. a *post hoc* test for treatment-effect interaction showed that refractory status was not a treatment effect modifier for this outcome, although patient numbers were small).
- 6.51 The evaluation considered that it was uncertain whether the results of the overall RAISE trial and treatment refractory subgroup can be generalised to the proposed PBS restriction, given differences in eligibility criteria between the populations (the trial required patients to have MG-ADL ≥ 6 ; QMG ≥ 12 and four or more QMG items scored ≥ 2 while the restriction only requires patients to have a MG-ADL ≥ 6).
- 6.52 The July 2024 submission claimed the limited evidence base available for chronic IVIg/PLEX precludes any robust clinical conclusion on the comparative efficacy and safety of treatments. However, the submission considered that it is likely that zilucoplan is at least non-inferior in terms of efficacy and safety compared to chronic IVIg/PLEX.
- 6.53 The ESC and the PBAC acknowledged the limitations of the available evidence for chronic IVIg but considered there was insufficient evidence to suggest superior efficacy or safety of any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab) versus chronic IVIg or PLEX.
- 6.54 Further, the ESC and the PBAC considered there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies. The ESC considered that the published network meta-analyses had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of Fc Receptor (FcRn) blockers waning over time during the off-treatment period.
- 6.55 Overall, the PBAC considered that zilucoplan has non-inferior comparative effectiveness and safety versus chronic IVIg and also against ravulizumab, efgartigimod and rozanolixizumab.

Economic analysis

- 6.56 The resubmission presented a stepped economic evaluation of zilucoplan in combination with standard therapy compared to placebo in combination with standard therapy for the treatment of AChR-positive generalised myasthenia gravis in the treatment refractory setting. The economic evaluation was based on a direct

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randomised trial (RAISE) and extension study with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

- 6.57 In contrast to the clinical management algorithm and financial implications (which positioned zilucoplan as an alternative to IVIg/PLEX), in the economic model, zilucoplan was assumed to be used primarily as a subsequent therapy after treatment failure with chronic IVIg/PLEX. The PSCR advised that this was to address PBAC’s previous concerns (from July 2024) that the model should more explicitly capture the costs and outcomes of subsequent treatments (e.g. IVIg, PLEX, SoC). The evaluation considered that it may have been more appropriate to compare zilucoplan with rituximab and cyclophosphamide rather than standard therapy alone.
- 6.58 However, the ESC reiterated the PBAC’s previous advice (from July 2024) that chronic IVIg/PLEX was a relevant comparator for providing a frame of reference for interpreting the cost per patient of zilucoplan in the refractory setting. A comparison of annual costs per patient per year for zilucoplan and IVIg/PLEX is presented in the Drug cost/patient/year section.
- 6.59 The main changes to the economic evaluation in the current resubmission compared with the July 2024 submission include:
- The economic model positioned zilucoplan primarily as a subsequent therapy after treatment failure with chronic IVIg/PLEX (compared to second line and treatment refractory patients in the July 2024 submission).
 - The mix of subsequent therapy following discontinuation of zilucoplan and placebo was revised from 100% chronic IVIg/PLEX to 20% chronic IVIg/PLEX and 80% escalated standard therapy (including rituximab). The model structure was revised to allow response to chronic IVIg/PLEX (70%; previously 0%); however, response to escalated standard therapy was not possible.
 - Treatment discontinuation due to loss of response was introduced in the placebo arm (16% per 2-week cycle).
 - Use of high-dose corticosteroids was revised for responders (0% in the previous submission versus 6.9% in the resubmission) and non-responders (63.8% versus 100%).
 - The proportion of zilucoplan and placebo non-responders who receive IVIg/PLEX was revised (from 100% to 20%), and a treatment effect associated with IVIg/PLEX therapy included (70%; previously 0%).
 - An 1% increase in the proposed AEMP for zilucoplan.

6.60 Table 10 summarises the key components of the economic evaluation.

Table 10: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-effectiveness analysis/cost-utility analysis
Outcomes	Patients with response; life years; quality adjusted life years

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Component	Description
Time horizon	10 years versus 12 weeks in the key trial.
Treatments	Zilucoplan and placebo in combination with standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil and azathioprine). Treatment non-responders/discontinuers were assumed to receive subsequent treatment with escalated standard therapy (including rituximab) or chronic IVIg/PLEX.
Methods used to generate results	Markov cohort model
Health states	Non-responder (on and off initial treatment; on and off subsequent treatment), responder (on initial treatment; on subsequent treatment), acute exacerbation (on and off initial treatment; on and off subsequent treatment), myasthenic crisis and dead.
Cycle length	2-weeks (no half-cycle correction)
Patient characteristics	Age, sex, mean weight, distribution across weight categories, BMI, baseline MG-ADL score, and baseline EQ-5D utility value were based on data from the combined treatment arms of the RAISE trial.
Circumstances of use	<p>The resubmission assumed that the majority of patients entering the model had failed prior therapy with chronic IVIg/PLEX.</p> <p>All patients were assumed to be fully adherent to standard therapy (consisting of anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil and azathioprine).</p> <p>Patients were assumed to be fully adherent with initial treatment (zilucoplan or placebo) and could discontinue due to a lack of response (at Week 16), an exacerbation event, a myasthenic crisis event or death. Placebo-treated patients could also discontinue due to loss of response. Zilucoplan-treated patients could also discontinue due to an adverse event.</p> <p>Patients who discontinue initial treatment could receive escalated standard therapy (including high-dose corticosteroids and rituximab); or IVIg/PLEX with standard therapy.</p> <p>Patients treated with IVIg/PLEX could discontinue due to a lack of response (at Week 24), an exacerbation event, a myasthenic crisis event, death, or non-persistence. Patients who discontinue IVIg/PLEX receive escalated standard therapy.</p> <p>It is assumed that escalated standard therapy would not improve symptom control and would be maintained until death.</p>
Transition probabilities	<p>Treatment response rates for zilucoplan and placebo were based on the RAISE trial and extension study. Response in patients treated with subsequent IVIg/PLEX was based on the Bril 2024 trial.</p> <p>Changes in MG-ADL scores in treatment responders up to Week 12 were separately estimated for each treatment arm based on responders in the RAISE trial; with subsequent changes in MG-ADL based on data from the RAISE extension study, assumed the same for each treatment arm. Patients responding to subsequent IVIg/PLEX were assumed to have the same changes in MG-ADL scores as zilucoplan responders. Treatment non-responders were assumed to remain at baseline MG-ADL scores.</p> <p>The incidence of exacerbation and myasthenic crisis were based on the published literature (Parthan 2023; Gadjos 2005).</p> <p>All non-responders to initial treatment were assumed to discontinue treatment at 16 weeks. All patients were assumed to remain on treatment following an exacerbation event in the first 16 weeks, with 80% of patients remaining on treatment following an exacerbation after Week 16. All patients discontinue treatment following myasthenic crisis. Further risks of discontinuation were applied to zilucoplan patients (based on discontinuations due to adverse events in the RAISE extension study); placebo patients (based on assumed loss of response); and patients receiving subsequent IVIg/PLEX (based on treatment persistence estimates from a US claims database; Qi 2022).</p> <p>Transition probabilities for myasthenic crisis-related death were based on published estimates (Alsheklee 2009). Transition probabilities for general population mortality were based on Australian life tables.</p>
Utility values	Health state utility values were estimated using a regression equation derived from a <i>post hoc</i> analysis of the RAISE trial data (Grimson 2023; poster presentation). Health state utility values were updated in

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Component	Description
	<p>each cycle based on modelled changes in MG-ADL scores for treatment responders and non-responders.</p> <p>Exacerbation and myasthenic crisis disutility values were based on estimates used in the eculizumab 2020 CADTH submission for treatment refractory generalised myasthenia gravis.</p> <p>The disutility associated with high-dose corticosteroids was estimated based on the 2000-2003 United States Medical Expenditure Survey Panel for a subset of adult patients who have conditions for which systemic corticosteroids are commonly prescribed (Sullivan 2017).</p>
Costs	<p>Treatment costs for zilucoplan were estimated based on the proposed effective price and assuming that patients will require a specialist visit for drug administration training and a proportion will require meningococcal vaccination. Training costs were estimated based on the MBS item for a subsequent specialist visit, while the cost of vaccination was estimated based on the Charles Sturt Health Services Price list.</p> <p>The distribution of standard care therapies was estimated based on concomitant use for the combined treatment arms of the RAISE trial. Escalated standard care was based on the distribution of standard care therapies, with adjustments to redistribute patients from tacrolimus to azathioprine; and to incorporate the assumption that all patients receive high-dose corticosteroids. It was also assumed that all patients would receive treatment with rituximab. Treatment costs were estimated based on current PBS items and dosing information from various published sources.</p> <p>The proportion of non-responders proceeding to IVIg/PLEX (20%) was assumed, based on the majority of treatment refractory patients in the RAISE trial having previously received IVIg or PLEX. The distribution of chronic IVIg and chronic PLEX use was based on a published estimate (Li 2021). The costs associated with IVIg/PLEX were estimated assuming patients receive 60% of the maximum subsidised dose for IVIg and would use a high intensity PLEX regimen. The cost of blood products was estimated based on the National Product Price List from the National Blood Authority. The cost of administration was estimated based on MBS items.</p> <p>The costs associated with exacerbations and myasthenic crises were calculated assuming all patients are hospitalised. The cost of hospitalisation was based on published AR-DRG cost weights (NHCCDC 2021-2022).</p> <p>Disease management costs were based on expert opinion of resource use (nurse, GP and specialist visits as well as electrophysiology, physiotherapy and blood tests) for treatment responders and non-responders; with unit costs based on MBS fees.</p> <p>Terminal care costs were based on the average cost per separation for sub-acute episodes relating to palliative care according to the AN-SNAP classification system (NHCCDC 2021-2022).</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1-2, pp129-130 of the resubmission.

Abbreviations: AN-SNAP, Australian National Subacute and Non-Acute Patient; AR-DRG, Australian Refined Diagnosis Related Groups; GP, general practitioner; IVIg, intravenous immunoglobulin; MBS, Medicare Benefits Schedule; MG-ADL, Myasthenia Gravis Activities of Daily Living; NHCCDC; National Hospital Cost Data Collection; PBS, Pharmaceutical Benefits Scheme; PLEX, plasma exchange.

6.61 The resubmission assumed that the majority of patients entering the model had failed prior therapy with chronic IVIg/PLEX based on 89.8% of treatment refractory patients in the RAISE trial having received prior IVIg or PLEX and being uncontrolled at baseline (MG-ADL ≥ 6). The evaluation considered that this assumption was not adequately supported. Estimates of prior use of IVIg/PLEX do not differentiate between chronic and acute therapy. Further, given the fluctuating nature of myasthenia gravis, prior history of chronic therapy does not indicate patients are refractory to therapy.

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- 6.62 All patients begin the model in the non-responder (on-treatment) health state in the treatment refractory setting.
- 6.63 During the first 16 weeks of the model, patients may remain in their current state, achieve response, experience an exacerbation or myasthenic crisis event, discontinue treatment (due to adverse events for zilucoplan; due to loss of response for placebo), or die in each 2-week cycle. Patients who experience an exacerbation event continue therapy and have an increased risk of a myasthenic crisis event in the next cycle. Patients who experience a myasthenic crisis event discontinue therapy and have an increased risk of a crisis-related death in the next cycle.
- 6.64 After 16 weeks of treatment, all non-responders are assumed to discontinue treatment with zilucoplan or placebo. During each cycle of the model, patients may remain in their current state, experience an exacerbation or myasthenic crisis event, discontinue treatment (due to adverse events for zilucoplan; due to loss of response for placebo), or die. A proportion of treatment responders who experience an exacerbation event discontinue therapy, and all patients with an exacerbation have an increased risk of a myasthenic crisis event in the next cycle. Treatment responders who experience a myasthenic crisis event discontinue therapy, and all patients with a crisis event have an increased risk of a crisis-related death in the next cycle.
- 6.65 In each cycle, new treatment non-responders/discontinuers are allocated to subsequent treatment with either chronic IVIg/PLEX with standard therapy or escalated standard therapy (including rituximab).
- 6.66 Patients allocated to chronic IVIg/PLEX enter the IVIg/PLEX module in the non-responder (on-treatment) health state, and may experience response, an exacerbation or myasthenic crisis event, treatment discontinuation, or death (due to myasthenic crisis or general population mortality) in each 2-week cycle. All IVIg/PLEX non-responders at 24 weeks are assumed to discontinue IVIg/PLEX and receive escalated standard therapy.
- 6.67 Patients allocated to escalated standard therapy (including rituximab) may experience an exacerbation or myasthenic crisis event, or death (due to myasthenic crisis or general population mortality) in each 2-week cycle. Patients accrue the costs of escalated standard therapy but cannot achieve response.
- 6.68 The model also assumed that patients would not re-initiate zilucoplan therapy after discontinuation.
- 6.69 During the evaluation, a number of errors were identified in the model affecting exacerbation rates in responders; the in-hospital mortality rate associated with myasthenic crisis; rituximab costs in escalated standard therapy; maintenance PLEX costs; drug, disease management and exacerbation costs beyond 16 weeks for patients on escalated standard therapy; and QALYs accrued in the exacerbation and myasthenic crisis health states. These errors were not corrected during the evaluation (refer to paragraph 6.75).

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6.70 Key drivers of the economic model are summarised in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Loss of response in placebo responders	In the economic model, discontinuing placebo treatment resulted in a change in therapy from standard therapy to chronic IVIg/PLEX or escalated standard therapy (including rituximab). The economic model was highly sensitive to the introduction of an assumed treatment discontinuation due to loss of response in the placebo arm (16% per 2-week cycle) that was inconsistent with the clinical evidence, which suggested similar discontinuation risks between treatment arms (4.7% in the zilucoplan arm; 4.5% in the placebo arm over 12 weeks). Alternative assumptions removing treatment discontinuation or assuming the same discontinuation as the zilucoplan arm resulted in an ICER exceeding \$█ ¹ per QALY gained.	High, favours zilucoplan
Use of high-dose corticosteroids in responders and non-responders	Use of high-dose corticosteroids in treatment responders was revised in the economic model (from 0% to 6.9%, based on baseline use in the RAISE trial) to address feedback that a substantial proportion of responders would not be able to discontinue high-dose corticosteroids (Table 14, zilucoplan PBAC PSD, July 2024 PBAC meeting). However, use of high-dose corticosteroids in non-responders was also increased (from 63.8% to 100%), which was not justified in the resubmission. This resulted in the difference in use of high dose corticosteroids between treatment responders and non-responders increasing from 63.8% in the July 2024 submission to 93.1% in the current submission; and a greater reduction in the use of high-dose corticosteroids for zilucoplan versus placebo, due to the higher proportion of responders. The ESC previously considered that it was unclear whether zilucoplan is steroid-sparing as there are no comparative data on steroid use without zilucoplan (given the randomised controlled phase of RAISE required corticosteroid doses to be stable, and there are no comparative data for the open label extension phase) (paragraph 6.30, zilucoplan PBAC PSD, July 2024 PBAC meeting).	Moderate, favours zilucoplan

Source: Constructed during the evaluation.

Abbreviations: MG-ADL, Myasthenia Gravis Activities of Daily Living; PBS, Pharmaceutical Benefits Scheme; QMG, Quantitative Myasthenia Gravis score; PSD = Public Summary Document.

The redacted values correspond to the following ranges:

¹ \$955,000 to < \$1,055,000

6.71 The resubmission claimed that the modelled population aligned with both the key clinical data and the proposed PBS restriction. The evaluation considered this was not reasonable. The assumption that the patient characteristics of the whole trial population were representative of the refractory population was not consistent with the clinical data. Further, the resubmission did not adequately address the impact of differences in the trial compared to the requested PBS population in baseline functional impairment (the trial required patients to have MG-ADL ≥ 6 ; QMG ≥ 12 and 4 or more QMG items scored ≥ 2 while the proposed restriction requires patients to have MG-ADL ≥ 6 only) and medication use (the trial required no specific therapies while the proposed restriction requires at least one corticosteroid or immunosuppressant therapy). Due to limitations of the model structure and data inputs, it was not possible to assess the impact of different levels of baseline functional impairment and concomitant medication use during the evaluation.

6.72 The economic model was highly sensitive to the introduction of an assumed treatment discontinuation due to loss of response in the placebo arm (16% per 2-week cycle) that was inconsistent with the clinical evidence, which suggested similar

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discontinuation risks between treatment arms (4.7% in the zilucoplan arm; 4.5% in the placebo arm over 12 weeks). The PSCR stated that these were discontinuation rates at 12 weeks only, and ‘most patients in the placebo arm discontinued due to withdrawal by patient (2.3%) or physician decision (1.1%). The discontinuation rate of 4.5% in the placebo arm therefore predominantly reflects the early stages of treatment and therefore does not capture the long-term discontinuation risk resulting from lack of efficacy. Considering that these patients receive placebo plus standard of care, it is unlikely that any response is maintained long-term and increasing the discontinuation rate to 16% was reasonable.’ However, the ESC noted that longer-term data were not available to inform the placebo arm, and that alternative assumptions removing treatment discontinuation or assuming the same discontinuation as the zilucoplan arm resulted in an ICER exceeding \$955,000 to < \$1,055,000 per QALY gained.

- 6.73 Use of high-dose corticosteroids in treatment responders was revised in the economic model (from 0% to 6.9%, based on baseline use in the RAISE trial) to address feedback that a proportion of responders would not be able to discontinue high-dose corticosteroids. However, use of high-dose corticosteroids in non-responders was also increased (from 63.8% to 100%), which was not adequately justified in the resubmission. The ESC (June 2024) had previously considered that it was unclear whether zilucoplan is steroid-sparing as there are no comparative data on steroid use without zilucoplan. The PSCR outlined that ‘in contrast to the July 2024 submission, the population for whom listing of zilucoplan is sought are those with refractory gMG’ who have limited treatment options and, as such non-responders in this setting may have a higher requirement for treatment with high-dose corticosteroids. However, the ESC considered the rates used in the resubmission remained inadequately justified, and overall considered there was a lack of long-term data available to reliably inform the model.
- 6.74 The results of the stepped economic evaluation are summarised in Table 12.

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Table 12: Results of the stepped economic evaluation

Step and component	Zilucoplan	Placebo	Increment
Step 1: Trial and extension study-based response rate (≥3-point improvement in MG-ADL) at Week 12 for placebo and Week 16 for zilucoplan; drug costs only (including costs of zilucoplan administration training and meningococcal vaccination)			
Costs	\$ ^a	\$443	\$
Patients with response	85%	47% ^b	38%
Incremental cost per additional patient with response			\$ ^{1a}
Step 2a: Modelled outcomes (life years) to Week 16 including response, exacerbation, myasthenic crisis and death events; drug costs only^c			
Costs	\$	\$457	\$
Life years	0.345	0.345	0
Incremental cost per life year gained			Zilucoplan dominated
Step 2a: Modelled outcomes (QALYs) to Week 16 including response, exacerbation, myasthenic crisis and death events; drug costs only^b			
Costs	\$	\$457	\$
QALYs	0.2157	0.2034	0.0123
Incremental cost per QALY gained			\$ ²
Step 3: Modelled outcomes (QALYs) to 10 years, including response, exacerbation, myasthenic crisis and death events, discounting, general population mortality, treatment discontinuation and subsequent treatment with IVIg/PLEX; drug costs only^d			
Costs	\$	\$39,130	\$
QALYs	4.7256	4.1171	0.6085
Incremental cost per QALY gained			\$ ³
Step 4: Modelled outcomes (QALYs) to 10 years as for Step 3; drug costs, drug administration costs, meningococcal vaccination costs, disease management state costs and clinical event costs included.			
Costs	\$	\$140,215	\$
Life years	7.7886	7.7869	0.0017
QALYs	4.7256	4.1171	0.6085
Incremental cost per life year gained			\$ ²
Incremental cost per QALY gained			\$ ⁴

Source: Tables 3.8-1 and 3.8-2, pp193-195 of the resubmission.

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; PLEX, plasma exchange; QALY, quality adjusted life year

Note: Estimates have not been corrected for model errors identified during the evaluation (see paragraph 6.75 above).

^a The estimate in the submission was based on the costs of zilucoplan treatment and zilucoplan administration training. This was corrected during the evaluation to include the costs of standard care and exclude the cost of administration training (for consistency with subsequent steps in the model; zilucoplan administration training costs and meningococcal vaccination costs are not included until Step 4).

^b The estimate (based on the proportion of responders < 500 / < 500 patients) differs from the estimate in Table 6 and Table 9 (46.1%), which was based on the mixed model for repeated measures (MMRM) imputed value.

^c Excludes general population mortality and treatment discontinuation, and zilucoplan administration training and vaccination costs.

^d Includes the cost of IVIg/PLEX but excludes their administration costs; excludes zilucoplan administration training and vaccination costs.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² > \$1,055,000

³ \$455,000 to < \$555,000

⁴ \$355,000 to < \$455,000

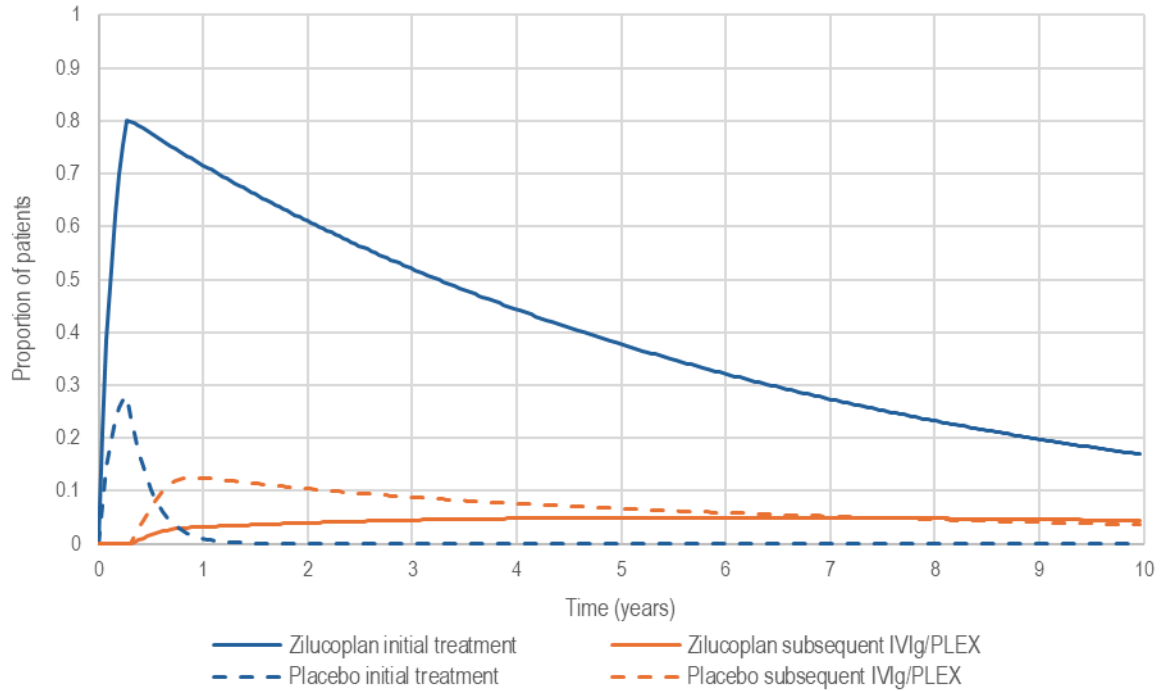
6.75 Based on the economic model, treatment with zilucoplan versus placebo in patients with treatment refractory generalised myasthenia gravis was associated with an incremental cost per QALY gained of \$355,000 to < \$455,000. The PSCR stated ‘after correcting the matters highlighted in the commentary as well as revising the cost of IVIg to \$ [redacted] per gram and adjusting the dose to 40% while keeping all other settings unchanged, the revised ICER is \$355,000 to < \$455,000 per QALY gained’. However,

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the PSCR did not provide details of the changes made to the model, and the revised ICER could not be replicated.

- 6.76 The resubmission base case ICER of \$355,000 to < \$455,000 per QALY gained represented a 1% increase compared to the July 2024 submission (incremental cost per QALY gained of \$255,000 to < \$355,000). The PBAC previously considered the incremental cost-effectiveness ratio presented in the July 2024 submission was very high and likely to have been underestimated, and the proposed price was also very high.
- 6.77 The revised economic model generates larger incremental costs (primarily due to smaller cost offsets for chronic IVIg/PLEX); and smaller incremental QALYs (primarily due to the smaller disutility associated with high-dose corticosteroids; -0.180 versus -0.047) than the July 2024 submission. Despite the higher cost per vial of zilucoplan, the cost of zilucoplan treatment in the current economic model was lower than in the July 2024 model, due to the shorter average duration of treatment resulting from greater proportions of patients discontinuing treatment due to clinical events (the higher rates of clinical events offset the revised assumptions regarding treatment discontinuations).
- 6.78 During the evaluation, it was noted that 97.3% of incremental QALYs and ██████% of incremental costs in the model are accrued in the extrapolated period beyond 16 weeks.
- 6.79 The ESC noted that the modelled benefits were driven by improvements in quality of life, with the economic model estimating 0.6085 incremental QALYs and 0.0017 incremental life years gained. Figure 2 presents a model trace of the proportion of responders over time.

Figure 2: Model trace of responders over time: initial and subsequent treatment



Source: Constructed during the evaluation using the 'Zilbrysq (zilucoplan) - gMG – CEA' Excel spreadsheet provided with the resubmission

6.80 Both treatment arms achieved a peak response at 16 weeks, consistent with the modelled response assessment point, however, the modelled peak response was lower than the source trial/extension study treatment response estimate for the zilucoplan arm (79.96% versus 84.90%) and placebo arm (27.90% versus 46.10%), with a greater difference observed in the placebo arm, predominantly due to differential discontinuation rates (0.19% in the zilucoplan arm versus 16% in the placebo arm per 2-week cycle in the placebo arm). The trace shows a gradual loss of response over time in the zilucoplan arm, but a rapid loss of response in the placebo arm due to the assumed high loss of response per cycle for the placebo arm.

6.81 For patients treated with zilucoplan versus placebo and followed up for 10 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- A reduction in hospitalised exacerbation events (73 fewer events per 100 patients) and myasthenic crisis events (23 fewer events per 100 patients).
- An increase in the time spent in treatment response of 3.11 years, with a decrease in the time spent in non-response of 3.07 years.
- Additional treatment costs of \$ \downarrow , with reduced costs associated with exacerbation and myasthenic crisis events (-\$36,867) and disease management costs (-\$9,916).

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

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Table 13: Results of sensitivity analyses

Analysis	Incremental cost (\$)	Incremental QALYs	ICER	Change from base case ICER
Base case		0.6085	\$1	-
Discount rate (base case: 5% for benefits and costs)				
3.5% discount rate		0.6434	1	- %
0% discount rate		0.7396	1	- %
Time horizon (base case: 10 years)				
20 years		0.6839	1	- %
5 years		0.4164	2	+ %
Patient characteristics (base case: derived from the RAISE whole trial population)				
Based on the RAISE treatment refractory subgroup	\$	0.6095	1	- %
Initial treatment response rates (response rates based on a 3-point reduction in MG-ADL; zilucoplan response rates based on Week 16 data from the extension study and placebo response rate based on Week 12 data from the RAISE trial)				
Both treatment arms based on Week 12 RCT data; with response assessment at Week 12		0.5115	1	- %
Use of subsequent IVIg/PLEX (base case: 20% of non-responders use subsequent IVIg/PLEX)				
0% of non-responders use IVIg/PLEX		0.6528	1	- %
100% of non-responders use IVIg/PLEX		0.5898	2	+ %
Treatment discontinuations (base case: zilucoplan discontinuation due to adverse events 0.19% per cycle; placebo discontinuation due to loss of response 16% per cycle; IVIg/PLEX discontinuation for any cause 2.01% per cycle)				
Placebo discontinuation 5% per cycle		0.5690	2	+ %
Placebo discontinuation same as zilucoplan (0.19%)		0.2549	3	+ %
No treatment discontinuation (0% for placebo and zilucoplan)		0.3050	3	+ %
Discontinuation for zilucoplan and placebo based on RAISE trial (4.6% over 12 weeks; 0.78% per 2-week cycle)		0.1616	3	+ %
Exacerbation/myasthenic crisis events (base case: event rates based on Parthan 2024. Exacerbation events 0.148 per patient-year in zilucoplan/placebo responders, 0.489 in zilucoplan/placebo non-responders, 0.566 in IVIg/PLEX patients; myasthenic crisis events 0.039 per patient-year in zilucoplan/placebo responders, 0.086 in zilucoplan/placebo non-responders, 0.086 in IVIg/PLEX patients)				
Rate of exacerbation events per patient-year in initial treatment responders (0.470) and non-responders (1.024) and IVIg/PLEX patients (1.500) based on Jacob 2020 (proxied by eculizumab use)		0.5823	1	- %
Rate of exacerbation events per patient-year in initial treatment responders (0.028) and non-responders (0.085) based on Qi 2022 (proxied by efgartigimod use); IVIg/PLEX patients assumed equal to initial treatment non-responders (0.085).		0.7614	2	+ %
Exacerbation and myasthenic crisis events removed from model		0.9272	2	+ %
Risk of death from myasthenic crisis (corrected from 0.176% to 4.47%)		0.6302	1	- %
High-dose corticosteroid use in non-responders (base case: 100%)				
High-dose corticosteroid use in non-responders 63.2% based on proportion of patients using corticosteroids at baseline in RAISE; assuming all receiving high-dose corticosteroids.		0.5575	2	+ %
Utility values (base case: health state utility values based on a post hoc analysis of the RAISE trial and MG-ADL data from trial and extension; exacerbation, myasthenic crisis and high-dose corticosteroid disutility values from the published literature)				

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Analysis	Incremental cost (\$)	Incremental QALYs	ICER	Change from base case ICER
Base case		0.6085	\$ ¹	-
Health state utility values based on equation derived in responder population ^a ; using baseline EQ-5D and BMI from the RAISE treatment refractory subgroup		0.6547	¹	-█%
Use US value set for high-dose corticosteroid disutility (-0.032)		0.5674	²	+█%
Remove high-dose corticosteroid disutility		0.4799	⁴	+█%
Costs (base case: resource use and unit costs based on various sources)				
Proposed zilucoplan price in July 2024 submission (\$█ compared with \$█ per mg in the current submission)		0.6085	¹	-█%
Chronic IVIg costs based on Australian utilisation data (approximately 40% of July 2024 estimates)		0.6085	²	+█%
IVIg costs \$█ per gram based on the total cost divided by total mg dispensed of IVIg in NBA Annual Report 2023-2024		0.6085	¹	-█%
Correction to include treatment, disease management and exacerbation costs beyond Week 16 for non-responders who do not proceed to IVIg/PLEX		0.6085	²	+█%
Rituximab costs in escalated standard therapy (corrected from \$5.19 to \$67.75 per 2-week cycle)		0.6085	¹	-█%

Source: Table 3.9-1, p198 of the resubmission and 'Zilbrysq (zilucoplan) - gMG – CEA' Excel spreadsheet

Abbreviations: ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; NBA, National Blood Authority; PLEX, plasma exchange; QALY, quality adjusted life year

Note: Estimates have not been corrected for model errors identified during the evaluation (see paragraph 6.75 above).

The redacted values correspond to the following ranges:

¹ \$355,000 to < \$455,000

² \$455,000 to < \$555,000

³ > \$1,055,000

⁴ \$555,000 to < \$655,000

- 6.83 The results of the sensitivity analyses indicate that the model is most sensitive to the assumed treatment discontinuation for the placebo arm, the proposed price of zilucoplan, high-dose corticosteroid use in treatment non-responders and the associated disutility, exacerbation event rates and time horizon.
- 6.84 The evaluation and the ESC considered that it was unclear whether the results of the economic model and sensitivity analyses are robust given the multiple errors identified during the evaluation (as outlined in paragraph 6.69 above).
- 6.85 However, due to the limitations of the model structure and data inputs it was not possible to assess the impact of different modelled patient populations (with different functional impairment criteria and concomitant therapies) or different response definitions (MGC ≥3-point reduction from baseline, QMG ≥5 point reduction from baseline; the proportion of patients achieving minimal manifestations of disease).
- 6.86 Overall, 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:
- impacts on the treatment algorithm were unclear, noting the economic model positioned zilucoplan primarily as a subsequent therapy after treatment failure

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with chronic IVIg/PLEX, in contrast to the clinical management algorithm and financial implications which positioned zilucoplan primarily as an alternative to IVIg/PLEX.

- the economic model was highly sensitive to the introduction of an assumed treatment discontinuation due to loss of response in the placebo arm (16% per 2-week cycle) that was inconsistent with the clinical evidence, which suggested similar discontinuation risks between treatment arms (4.7% in the zilucoplan arm; 4.5% in the placebo arm over 12 weeks). The ESC noted that longer-term data were not available to inform the placebo arm. Alternative assumptions removing treatment discontinuation or assuming the same discontinuation as the zilucoplan arm resulted in an ICER exceeding \$955,000 to < \$1,055,000 per QALY gained.
- use of high-dose corticosteroids in treatment responders was revised in the economic model (from 0% to 6.9%, based on baseline use in the RAISE trial) to address feedback that a proportion of responders would not be able to discontinue high-dose corticosteroids. However, use of high-dose corticosteroids in non-responders was also increased (from 63.8% to 100%), which was not adequately justified in the resubmission.

6.87 As outlined in Section 7, 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 therapies in the refractory setting. The ESC was less certain as to whether this approach would be appropriate in the bridging setting, and 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.

Drug cost/patient/year

- 6.88 The calculation of zilucoplan drug costs was consistent between the economic and budget impact models.
- 6.89 The estimated annual drug cost for zilucoplan was \$ [REDACTED] (based on patients receiving 13.04 scripts per year, assuming the same distribution of patients across weight categories as the RAISE trial and using the effective AEMP of \$ [REDACTED] per mg, with appropriate fees and mark-ups). This compares with estimated annual drug costs for zilucoplan of \$ [REDACTED] in the first year and \$ [REDACTED] in subsequent years from the July 2024 submission (based on an AEMP of \$ [REDACTED] per mg).
- 6.90 The estimated annual drug cost for standard therapy (anticholinesterases, corticosteroids and other immunosuppressive agents) was \$1,357 per year (corrected for the error in the cost of mycophenolate mofetil) and for escalated standard therapy (including all patients receiving high-dose corticosteroids and rituximab) was \$3,554 per year (corrected for the error in the cost of rituximab).
- 6.91 The resubmission estimated that the annual cost for chronic IVIg therapy (including procedure costs) was \$ [REDACTED] in the first year and \$ [REDACTED] in subsequent years (based on:

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cost of IVIg of \$ [REDACTED] per gram; 60% of maximum IVIg dose and assuming the average body weight of patients in the RAISE trial at baseline; and the cost of administration was estimated based on the July 2024 MBS fee for item 14245 (administration of an immunomodulating agent; \$111.60) assuming 2 administrations for the loading dose, then one administration every 4 weeks).

- 6.92 As outlined in Section 7, the ESC noted that, based on data received from the NBA on the utilisation of IVIg as maintenance therapy for Myasthenia Gravis in 2023-24, the average annual drug cost for chronic IVIg therapy per patient 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).
- 6.93 The estimated annual cost for chronic PLEX (including procedure costs) was \$45,107 in the first year and \$42,642 in subsequent years (corrected to include procedure costs associated with administering maintenance sessions).

Cost-comparison

- 6.94 The pre-PBAC response outlined equi-effective doses of zilucoplan and IVIg for the purposes of a cost-comparison, as shown in Table 14.

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Table 14: Comparison of the annual dose and drug cost of maintenance therapy with zilucoplan and IVIg

Treatment	Annual cost or dose	Source
Zilucoplan (pre-PBAC response)	10,475 mg per year	28.68 mg daily x 365.25 days. The average daily dose was based on the following dose categories: - patient weight: ≥ 43 to < 56 kg, dose 16.6 mg; 7.9% of patients in the trial; - patient weight: ≥ 56 to < 77 kg, dose 23.0 mg; 26.3% of patients in the trial; - patient weight: ≥ 77 to < 150 kg, dose 32.4 mg; 65.8% of patients in the trial. With 95% compliance, this would be 9,951 mg per year (10,475 mg x 95%).
IVIg costing scenarios		
ESC: IVIg (average IVIg dose per NBA data)	541 g per year; \$█ per year	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). ^a 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 based on Bril 2024	617.86 g per year; \$█ per year	The pre-PBAC response stated the 'equi-effective doses for zilucoplan versus IVIg should be established based on the dosing in NCT02473952 (published as Bril 2024). The data from this trial informed the indirect comparisons and the associated claims of non-inferior efficacy.' The dose used in Bril 2024 was a loading dose of 2g/kg over 2-4 days, and maintenance dose of 1g/kg every 3 weeks. This was higher than outlined in the Product Information. The pre-PBAC response assumed patients would use 40% of the IVIg dose outlined in Bril 2024. The pre-PBAC response assumed an average patient weight of 80.2 kg, and assumed that patients would receive 19.26 infusions per year. The cost is based on an IVIg cost of \$█ per gram.
IVIg costing scenarios: sensitivity analyses		
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 ^b 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.
Maximum dose recommended in IVIg Product Info 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 for a total of 1,172 g per year.

Source: Compiled during preparation of the PBAC PSD

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

^a Actual IVIg dose used in the calculations was 541.0625 g

^b 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

6.95 The PBAC noted that the pre-PBAC response estimated the average dose of zilucoplan would be 10,475 mg per year based on the dose outlined in the Product Information, with 100% dose intensity and compliance, and assuming the same weight distribution as patients in the trial (refer to Table 14). With 95% dose intensity, this would be 9,952 mg per patient per year.

6.96 Additional costs associated with zilucoplan include:

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- meningococcal vaccines (meningococcal B and ACWY boosters), and for patients who initiate zilucoplan less than 2 weeks after receiving a meningococcal vaccine, prophylactic antibiotics are required until 2 weeks after vaccination; and
 - there may be no administration costs given the Product Information states zilucoplan is a self-administered daily subcutaneous injection.
- 6.97 The pre-PBAC response stated the IVIg equi-effective dose should be ‘established based on the dosing in NCT02473952 (published as Bril 2024). These data from this trial informed the indirect comparisons and the associated claims of non-inferior efficacy’. In its calculation of equi-effective doses, the pre-PBAC response assumed patients would use 40% of the IVIg dose outlined in Bril 2024. The rationale for this was not stated in the zilucoplan submission though appeared to be based on a sensitivity analysis in the previous PSD (Table 16, zilucoplan PSD, July 2024 PBAC meeting).

Cost-per-responder

- 6.98 The PBAC noted that, at the price proposed by the sponsor, the incremental cost-per-responder versus placebo would be \$115,000 to < \$135,000 (based on 16.5% difference in the proportion of patients with ≥ 2 point reduction in MG-ADL at 12 weeks, and a cost of \$| for 12 weeks of therapy). The PBAC advised that this was unacceptably high in the context of previous cost-per-responder analyses.
- 6.99 The PBAC noted that, at a cost per patient per year of \$█, 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 ≥ 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

- 6.100 This resubmission was not considered by DUSC.
- 6.101 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing zilucoplan for adult patients with AChR positive generalised myasthenia gravis who are treatment refractory. Key inputs used in the resubmission are summarised in Table 15.

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Table 15: Key inputs for financial estimates presented in the resubmission

Parameter	Value applied and source	Comment
Prevalence of myasthenia gravis	<p>22.4 per 100,000 persons.</p> <p>The resubmission identified a published systematic review and meta-analysis of myasthenia gravis epidemiology studies published between 1952 and 2022 (Sciancalepore 2024). The study noted that the average prevalence increased from 9.7 cases per 100,000 persons in 1952-2007 to 22.0 cases per 100,000 in 2008-2021.</p> <p>The resubmission also conducted a supplementary literature search to identify more recently published studies (Ye 2024, Vissing 2024, Keovilayhong 2024, Tsai 2024, Salort-Campana 2024, Sechi 2024, Engebretsen 2024). A meta-analysis of studies published between 2014-2024 indicated a global prevalence of 22.4 cases per 100,000 persons. The submission claimed that this analysis suggested that the prevalence of the disease has stabilised over time.</p>	<p>The Sciancalepore 2024 review noted significant variation in frequencies of myasthenia gravis between and within countries because of methodological biases and complex heterogeneity of the disease characterised by several phenotypes and different clinical responses.</p> <p>The supplementary literature search and meta-analysis presented in the submission was not adequately documented (such as the exclusion of Bettini 2017 study from prevalence estimates and the selection of a sensitivity analyses over the main analysis in the Antonini 2023 study).</p> <p>Published prevalence estimates presented in the submission varied widely from 0.9 to 55.3 cases per 100,000 persons in the last 10 years.</p> <p>In regard to changes over time, the average prevalence from studies published in the last 5 years (27.9 per 100,000 persons) suggests that prevalence may still be increasing over time.</p>
Proportion of patients with generalised myasthenia gravis who are AChR+	<p>85.57%. Pooled estimate derived from 12 studies identified in a literature search conducted for the resubmission. Estimates ranged from 42.1% to 98.2% across the studies.</p>	<p>DUSC previously considered that this estimate was reasonable (Table 17, zilucoplan PBAC PSD, July 2024 PBAC meeting).</p>
Proportion of patients with AChR+ generalised myasthenia gravis that are treatment refractory	<p>20.78%. Pooled estimate (weighted by sample size) derived from 4 international studies identified in a literature search conducted for the resubmission. Estimates ranged from 9.2% to 37.0% across the studies. The resubmission acknowledged the definitions of refractory were not identical to the clinical criteria in the proposed restriction but claimed that the definitions were otherwise aligned in terms of treatment criteria and requirements for patients to be uncontrolled.</p>	<p>Definitions of inadequate symptom control/disease burden differed across the studies with no defined instruments in two studies (Tokuyasu 2024, Ojha 2023) and different instruments and thresholds applied in two other studies (Li 2024, Rath 2020). There were additional differences in terms of treatment criteria between studies (e.g. prior/concomitant, duration and doses). These definitions also differed from the functional impairment and treatment criteria in the proposed restriction. The evaluation and the ESC considered that the pooled estimate was uncertain given the wide range of estimates from the included studies. The PSCR outlined that this was informed by the best available evidence.</p>
Zilucoplan uptake rate	<p>Derived based on assumed uptake rates of █%, █%, █%, █% and █% in eligible patients who had not previously been treated with zilucoplan.</p>	<p>DUSC previously considered the zilucoplan uptake rates were overestimated (Table 17, zilucoplan PBAC PSD, July 2024 PBAC meeting).</p>

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Parameter	Value applied and source	Comment
Zilucoplan response rate	84.9%. Based on the proportion achieving a ≥ 3 -point reduction in MG-ADL at 16 weeks in the RAISE extension study. All responders were assumed to remain on treatment for the remainder of the first year.	<p>The evaluation considered that the appropriateness of this estimate is dependent on the optimal timing of response assessment. The response assessment in the proposed restriction (either 16 or 24 weeks of initial script coverage) was longer than the 12 weeks suggested at the stakeholder meeting (May 2024 Myasthenia Gravis Stakeholder Meeting Outcomes Statement). The response rate for zilucoplan at 12 weeks in the RAISE trial was 73.1%, which is lower than the response rate at 16 weeks.</p> <p>There is potential for ongoing use in patients who do not meet the proposed response threshold given it is greater than the MCID of ≥ 2-point reduction in MG-ADL.</p>
Zilucoplan persistence	Yr 1 to 2: 83.08%, Yr 2 to 3: 85.02%, Yr 3 to 4: 85.27%, Yr 4 to 5: 85.24%, Yr 5 to 6: 85.21%. Derived from the economic model for the zilucoplan arm. The persistence estimate was applied to the recommended number of scripts per year ($365.25 \div 28 = 13.04$ scripts per year) to derive the number of scripts per patient in each subsequent year	The evaluation considered that the appropriateness of persistence estimates is dependent on the validity of assumptions regarding treatment discontinuation (due to adverse events, exacerbation, myasthenic crisis and deaths) in the economic model. The lower persistence estimates compared to the previous submission appear to be the result of higher clinical events rates compared to the July 2024 submission (previously considered likely to have substantially overestimated event risks), offsetting revised assumptions regarding discontinuation following an event.
Proportion of patients initiating zilucoplan who would otherwise receive chronic IVIg/PLEX	89.8%. Based on the subgroup of patients in the RAISE trial who are treatment refractory (as per trial definitions) with prior recorded use of rescue/chronic IVIg/PLEX.	The evaluation considered that the trial-based estimate may not be applicable to the PBS population given the recorded usage did not differentiate between rescue and chronic treatment. Additionally, the trial excluded patients with recent use (28 days) of IVIg/PLEX.
Chronic IVIg/PLEX response rate	70%. Based on the proportion of patients treated with chronic IVIg achieving a ≥ 2 -point reduction in MG-ADL at 24 weeks in the Brill 2024 trial (NCT02473952).	<p>The evaluation noted that the dosing regimen used in the Brill 2024 trial is unlikely to reflect Australian clinical practice as it is inconsistent with the approved product information, exceeds the maximum subsidised dose under the NBA and is substantially higher than supported by the available Australian IVIg utilisation data.</p> <p>This was inconsistent with the National Blood Authority continuing treatment criteria for IVIg that required a ≥ 3-point improvement in MGC score OR clinical benefit but with end-of-cycle deterioration after 16 weeks of therapy.</p>
Chronic IVIg/PLEX persistence	Assumed to be the same as for zilucoplan.	<p>DUSC previously considered the assumption of the same treatment persistence for IVIg and PLEX as zilucoplan was not adequately justified (Table 17, zilucoplan PBAC PSD, July 2024 PBAC meeting).</p> <p>The persistence estimates were substantially higher than applied in the economic model.</p>

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Parameter	Value applied and source	Comment
Dispensed IVIg per patient	<p>Responder initial year: 718 g, responder subsequent year: 696 g, non-responder: 260 g. Doses were calculated based on mean body weight in the RAISE trial and the maximum doses recommended in the IVIg (Privigen®) product information.</p> <p>In the previous submission, doses were calculated based on mean body weight in the RAISE trial (89.1 kg) and maximum doses recommended in the IVIg product information. The resubmission noted that a sensitivity analysis in the zilucoplan July 2024 PBAC PSD assumed a 60% reduction in the estimated IVIg dose (i.e. to a dose consistent with average dose reported in the MSAC review of IVIg use for myasthenia gravis of 492 g per patient), but argued that a 40% reduction (resulting in a higher dose) would be more appropriate in a treatment refractory population.</p> <p>The resubmission stated that the highest dose frequency in the recommended range was chosen (i.e. induction dose split over 2 administrations and maintenance dose every 4 weeks). Additionally, the number of administrations in the initial year were adjusted assuming the same treatment durations as for zilucoplan for the initial 16-week period (15.55 weeks) and subsequent 16- to 52-week period (34.29 weeks). This approach yielded a total dispensed dose of 718 g (calculated as $[106.9 \text{ g} + (12 \times 53.5\text{g})] \times 95.9\%$) for initial year responders, 696 g for subsequent year responders (calculated as $53.5 \text{ g} \times 13$) and 260 g for non-responders (calculated as $[106.9 \text{ g} + (53.5 \text{ g} \times 3)] \times 97.2\%$).</p>	<p>No data were provided to support the resubmission's claim that IVIg doses would be higher in treatment refractory populations.</p> <p>Overall, the resubmission's approach yielded an IVIg dose of 696 g for the majority of patients who receive ongoing treatment, which was higher than the mean IVIg maintenance dose among patients with myasthenia gravis reported in the MSAC review of immunoglobulin use for myasthenia gravis (492 g) and in the NBA data on the utilisation of IVIg as maintenance therapy in 2023-24 (541 g).</p>
Zilucoplan cost	16.6 mg: \$█, 23.0 mg: \$█, 32.4 mg: \$█ based on the proposed effective AEMP.	The proposed effective AEMP was \$█ per mg, representing an █% increase compared to \$█ per mg in the July 2024 submission.
IVIg cost	\$█ per gram. Based on the price of Intragam 10 (2.5 g/25 mL: \$█; NBA National Product Price List October 2024).	Based on data from the NBA, the average cost per gram of IVIg was \$█ in 2023-24.

Source: Section 4, pp199-234 of the resubmission; Section 4 utilisation and financial impacts Excel workbook
 Abbreviations: AChR+, acetylcholine receptor antibody positive; AEMP, approved ex-manufacturer price; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite score; MSAC, Medical Services Advisory Committee; NBA, National Blood Authority; PLEX, plasma exchange; PSD = Public Summary Document; Yr, Year

6.102 Table 16 summarises the submission's estimated eligible population, scripts dispensed and net cost to PBS/RPBS/NBA/MBS of listing zilucoplan adult patients with AChR positive generalised myasthenia gravis who are treatment refractory.

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Table 16: Estimated use and financial implications of listing zilucoplan

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent MG patients	¹	¹	¹	¹	¹	¹
Eligible refractory population	²	²	²	²	²	²
July 2024 submission, eligible population	²	²	²	²	²	²
Treated refractory population	²	³	³	³	³	³
July 2024 submission, treated population	²	²	²	²	²	²
Zilucoplan 16.6 mg scripts	²	³	³	³	³	³
Zilucoplan 23.0 mg scripts	²	²	²	²	²	²
Zilucoplan 32.4 mg scripts	²	²	²	²	²	²
Cost to PBS/RPBS less copay	⁴	⁴	⁴	⁴	⁴	⁵
July 2024 submission, net PBS/RPBS cost	⁶	⁷	⁷	⁷	⁷	⁷
Reduced NBA costs for IVIg	⁸	⁸	⁸	⁸	⁸	⁸
Reduced NBA costs for PLEX	⁸	⁸	⁸	⁸	⁸	⁸
Increased MBS costs for zilucoplan administration training	⁹	⁹	⁹	⁹	⁹	⁹
Reduced MBS costs for IVIg administration	⁸	⁸	⁸	⁸	⁸	⁸
Reduced MBS costs for PLEX administration	⁸	⁸	⁸	⁸	⁸	⁸
Net cost to PBS/RPBS/NBA/MBS	¹⁰	¹⁰	¹⁰	¹⁰	¹⁰	¹⁰
July 2024 submission, net cost to PBS/RPBS/NBA/MBS	⁵	⁴	⁴	⁴	⁴	⁴

Source: Section 4 utilisation and financial impact Excel workbook

Abbreviations: IVIg, intravenous immunoglobulin; MG, myasthenia gravis; NBA, National Blood Authority; PBS, Pharmaceutical Benefits Scheme; PLEX, plasma exchange RPBS, Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 500 to < 5,000

³ < 500

⁴ \$40 million to < \$50 million

⁵ \$30 million to < \$40 million

⁶ \$60 million to < \$70 million

⁷ \$70 million to < \$80 million

⁸ net cost saving

⁹ \$0 to < \$10 million

¹⁰ \$20 million to < \$30 million

6.103 The submission estimated the net cost to the PBS/RPBS would be \$40 million to < \$50 million in Year 1, decreasing to \$30 million to < \$40 million in Year 6, a total cost of \$200 million to < \$300 million over the first six years of listing. The net cost to the PBS/RPBS was lower than estimated in the previous submission (\$400 million to < \$500 million over 6 years), primarily due to the reduced size of the eligible population who are treatment refractory, which is narrower than the second line/treatment refractory population proposed previously.

6.104 The estimated net cost to the PBS/RPBS/NBA/MBS was \$20 million to < \$30 million in Year 1, increasing to \$20 million to < \$30 million in Year 2, then decreasing to \$20 million to < \$30 million in Year 6; a total cost of \$100 million to < \$200 million over the

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first six years of listing. The net cost to the PBS/RPBS/NBA/MBS was lower than estimated in the previous submission (\$200 million to < \$300 million over 6 years), primarily due to the reduced size of the eligible population and correspondingly lower cost offsets due to substitution of IVIg/PLEX.

6.105 The ESC noted that the costs to the NIP for increased use of meningococcal vaccines were not included in the financial estimates.

6.106 The evaluation and the ESC considered that the estimated cost to PBS/RPBS/NBA/MBS was uncertain due to the following reasons:

- The prevalence of myasthenia gravis (22.4 per 100,000 persons) is unclear, with substantial variation in published international estimates (ranging from 0.9 to 55.3 cases per 100,000 persons in the last 10 years). Additionally, prevalence rates have been increasing over time and it is unclear whether rates have stabilised or will continue to grow.
- The pooled estimate informing the proportion of patients who are refractory (20.78%) was considered uncertain given the wide range of estimates from the included studies (9.2% to 37.0%). There were substantial differences in definitions of treatment refractory based on inadequate symptom control/disease burden as well as prior/concomitant treatment criteria between the included studies and compared to the proposed restriction.
- The appropriateness of the zilucoplan response rate based on response at 16 weeks was uncertain, given it is longer than the 12 weeks suggested at the stakeholder meeting (May 2024 Myasthenia Gravis Stakeholder Meeting Outcomes Statement)². The response rate for zilucoplan at 12 weeks in the RAISE trial was lower than the estimate at 16 weeks, which would reduce the proportion of patients eligible for continuing treatment.
- The resubmission claimed that the dose of IVIg would be higher in treatment refractory populations. No data were provided in support of this assumption. The estimated dose of IVIg (696 g in the majority of patients who are receiving ongoing treatment) was higher than the mean IVIg maintenance dose among patients with myasthenia gravis based on 2023-24 NBA data (541 g).
- The estimated cost per gram for IVIg (\$████) was based on published NBA prices for domestic IVIg products. Based on NBA data, the average cost per gram of IVIg was \$████ in 2023-24 (including the cost of domestic and international products and plasma fractionation).

6.107 The ESC noted that the resubmission estimated a reduction in costs to the NBA due to reduced use of IVIg of \$70 million to < \$80 million over six years. As such, the

² 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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submission estimated that 31% of the cost to the PBS/RPBS of zilucoplan would be offset by reductions in IVIg use.

6.108 As outlined in Section 7, 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.

6.109 The PBAC agreed with the ESC and advised the parameters outlined in Table 17 may be reasonable for determining the estimated use and financial implications of the new therapies for gMG.

Table 17: 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 18)
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. █ ¹ patients in Year 1)
Increase in uptake over time	█ percentage points each year for the first six years of listing (i.e. █ ² patients in Year 6).

Source: Compiled during preparation of the PBAC PSD

The redacted values correspond to the following ranges:

¹ < 500

²500 to < 5,000

6.110 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 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).

Financial Management – Risk Sharing Arrangements

6.111 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. The pre-PBAC response requesting two separate RSAs given there are two distinct places in therapy (i.e. bridging and refractory). Refer to paragraphs 8.32 and 8.33 for the PBAC’s advice regarding the RSA.

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) that the complement inhibitors should be available in both these settings.

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

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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.^{3,4} 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.
- 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 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:

³ 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/>

⁴ 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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- 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 IVIg⁵ 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 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 therapy (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 trialled 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

⁵ Criteria for Clinical Use of Immunoglobulin in Australia, accessed at: <https://www.criteria.blood.gov.au/MedicalCondition/View/2681>

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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).

- 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.
- 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 18 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 18: 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]
Data below is specific to the myasthenia gravis maintenance setting	
Average number of 'dispensing events' per patient in 2023-24	15.7 per patient per year
Average total annual dose in 2023-24 ^a	541.0625 grams
Average grams per 'dispensing event'	34.4 grams
Average cost per patient per year of IVIg for maintenance ^a	\$ [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) ^d	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%
Context of IVIg use for gMG ^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) ^c	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.

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

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

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

^d 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

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seen in the extension trials. The ESC requested that sponsors provide information to 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 zilucoplan 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

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- of the available evidence for chronic IVIg, however the PBAC considered that there was no evidence to suggest superior efficacy or safety of zilucoplan versus chronic IVIg or PLEX. Further, the PBAC considered that there was no reliable evidence to suggest that zilucoplan 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 (ravulizumab, 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 noted that the resubmission requested listing of zilucoplan in treatment refractory patients only, and acknowledged the key trial was not designed to specifically assess the efficacy of zilucoplan in the bridging setting. However, the PBAC considered the new gMG therapies (both complement inhibitors and FcRn blockers) should be listed in the bridging setting (in addition to the refractory setting) given the high unmet need, clinical rationale and strong clinician support for listing in this setting. The PBAC further acknowledged comments from clinicians advocating 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:

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- 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 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 ≥ 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 6.5b).
- 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 ≥ 2 (plus a corresponding MGC level to be

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- determined based on consultation with expert neurologists and immunologists), achieved at 2 to 16 weeks, per the clinician correspondence (paragraph 6.4e).
- 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 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

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- 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.
- 8.18 The PBAC noted the previous submission for zilucoplan had presented indirect comparisons versus chronic IVIg, including one that used NCT02473952 (subsequently published as Brill 2024) to inform the IVIg arm. The PBAC noted this indirect comparison found no statistically significant differences in functional outcomes between zilucoplan and chronic IVIg. The PBAC further noted the previous submission considered that it was likely that zilucoplan is at least non-inferior in terms of efficacy and safety compared to chronic IVIg/PLEX, albeit noting the submission's claim that the limited evidence base available for chronic IVIg/PLEX precluded any robust clinical conclusion. 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 no evidence to suggest superior efficacy or safety of any of the four new gMG therapies versus chronic IVIg or PLEX.
- 8.19 Overall, the PBAC considered that zilucoplan has non-inferior comparative effectiveness and safety versus chronic IVIg and also against ravulizumab, efgartigimod and rozanolixizumab.
- 8.20 The PBAC noted the economic model positioned zilucoplan primarily as a subsequent therapy after treatment failure with chronic IVIg/PLEX, 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)⁶ 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

⁶ 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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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.

- 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 18).
 - the zilucoplan dose recommended in the product information assuming the same weight distribution as patients in the trial (outlined in Table 14), not accounting for response rates. 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 zilucoplan would be: 9,951 mg per year (i.e. 10,475 mg x 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 6.99). 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 17). 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% as proposed by the sponsor).
- 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 17). This group would likely have relatively high uptake of the new therapies (potentially up to %).
 - uptake from prevalent patients (i.e. the remaining % of the AChR+ patient cohort) already established on IVIg (uptake of around %).

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- 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 17). 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 $\frac{1}{2}$ 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).
- 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.
- 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 $\frac{1}{2}$ RSA – with the $\frac{1}{2}$ 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

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- 17) with a rebate of less than 10%, then a 10% based on the total number of patients using IVIg for maintenance gMG with a rebate of 10%.
- 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 zilucoplan stated “vaccines against serogroups A, C, Y, W, and where available, serogroup B, are recommended for preventing the commonly pathogenic meningococcal serogroups. Vaccination, revaccination (boosters) and prophylactic antibiotic treatment should occur according to current relevant guidelines”. 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 zilucoplan is not suitable for prescribing by nurse practitioners.
- 8.37 Zilucoplan should be exempt from the Early Supply Rule as it does not apply to Section 100 Highly Specialised Drug listings.
- 8.38 The PBAC advised that zilucoplan should not be treated as interchangeable with any other drugs.
- 8.39 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 zilucoplan:
- 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.
- 8.40 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 point 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.