

**5.03 EFGARTIGIMOD ALFA,  
Solution concentrate of I.V. infusion 400 mg in 20 mL,  
Vyvgart<sup>®</sup>,  
ARGENX AUSTRALIA PTY LTD.**

**1 Purpose of submission**

- 1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug Program) Authority Required (Written) listing for the treatment of adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody positive.
- 1.2 The submission claimed there is an unmet clinical need for additional treatment options for the management of myasthenia gravis, given the limitations of current treatments including inadequate symptom control, slow onset of action, high treatment burden, significant side effects and risk of developing comorbidities.
- 1.3 The submission claimed that the target population for efgartigimod are major users of intravenous immunoglobulin (IVIg) in Australia which is subject to global supply constraints and is more burdensome than efgartigimod in terms of administration duration and frequency. These claims appeared inconsistent with the sponsor’s market research indicating that most patients are able to access IVIg if required. The evaluation considered that the claim of reduced administration burden may not be adequately justified as it was inconsistent with the average number of efgartigimod doses of approximately 19 per year (based on 4.72 annual treatment cycles) compared to IVIg doses of 14 per year assumed in the financial section of the submission.
- 1.4 Listing was requested on the basis of a cost-effectiveness analysis versus chronic IVIg.

**Table 1: Key components of the clinical issue addressed in the submission (as stated in the submission)**

Component	Description
Population	Adult patients with AChR-positive generalised myasthenia gravis who remain symptomatic despite standard therapy.
Intervention	Efgartigimod intravenous infusion once a week for 4 weeks (weight-based dosing at 10 mg/kg, maximum of 1,200 mg per dose); in combination with standard therapy (including anticholinesterases, corticosteroids and other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, ciclosporin). Subsequent treatment cycles with efgartigimod may be initiated based on clinical evaluation.
Comparator	<u>Primary:</u> Chronic intravenous immunoglobulin (IVIg) and chronic plasma exchange (PLEX). <u>Near market:</u> Zilucoplan, ravulizumab, rozanolixizumab.
Outcomes	Reduction in functional impairments, reduction in clinical exacerbations and myasthenic crisis events, corticosteroid-sparing effects, survival gain and improvements in quality of life.
Clinical claim	Efgartigimod is superior in terms of efficacy and non-inferior in terms of safety compared to chronic IVIg. No clinical claim was made against chronic PLEX.  Efgartigimod is potentially superior in terms of efficacy compared to its near market comparators (zilucoplan, ravulizumab, rozanolixizumab). No clinical claim was made in terms of safety.

Source: Table 1.1, p19 of the submission

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

## 2 Background

### Registration status

- 2.1 Efgartigimod was registered by the TGA on 24 February 2025 as ‘add-on to standard therapy for the treatment of adult patients with gMG who are AChR antibody positive’.
- 2.2 Two formulations of efgartigimod were registered by the TGA: 400 mg/20 mL concentrated solution for intravenous infusion vial and 1,000 mg/5.6 mL solution for injection vial (subcutaneous injection), however the submission only requested PBS-listing of the intravenous infusion formulation.

## 3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed price for Max. qty		Max. qty packs	Max. qty units	№.of Rpts	Available brands
	Published	Effective				
EFGARTIGIMOD ALFA						
Initial/Continuing/Re-initiating/Grandfathering (Section 100)						
Efgartigimod alfa 400 mg/20 mL injection, 20 mL vial	\$█ (Public hospital) \$█ (Private hospital)	\$█ (Public hospital) \$█ (Private hospital)	1	3 vials	11	Vyvgart

<b>Category / Program:</b> Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)
<b>Authority type:</b> Complex Authority Required (CAR)
<b>Episodicity:</b> Treatment cycles of one dose per week for four weeks
<b>Severity:</b> MGFA Classification Class II, III or IV
<b>Indication:</b> Treatment of AChR-Ab+ gMG in adult patients with moderate-severe, symptomatic disease, despite use of conventional oral therapies
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b>
Patient must have a diagnosis of AChR-Ab+ MG, confirmed by a positive serologic test for anti-AChR antibodies
Patient must have a diagnosis of non-ocular gMG as defined by an MGFA classification II-IV
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have received a stable dose for three months of at least two prior oral therapies (i.e. AChEIs, NSiSTs, corticosteroids) prior to treatment initiation unless contraindicated/intolerant necessitating treatment withdrawal
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have an MG-ADL score of ≥5 (with more than 50% of the total score due to non-ocular symptoms) or MGC score of ≥10
<b>Treatment criteria:</b>

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<p>Authority applications for initial treatment must be made in writing and must include:</p> <p>(a) Completed authority prescription form; and</p> <p>(b) Completed PBS authority application form, which includes:</p> <p>(i) Report confirming evidence of AChR-Ab+ MG confirmed by a positive serologic test for anti-AChR antibodies and tick a box to state the person has MGFA Class II to IV disease;</p> <p>(ii) Dates of prior treatment with AChEIs, NSISTs, Corticosteroids or IVIg/PLEX; and</p> <p>(iii) Date of demonstration of persistent symptoms following treatment with AChEIs, NSISTs or Corticosteroids, alone or in combination.</p> <p>If intolerance to treatment develops during the relevant period of use, which is of a severity necessitating permanent treatment withdrawal, please provide details of the degree of this toxicity at the time of application (grade and nature of toxicity).</p>
<p><b>Prescribing Instructions:</b></p> <p>MG-ADL and/or MGC score must be provided by the physician at baseline.</p> <p>Efgartigimod alfa should be prescribed by or in consultation with a neurologist with expertise in managing patients with gMG.</p> <p>Efgartigimod alfa should not be used concomitantly with rituximab or complement inhibitors.</p> <p>The maximum duration of initial authorisation is 3 cycles. Patient should be reviewed 6 months after treatment initiation.</p>
<p><b>Administrative Advice:</b></p> <p>No increase in the maximum number of repeats may be authorised (initial treatment).</p>
<p><b>Treatment Phase:</b> Continuing treatment</p>
<p><b>Clinical criteria:</b></p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p>
<p><b>AND</b></p>
<p><b>Clinical criteria:</b></p> <p>During the first two treatment cycles, there is documented reduction in MG-ADL score of at least a 2-point reduction in MG-ADL (3 points in MGC).</p>
<p><b>Prescribing Instructions:</b></p> <p>MG-ADL and/or MGC score must be measured during the initial treatment authorisation (at any time during the first two treatment cycles), documenting at least a 2-point reduction in MG-ADL (3 points in MGC). Reassessment of continued response should occur every 12 months thereafter.</p> <p>Efgartigimod alfa should be prescribed by or in consultation with a neurologist with expertise in managing patients with gMG.</p> <p>Efgartigimod alfa should not be used concomitantly with rituximab or complement inhibitors.</p>
<p><b>Treatment Phase:</b> Re-initiating treatment</p>
<p><b>Clinical criteria:</b></p> <p>Patient must have demonstrated previous treatment response to PBS-subsidised EFG, defined as a patient who has shown a reduction of at least 2 points in MG-ADL score (3 points in MGC score).</p>
<p><b>AND</b></p>
<p><b>Clinical criteria:</b></p> <p>Patient must have an MG-ADL score of <math>\geq 5</math> (with more than 50% of the total score due to non-ocular symptoms) or MGC score of <math>\geq 10</math></p>
<p><b>AND</b></p>
<p><b>Clinical criteria:</b></p> <p>Patients should not be experiencing a myasthenic crisis at the time of treatment re-initiation (MGFA Class V)</p>
<p><b>Prescribing Instructions:</b></p>

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MG-ADL and/or MGC score must be measured and provided by the physician at baseline. Efgartigimod alfa should be prescribed by or in consultation with a neurologist with expertise in managing patients with gMG. Efgartigimod alfa should not be used concomitantly with rituximab or complement inhibitors. The maximum duration of initial authorisation (re-initiating treatment) is 3 cycles, then continuing treatment criteria apply.
<b>Treatment Phase:</b> Grandfathering
<b>Clinical criteria:</b>
Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing]
<b>AND</b>
<b>Clinical criteria:</b>
Before initiating non-PBS treatment with this drug for this condition, patient must have received a stable dose for three months of at least two prior oral therapies (i.e. AChEIs, NSiSTs, corticosteroids) prior to treatment initiation unless contraindicated/intolerant necessitating treatment withdrawal
<b>AND</b>
<b>Clinical criteria:</b>
Before initiating non-PBS treatment with this drug for this condition, patient must have MG-ADL score of $\geq 5$ or MGC score of $\geq 10$ with more than 50% of the total score due to non-ocular symptoms
<b>Prescribing Instructions:</b>
For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
<b>Treatment Phase:</b> Stopping treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
After initial treatment, there is no improvement in MG-ADL score of 2 points or greater (or MGC score of 3 points or greater)
<b>OR</b>
<b>Clinical criteria:</b>
Patient fails to achieve the specified benefit/response following treatment.

- 3.1 The submission proposed a special pricing arrangement for efgartigimod which represented a rebate of  $\frac{1}{2}$  of the published AEMP of \$1 per vial.
- 3.2 The submission indicated that the intended place in therapy was in refractory patients (with moderate-severe, symptomatic disease, despite use of conventional oral therapies) though the evaluation noted the proposed restriction was broad and would allow use in the bridging setting. The Pre-Sub-Committee Response (PSCR) stated that the proposed place is for patients who are currently being maintained on IVIg or would otherwise be prescribed human blood products, but with a higher threshold (functional impairment) for treatment based on the recommendation of clinicians. Refer to paragraph 8.6 for the PBAC’s advice regarding the place in therapy.
- 3.3 As outlined in Section 7, the ESC recalled advice from the clinicians present at the gMG stakeholder meeting (May 2024) that the new gMG therapies should be available in both the bridging and refractory settings. The ESC considered that separate PBS restrictions would be required in each of these settings.

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- 3.4 The proposed PBS restrictions are narrower than the registered TGA indication due to additional clinical criteria for prior therapies, functional impairments and treatment response.
- 3.5 The submission proposed using the Myasthenia Gravis Activities of Daily Living (MG-ADL) and Myasthenia Gravis Composite (MGC) instruments to assess functional impairment criteria under the requested PBS restriction. The submission noted that the use of MG-ADL scores was consistent with eligibility criteria in the key trial, but that MGC is the predominant instrument used in Australia based on feedback from Australian physicians (METIS Healthcare Research, October 2024). The evaluation considered this proposal appeared reasonable based on results from the sponsor-commissioned survey that indicated that the use of MGC is common (60%), although fewer respondents used MG-ADL (20%), and a substantial proportion of respondents did not use any particular instrument (33%).
- 3.6 The submission proposed functional impairment criteria based on an MG-ADL score of  $\geq 5$  (with  $> 50\%$  of the total score due to non-ocular symptoms) or MGC score of  $\geq 10$ . The submission claimed that while MG-ADL and MGC share six out of eight symptom domains and are strongly correlated, it is not possible to directly translate an MG-ADL score to an MGC score. The submission stated that the proposed MGC threshold of 10 was based on feedback from Australian physicians, and that this would also capture the majority of the key trial population (94% with MGC  $\geq 10$ ). The MG-ADL criterion was consistent with eligibility criteria in the key trial. The PSCR stated that MG-ADL is the preferred restriction criteria as it was the primary endpoint in the ADAPT trial, but stated that the sponsor would support a standardised approach to assessing functional impairment across the subsidised therapies. Refer to paragraphs 8.7 to 8.8 for the PBAC's advice regarding initiation criteria.
- 3.7 The pre-PBAC response reiterated that the proposed PBS restriction for efgartigimod requires a higher disease severity score than the IVIg criteria, and noted that not all patients on human blood products are anticipated to be eligible for treatment with efgartigimod, and some may not wish to transition to a new therapy if they are satisfied with IVIg treatment.
- 3.8 The evaluation and the ESC considered that the proposed prior therapy criteria of stable doses for 3 months with at least two prior oral therapies (anticholinesterase, corticosteroid and/or non-steroidal immunosuppressive therapy (NS-IST)) was broad as it did not require the corticosteroid/immunosuppressive therapy to have been optimised, nor require combination corticosteroids plus NS-IST to have been trialled. The PSCR argued that "stable" doses were proposed in the criteria because Australian clinicians advised that there is no clear definition of "optimal" doses whereas a "stable" dose is quantifiable and achievable. Refer to paragraphs 8.7 to 8.9 for the PBAC's advice regarding initiation criteria.

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- 3.9 The proposed restriction did not require concomitant use of standard therapies, which was inconsistent with the TGA indication for efgartigimod, which is as an add-on to standard therapy.
- 3.10 The submission proposed separate initial, continuing and re-initiating restrictions with each script providing sufficient quantities and repeats for 3 treatment cycles. The submission claimed that patients achieving response in the initial treatment period could continue treatment with annual assessments for response. However, should this continuum be broken, then patients must meet re-initiation criteria to restart therapy.
- 3.11 The proposed script coverage of 3 treatment cycles for the initial restriction was inconsistent with the submission's continuing restriction that required prior response during the first 2 treatment cycles of the initial period. The evaluation considered it may be more appropriate for the initial restriction to have sufficient script coverage for the first initial treatment cycle, with a balance of supply script for a second initial treatment cycle. The evaluation also considered that a lifetime maximum of 2 initial treatment cycles may also be necessary to reduce the risk of ongoing use in patients who do not achieve response. The PSCR argued that, "The initial script must provide coverage for at least two full treatment cycles in order to adequately assess the efficacy of efgartigimod. According to the ADAPT trial, 80 per cent of patients achieve response by the end of the second cycle. A "lifetime maximum" of two initial treatment cycles would potentially disadvantage patients whose response may be impacted by other factors (e.g. concurrent acute illness, reversible damage to the neuromuscular junction)." The pre-PBAC response further argued that patients with severe disease should have the option of being treated with three full cycles to provide an optimum chance to respond.
- 3.12 The evaluation considered that the proposed script coverage of 3 treatment cycles for the continuing and re-initiating restrictions was inconsistent with the intended cyclical use of efgartigimod as per the product information, with initiation of subsequent treatment cycles subject to individualised clinical evaluation. The evaluation considered that it may be more appropriate to provide script coverage for a single treatment cycle, as clinical assessments should be conducted prior to each treatment cycle. However, the ESC considered that any requirement for patients to obtain a new script for each cycle may be impractical in terms of patients being required to access a specialist when their condition deteriorates, particularly given the longer-term extension studies suggest the treatment-free interval reduces over time including gradually reducing to approximately 4 weeks by the thirteenth treatment cycle in Part B of the extension study (refer to paragraph 6.40).
- 3.13 The continuing treatment criteria proposed in the submission:
- defined treatment response as  $\geq 2$ -point reduction in MG ADL or  $\geq 3$ -point reduction in MGC based on minimal clinically important differences for these instruments. The MG-ADL response threshold was consistent with key outcomes

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in the trial. However, it was unclear whether response based on the MGC  $\geq 3$  threshold is equivalent to the MG-ADL  $\geq 2$  threshold.

- did not include a functional impairment criterion. During the first year of the ADAPT+ extension study (Part A), re-treatment was allowed if patients had significant symptoms based on MG-ADL  $\geq 5$  (with  $> 50\%$  of the total score due to non-ocular symptoms). In subsequent years of the extension study (Part B), re-treatment was based on patient and investigator discretion only.
  - did not require patients to demonstrate loss of treatment response. The ADAPT trial and Part A of the ADAPT+ extension study required patients to demonstrate loss of response from the previous treatment cycle, defined as a  $< 2$ -point reduction in MG-ADL compared to the previous baseline. Loss of treatment response was not a requirement for re-treatment in Part B of the ADAPT+ extension study.
- 3.14 The evaluation considered that it was unclear whether eligibility for subsequent treatment cycles should include both functional impairment and loss of response criteria based on the trial's strict re-treatment criteria, which may be difficult to implement in practice. The PSCR noted that, "strict re-treatment criteria considered in the ADAPT/ADAPT+ trial (i.e., requirement for patients to return to baseline) were specifically designed to evaluate repeatability of treatment effect over cycles for a regulatory purpose. In clinical practice, patients would not be expected to return to baseline prior to receiving the next treatment cycle." The ESC agreed with the evaluation and the PSCR that the strict re-treatment criteria in the trial (ADAPT trial and Part A of the ADAPT+ extension study) may be difficult to implement in practice.
- 3.15 In terms of re-treatment criteria, the ESC noted that clinical evidence in this space is evolving, and appropriate dosing regimens may change over time. A study not provided as part of the submission, ADAPT-NXT, assessed the efficacy of two different regimens of efgartigimod, neither of which used re-treatment criteria: fixed-cycle (4 once-weekly infusions with a 4-week intertreatment period); versus continuous dosing (every 2 weeks). Both these regimens (fixed or continuous) would result in more frequent dosing than observed overall throughout the ADAPT trial and the ADAPT+ extension studies (which required re-treatment criteria to be met, including meeting functional impairment and loss of response criteria in the ADAPT trial and ADAPT+ Part A study), though by the thirteenth treatment cycle of Part B of the extension study (which had less strict re-treatment criteria), the median treatment free interval was four weeks i.e. similar to the fixed-cycle regimen of ADAPT-NXT. Refer to paragraph 8.11 for the PBAC's advice regarding re-treatment criteria for the FcRn blockers.
- 3.16 The ESC considered that it was unclear whether, in clinical practice, patients and clinicians would follow the more frequent dosing protocols used in ADAPT-NXT, which would increase treatment costs (refer to paragraph 6.103).

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- 3.17 The submission proposed a stopping rule for patients who do not achieve response following initial treatment, however the evaluation noted that this appeared redundant given specific treatment response criteria under the continuing treatment restriction. The PBAC previously agreed with stakeholder meeting outcomes that there should be robust stopping rules to prevent ongoing use of newer therapies including efgartigimod, noting that this would be harder in patients with treatment-refractory disease (paragraph 2.4, ravulizumab Public Summary Document (PSD), July 2024 PBAC meeting). No stopping rules (i.e. requiring cessation in patients with response in order to prevent ongoing use that may be unnecessary) were proposed in the submission. Refer to Section 7 for ESC Advice relevant to stopping rules. The pre-PBAC response argued that it is unnecessary to impose a stopping rule after the initial six months of treatment for newly initiated patients because efgartigimod's cyclical dosing is intended to incorporate pauses after each four-week cycle, to enable the treating clinician (and patient) to assess the need for ongoing therapy. Refer to paragraphs 8.6 and 8.9 for the PBAC's advice regarding therapy cessation.
- 3.18 The proposed prescribing instructions state that efgartigimod should not be used concomitantly with rituximab or complement inhibitors. However, the evaluation considered that additional classes could be added noting the product information outlines potential interactions with compounds that bind to the Fc Receptor (FcRn) which include established myasthenia gravis treatments such as IVIg and monoclonal antibodies (rituximab, eculizumab, ravulizumab).
- 3.19 The submission proposed a grandfathering restriction to enable patients to transition from the sponsor's early access program for efgartigimod to PBS-funded treatment when available. The proposed grandfathering restriction incorporated clinical criteria from both the proposed initial and continuing restrictions. The submission stated that approximately 30 patients in the early access program would achieve response and be eligible for treatment under the grandfathering restriction.

*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). Typical symptoms associated with myasthenia gravis include drooping eyelids, blurred or double vision, shortness of breath, difficulty chewing and swallowing, impaired speech, fatigue, pain, muscle spasms and general muscle weakness.

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- 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. Transient periods of rapid symptom worsening are referred to as disease exacerbations. Of particular concern are myasthenic crises, which are severe, life-threatening exacerbations that are due to weakness in respiratory muscles which results in respiratory failure requiring mechanical ventilation. However, the submission noted that the mortality of patients with myasthenia gravis has decreased over the years and most patients have a normal lifespan.
- 4.4 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.
- 4.5 The submission presented a simplified clinical algorithm for the treatment of generalised myasthenia gravis. The algorithm did not adequately capture the sequential use and optimisation of anticholinesterases, corticosteroids and NS-ISTs prior to consideration of chronic IVIg/PLEX. Additionally, the algorithm did not present the use of chronic IVIg/PLEX as bridging therapies while patients adjust to slower-acting immunosuppressive agents. Overall, the evaluation considered that the algorithm lacked sufficient detail to understand the proposed place in therapy for efgartigimod.
- 4.6 The PBAC previously considered the current treatment algorithm for AChR antibody-positive myasthenia gravis, based on international guidelines (Sanders 2016, updated in Narayanaswami 2021) (paragraph 4.6, ravulizumab PSD, July 2024 PBAC meeting), recommends the sequential use and optimisation of:
- Anti-cholinesterases (i.e. pyridostigmine).
  - Immunosuppressive therapy (required in the majority of patients), with corticosteroids as the main first-line treatment option. The guidelines state that other immunosuppressive agents may also be used as monotherapies (for patients who refuse corticosteroids or who are contraindicated to corticosteroids) or in combination with corticosteroids (for patients with an inadequate response, for patients with significant steroid side-effects or who require high corticosteroid doses that cannot be tapered down).
  - Chronic IVIg/PLEX can be used as (i) bridging therapies while patients adjust to slower-acting immunosuppressants; and/or (ii) for treatment-refractory disease (variable definitions in literature).

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- Patients with refractory disease can receive chronic IVIg/PLEX, eculizumab (not registered 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.
  - Thymectomy can be considered in small subset of patients, particularly younger patients.
- 4.7 Efgartigimod is a human IgG1 antibody fragment that binds to the neonatal FcRn and inhibits the recycling of IgG back into circulation. The inhibition of FcRn function is expected to reduce the levels of circulating IgG including pathogenic IgG autoantibodies. It is presumed that the therapeutic effects of efgartigimod are due to a reduction in IgG autoantibodies (which impair neuromuscular transmission), although the exact mechanism of action in generalised myasthenia gravis is currently unknown.
- 4.8 Based on the clinical algorithm previously considered by PBAC (as outlined in paragraph 4.6), the submission's proposed restriction would allow efgartigimod to be used at multiple, distinct places in therapy:
- As an alternative to optimised therapy in patients treated with an anticholinesterase and at least one immunosuppressive treatment (referred to as second-line therapy during the evaluation; optimisation of therapy could include type of immunosuppressant, dose titration as well as number of immunosuppressants).
  - As an alternative to IVIg/PLEX as bridging therapy until optimal dosing is achieved with slower-acting NS-ISTs.
  - As an alternative to chronic IVIg/PLEX in patients with treatment refractory disease.
  - As an alternative to rituximab and cyclophosphamide in patients who fail treatment with chronic IVIg/PLEX.
- 4.9 The evaluation considered that the clinical place in therapy for efgartigimod is currently unclear, particularly as the use of newer agents such as complement inhibitors (ravulizumab, zilucoplan) and FcRn blockers (efgartigimod, rozanolixizumab) have yet to be incorporated into most treatment guidelines.
- 4.10 As outlined in Section 7, the ESC recalled advice from the clinicians present at the gMG stakeholder meeting (May 2024) that the new gMG therapies should be available in both the bridging and refractory settings.

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

## 5 Comparator

- 5.1 The submission nominated chronic IVIg as the main comparator, with PLEX as a supplementary comparator. IVIg was nominated as the main comparator as it is more commonly used than PLEX, with PLEX available mostly in major metropolitan hospitals across Australia. The PBAC previously considered that chronic IVIg/PLEX is a relevant comparator in the treatment refractory setting (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).
- 5.2 The evaluation noted that the proposed restriction allows for earlier use in the second line setting, among patients who have only used one immunosuppressive therapy with additional treatment options using existing therapies. The PBAC previously considered that for non-refractory patients, the comparator should be optimisation of existing therapies (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).
- 5.3 As outlined in Section 7, the ESC reiterated the PBAC's previous advice that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost per patient of the newer gMG therapies in the refractory setting (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).
- 5.4 The submission identified multiple near-market comparators for the treatment of generalised myasthenia gravis including zilucoplan, ravulizumab and rozanolixizumab. The ESC and the PBAC 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.

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

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the mechanism of action of efgartigimod, the limitations of currently available treatments, and the clinical trial results including the rapid onset of action of efgartigimod.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (28), health care professionals (1 individual health care professional 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 also described a

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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 efgartigimod and its rapid onset of action.
- 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 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 be restricted to generalised MG 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 National Blood Authority (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.

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- c) The therapy should be co-administered with two other therapies with remission induction intent, including corticosteroids and NS-ISTs. This does include therapeutic thymectomy which should be treated as equivalent to an NS-IST. This does not include pyridostigmine or other cholinesterase inhibitors.
- d) Patients should either have had an adequate dose AND duration of these two other therapies, perhaps one year; OR be taking an adequate dose of these two other therapies without requiring a set duration AND have failed a loading course of IVIg or plasma exchange.
- e) Response to therapy should be assessed and the therapy only continued if there is a clear response, at least minimal clinically important differences (MCID) values of MG-ADL improvement by  $\geq 2$  points, MGC by  $\geq 3$  points. The timing of the test of response to therapy should be early (at 2-16 weeks).
- f) “FcRn inhibitors are naturally stopped after 4 (efgartigimod) to 6 (rozanolixizumab) weeks of therapy. These therapies can be restarted if the severity of MG worsens to the minimum commencement threshold. Note on second or subsequent cycles the starting severity score while at or above threshold might be better, the same or worse than the first cycle – the underlying MG severity can worsen over time in some patients. Over the course 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 submission was primarily based on one head-to-head randomised trial comparing efgartigimod to placebo in patients with generalised myasthenia gravis (ADAPT). Results from the open-label extension study (ADAPT+) were also presented during the evaluation as data from this study were used to inform the economic model and financial estimates of the submission.
- 6.7 The submission also presented a network meta-analysis comparing efgartigimod (ADAPT) with chronic IVIg (NCT02473952, published during the evaluation and

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referred to as Brill 2024; Wolfe 2002), ravulizumab (CHAMPION-MG), rozanolixizumab (MycarinG) and zilucoplan (RAISE) using placebo as a common reference arm.

6.8 The submission did not identify any trials that would allow for an indirect comparison of efgartigimod with chronic PLEX.

6.9 Details of the trials included in the submission are summarised in Table 2.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Efgartigimod studies</b>		
ADAPT (NCT03669588)	argenx BV (2020). A randomized, double-blind, placebo-controlled, multicenter phase 3 trial to evaluate the efficacy, safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalized muscle weakness. Howard et al (2021). Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Sacca et al (2023). Efgartigimod improved health-related quality of life in generalized myasthenia gravis: results from a randomized, double-blind, placebo-controlled, phase 3 study (ADAPT). Dewilde et al (2023). Association between Myasthenia Gravis–Activities of Daily Living (MG-ADL) and EQ-5D-5L utility values: the additional effect of efgartigimod on utilities. Bril et al (2023). Effect of efgartigimod on muscle group subdomains in participants with generalized myasthenia gravis: post hoc analyses of the phase 3 pivotal ADAPT study.	Internal study report  Lancet Neurology; 20:526-36  Journal of Neurology; 270:2096-2105  Advances in Therapy; 40:1818-1829  European Journal of Neurology; 31:e16098
ADAPT+ (NCT03770403)	argenx BV (2023). A long-term, single-arm, open-label, multicenter, phase 3 follow-on study of ARGX-113-1704 to evaluate the safety and tolerability of ARGX-113 in patients with myasthenia gravis having generalized muscle weakness. Howard et al (2024). Long-term safety, tolerability, and efficacy of efgartigimod (ADAPT+): interim results from a phase 3 open-label extension study in participants with generalized myasthenia gravis. Dewilde et al (2024). Post-hoc analyses from the ADAPT clinical study demonstrate aggregate sustained benefit of Efgartigimod in generalized myasthenia gravis.	Internal study report  Frontiers in Neurology; 14:1284444  Journal of the Neurological Sciences; 466:123264
<b>Chronic IVIg studies</b>		
Brill 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.	Muscle & Nerve; 1-12
Wolfe (2002)	Wolfe et al (2002). Myasthenia Gravis-IVIg Study Group. Randomised, controlled trial of intravenous immunoglobulin in myasthenia gravis.	Muscle & Nerve 26:549-552
<b>Ravulizumab studies</b>		
CHAMPION-MG (NCT03920293)	Vu et al (2022). Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. Vu et al (2023). Ravulizumab pharmacokinetics and pharmacodynamics in patients with generalized myasthenia gravis. Meisel et al (2023). Long-term efficacy and safety of ravulizumab in adults with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis: results from the phase 3 CHAMPION MG open-label extension.	New England Journal of Medicine Evidence 1(5) Journal of Neurology 270: 3129-3137 Journal of Neurology 270: 3862-3875

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Trial ID	Protocol title/ Publication title	Publication citation
<b>Rozanolixizumab studies</b>		
MycarinG (NCT03052751)	Bril et al (2023). Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study.	Lancet Neurology; 22(5):383-394
<b>Zilucoplan studies</b>		
RAISE (NCT03315130)	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.	Lancet: Neurology 22: 395-406
RAISE-XT (NCT04225871)	Weiss et al (2024). Improvement of fatigue in generalised myasthenia gravis with zilucoplan.	Journal of Neurology doi: 10.1007/s00415-024-12209-3

Source: Table A3.1, Section 2 Appendices of the submission

Note: Abstracts of studies with full publications are not presented

6.10 The key features of the ADAPT trial are summarised in Table 3.

**Table 3: Key features of the ADAPT trial**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ADAPT	167	MC, R, DB, PC, 26 weeks duration with an open-label extension	Unclear	Myasthenia gravis, with or without AChR antibodies, who have generalised mild-to-severe symptoms and functional impairments (MG ADL $\geq$ 5 with > 50% of the total score due to non-ocular symptoms) with stable background therapy	Primary: Based on AChR+ subgroup, proportion with MG-ADL response in the first treatment cycle <sup>a</sup>  Other outcomes: Change in MG-ADL, MGC and QMG, QMG responders; quality of life (EQ-5D-5L, MG-QoL15r)	Baseline characteristics, treatment response, patient-level MG-ADL scores over time, treatment discontinuation, health state utility values, adverse events

Source: Sections 2.4.1-2.4.3, pp55-74 of the submission

Abbreviations: AChR+, acetylcholine receptor antibody positive; DB, double-blind; MC, multicentre; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite score; MG-QoL15r, revised Myasthenia Gravis Quality of Life; PC, placebo-controlled; QMG, Quantitative Myasthenia Gravis score; R, randomised

<sup>a</sup> Response defined as  $\geq$ 2-point reduction in MG-ADL score compared to baseline for  $\geq$ 4 consecutive weeks

6.11 The risk of bias in the ADAPT trial was considered unclear due to an imbalance in discontinuation rates between arms (placebo 12%, efgartigimod 6%), primarily due to withdrawal of consent and sponsor decision. A similar imbalance was observed in the AChR antibody positive subgroup informing key primary and secondary outcomes of the trial (placebo 14%, efgartigimod 5%). The impact of this imbalance is unclear as sensitivity analyses were performed using missing-is-failure imputation, with no other methods for handling missing data.

6.12 The risk of bias in the ADAPT+ extension study was considered high given the uncontrolled, open-label study design. Additionally, a substantial proportion of patients (70%) discontinued prematurely primarily due to rollover to another extension study (43%) resulting in relatively few patients receiving more than 10 treatment cycles in the study (maximum of 19 planned treatment cycles).

6.13 The majority of trial participants were acetylcholine receptor antibody positive (77%) while the remainder were acetylcholine receptor antibody negative (23%). There was

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- an equal percentage (16%) of acetylcholine receptor antibody negative patients who tested positive for muscle-specific kinase (MuSK) antibodies in each treatment arm.
- 6.14 There was an imbalance in the proportion of patients who had previously undergone thymectomy in the efgartigimod arm (70%) compared to placebo (43%). The submission claimed the difference did not appear to have favoured efgartigimod based on a post hoc analysis of subgroups with or without prior thymectomy that showed a numerically lower proportion of patients with prior thymectomy achieving MG-ADL response compared to those without prior thymectomy. While this may be the case within the context of this trial, the evaluation considered it remained uncertain whether prior thymectomy is a treatment effect modifier given the lack of statistical comparisons and treatment-effect interaction testing.
- 6.15 At baseline, 52% of patients were on combination immunosuppressive therapy (corticosteroids and NS-ISTs), 24% were on corticosteroids only and 9.0% were on an NS-IST only. Very few patients (1%) were on no therapy and 14% were using anticholinesterase treatments only. The trial eligibility criteria required patients to be using stable doses of standard therapies but did not require patients to be on optimised therapy.
- 6.16 The primary outcome and key secondary outcomes were planned for the AChR antibody positive subgroup. Baseline characteristics were broadly similar to the overall population, with a similar imbalance observed for the proportion of participants with prior thymectomy (efgartigimod 69%, placebo 47%).
- 6.17 Treatment cycles in the ADAPT trial and ADAPT+ extension study included four, once weekly infusions of efgartigimod, which was consistent with the product information. All patients in the ADAPT trial received an initial treatment cycle. The administration of subsequent treatment cycles was dependent on patients meeting re-treatment criteria as per the trial protocol which specified the presence of significant symptoms based on MG-ADL scores as well as loss of response from the prior treatment cycle, which were more rigorous than recommended in the product information (which notes that subsequent treatment cycles should be administered according to clinical evaluation, with no objective measures required).
- 6.18 The initiation of subsequent treatment cycles in the ADAPT+ extension study (1 year in Part A, up to 2 years in Part B) required  $\geq 4$  weeks between treatment cycles. Re-treatment criteria in Part A of ADAPT+ were similar to the ADAPT trial but also required discontinuation from the study in patients with treatment failure for 3 consecutive treatment cycles. Re-treatment criteria in Part B of ADAPT+ appeared similar to the product information given it was subjective, based on investigator discretion only.
- 6.19 The evaluation considered the applicability of the efgartigimod trial evidence to the Australian PBS population is unclear given the proposed restriction includes MGC thresholds which may not be equivalent to MG-ADL eligibility criteria in the trial. Additionally, the ADAPT trial applied rigorous re-treatment criteria which may not be applicable to clinical practice.

**Comparative effectiveness**

**Efgartigimod versus placebo**

6.20 Responder analyses of functional outcomes are summarised in Table 4.

**Table 4: Responder analysis after the first treatment cycle in the ADAPT trial**

Outcome	AChR+ group			Overall population		
	Efgartigimod N=65	Placebo N=64	Odds ratio (95% CI)	Efgartigimod N=84	Placebo N=83	Odds ratio (95% CI)
<b>MG-ADL responders (2-point reduction for ≥ 4 consecutive weeks)</b>						
Proportion of responders, n (%)	44 (67.7)	19 (29.7)	<b>4.95</b> <b>(2.21, 11.53)</b>	57 (67.9)	31 (37.3)	<b>3.70</b> <b>(1.85, 7.58)</b>
<b>QMG responders (3-point reduction in QMG score for ≥ 4 consecutive weeks)</b>						
Proportion of QMG responders, n (%)	41 (63.1)	9 (14.1)	<b>10.84</b> <b>(4.18, 31.20)</b>	51 (60.7)	16 (19.3)	7.10 (3.24, 16.49)

Source: Table 19-21, pp90-91 and Table 14.2.2.1.2, p1402 of the ADAPT trial report

Abbreviations: AChR+, acetylcholine receptor antibody positive; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis

Note: MG-ADL scores range from 0 to 24 with lower scores indicating better functional outcomes. QMG scores range from 0 to 39 with lower scores indicating better functional outcomes

**Bold** indicates statistically significant results, adjusted for multiplicity

- 6.21 Treatment with efgartigimod was associated with a statistically significant increase in the proportion of AChR antibody positive patients achieving MG-ADL response. The treatment difference was also statistically significant in the overall population (combined AChR seropositive and AChR seronegative); however, the incremental effect was larger in the AChR antibody positive group (which had a lower placebo response). Subgroup analyses showed no difference in MG-ADL response rates between efgartigimod and placebo in the AChR seronegative group.
- 6.22 Statistically significantly greater proportions of patients treated with efgartigimod achieved QMG response. Similar treatment effects were observed for the exploratory analysis conducted in the overall population.
- 6.23 Responder analyses beyond the first treatment cycle in the trial (maximum of 3 treatment cycles) were exploratory. Re-treatment was permitted in patients with functional impairment (defined as MG-ADL ≥ 5 with > 50% of the total score due to non-ocular symptoms) and also loss of response (defined as less than a 2-point reduction in MG-ADL compared to baseline). Overall, the data were supportive of higher MG-ADL response rates in the efgartigimod arm compared to placebo in patients who received a second cycle.
- 6.24 The submission did not present any analyses of responders based on the Myasthenia Gravis Composite (MGC) instrument. This would have been informative given the submission proposed using the MGC score to assess response in the requested PBS restriction. The PSCR presented additional information from a poster presentation of the ADAPT trial showing that 69.2% of patients in the efgartigimod group achieved an MGC response (defined as a ≥3-point reduction) versus 39.1% in the placebo group (noting this was an exploratory outcome).

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- 6.25 Subgroup analyses suggested variation in MG-ADL response rates across subgroups defined by AChR antibody status, race, region, baseline MG-ADL category and total number of treatment cycles received in the trial. However, the apparent differences should be interpreted with caution given the small patient numbers in some of the subgroup analyses.
- 6.26 The ADAPT+ extension study assessed MG-ADL response at any time point during treatment cycles. More than 80% of patients in the AChR antibody positive group had a  $\geq 2$ -point reduction in MG-ADL score from each treatment cycle baseline in the first 16 treatment cycles (more than 90% in the first 10 treatment cycles).
- 6.27 The submission provided a post hoc analysis of pooled data from the ADAPT trial and ADAPT+ extension study, assessing long-term response to cyclical use of efgartigimod among patients who were AChR antibody positive (Dewilde 2024). The analysis included up to 64 weeks of data from the ADAPT trial baseline. Response over time was based on  $\geq 3$ -point reduction in MG-ADL or  $\geq 5$ -point reduction in QMG, at any point compared to the baseline value.
- 6.28 Table 5 presents the average percentage of time in response and the proportion of patients with response in the ADAPT/ADAPT+ studies (AChR+ subgroup).

**Table 5: Average percentage of time in response in the ADAPT/ADAPT+ studies in the AChR+ group**

	Percentage of time in response, %			Proportion of patients with response, %		
	Efgartigimod		Placebo	Efgartigimod		Placebo
	Week 0 to 20	Week 0 to 64	Week 0 to 20	Week 0 to 20	Week 0 to 64	Week 0 to 20
MG-ADL $\geq 3$ -point reduction	59%	57%	30%	55%	57%	29%
QMG $\geq 5$ -point reduction	44%	56%	13%	43%	47%	13%

Source: Table 3, Dewilde 2024 publication

Abbreviations: AChR+, acetylcholine receptor antibody positive; MG-ADL, Myasthenia Gravis Activities of Daily Living; QMG, Quantitative Myasthenia Gravis

Note: MG-ADL scores range from 0 to 24 with lower scores indicating better functional outcomes. QMG scores range from 0 to 39 with lower scores indicating better functional outcomes

- 6.29 Treatment with efgartigimod was associated with statistically significantly greater percentage of time in response compared to placebo during the ADAPT trial and extension.
- 6.30 Additional analyses were conducted based on the proportion of efgartigimod patients with response over the 64-week duration (5-point reduction in QMG ranging from 28% to 75% and 3-point reduction in MG-ADL ranging from 42% to 73%). The study authors stated that observed fluctuations in the proportion of patients responding to treatment over time was an artifact of trial design that resulted in cyclical use of efgartigimod with variable inter-treatment periods. The authors claimed that the strict re-treatment criteria in the ADAPT studies (as opposed to more flexible dosing) may have limited the maximal benefit of administering subsequent cycles of efgartigimod. The authors noted that a different study, ADAPT-NXT, assessed efgartigimod use in either fixed or continuous dosing with no re-treatment criteria (refer to paragraph 3.15). The status of this trial is currently unclear.

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6.31 Mean change in functional outcome measures from baseline to Week 4 in the first treatment cycle for efgartigimod and placebo in the AChR antibody positive group are summarised in Table 6.

**Table 6: Mean change in functional outcome measures from baseline to Week 4 (AChR+ subgroup)**

Treatment arm	Baseline, mean (SE)	Week 4, mean (SE)	LS mean change (95% CI)	Treatment difference (95% CI)
<b>Myasthenia Gravis Activities of Daily Living (MG-ADL) score</b>				
Efgartigimod, N = 65	9.0 (0.31)	4.4 (0.44)	-4.10 (-5.01, -3.20)	-2.84 (-3.81, -1.86)
Placebo, N = 64	8.6 (0.27)	6.7 (0.39)	-1.27 (-2.20, -0.34)	
<b>Quantitative Myasthenia Gravis (QMG) score</b>				
Efgartigimod, N = 65	16.0 (0.64)	9.7 (0.68)	-5.77 (-7.02, -4.51)	-5.23 (-6.63, -3.82)
Placebo, N = 64	15.2 (0.56)	14.5 (0.62)	-0.54 (-1.85, 0.77)	
<b>Myasthenia Gravis Composite (MGC) score</b>				
Efgartigimod, N = 65	18.6 (0.75)	9.2 (0.82)	-8.91 (-10.84, -6.99)	-6.04 (-8.18, -3.90)
Placebo, N = 64	18.1 (0.65)	14.8 (0.88)	-2.87 (-4.86, -0.88)	

Source: Table 2.15, p84 of the submission; Tables 14.2.1.9.1 and Table 14.2.1.9.2, pp458-490, Tables 14.2.1.13.1 and 14.2.1.13.2, pp1339-1342 of the ADAPT trial report ; Table 14.2.2.8.1, p1424, Table 14.2.2.8.2, p1449, Table 14.2.2.14.2, p2725, of the ADAPT trial report; Table 14.2.4.1.1, p2753, Table 14.2.4.1.2, p2764, Table 14.2.4.2.1, p2775, Table 14.2.4.2.2, p2777 of the ADAPT trial report

Abbreviations: AChR+, acetylcholine receptor antibody positive; CI, confidence interval; LS, least squares; SE, standard error

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

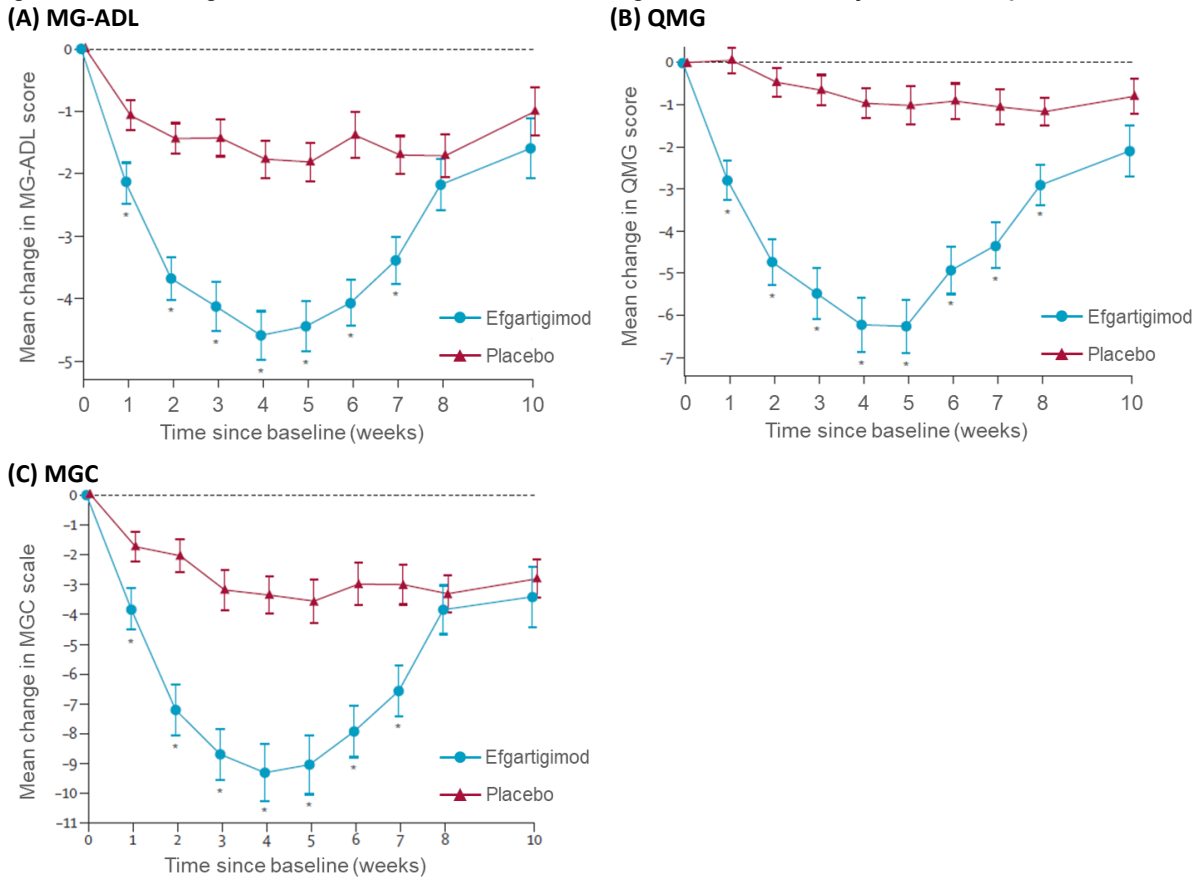
Note: QMG scores range from 0 to 39 with lower scores indicating better functional outcomes

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

6.32 Treatment with efgartigimod was associated with greater numerical improvements in functional outcomes compared to placebo from baseline to Week 4 after the first treatment cycle in the trial.

6.33 Figure 1 presents the change in functional outcome measures over time during the first treatment cycle and follow-up period in the AChR antibody positive subgroup.

Figure 1: Mean change in functional outcome measures during the first treatment cycle in AChR+ patients



Source: Figure 2.5, p83 of the submission

Abbreviations: AChR+, acetylcholine receptor antibody positive; MG-ADL, Myasthenic Gravis Activities of Daily Living; MGC, Myasthenic Gravis Composite; QMG, Quantitative Myasthenia Gravis

Note: Error bars show standard error and \* indicates p < 0.05

- 6.34 Treatment with efgartigimod was associated with rapid improvements in functional outcomes, with the maximum difference observed at Weeks 4 and 5 (after the last of four doses). The treatment difference was generally sustained up to Week 7-8 after which there was no observable difference between treatment arms. Similar patterns were observed based on MG-ADL and QMG scores in patients who were re-treated in the extension study. MGC outcomes were not assessed in the extension study.
- 6.35 The mean change in quality of life measures from baseline to Week 4 with efgartigimod and placebo in the AChR antibody positive subgroup are summarised in Table 7.

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Table 7: Mean change in quality of life scores from baseline to Week 4 with efgartigimod and placebo (AChR+)

Treatment arm	Baseline, mean (SE)	Week 4, mean (SE)	LS mean change (95% CI)	Treatment difference (95% CI)
<b>Revised Myasthenia Gravis Quality of Life score (MG-QoL15r)</b>				
Efgartigimod, N = 65	15.7 (0.78)	8.3 (0.82)	-7.21 (-8.80, -5.63)	-5.45 (-7.22, -3.69)
Placebo, N = 64	16.6 (0.68)	14.4 (0.78)	-1.76 (-3.38, -0.14)	
<b>EQ-5D-5L visual analogue scale</b>				
Efgartigimod, N = 65	58.2 (2.16)	74.4 (2.07)	NR	NR
Placebo, N = 64	56.7 (2.14)	60.6 (2.28)	NR	

Source: Table 14.2.3.1.1, p2727, Table 14.2.3.1.2, p2738, Table 14.2.3.2.1, p2749, Table 14.2.3.2.2, p2751, Table 14.2.5.2.1, p2860, Table 14.2.5.2.2, p2871 of the ADAPT trial report

Abbreviations: AChR+, acetylcholine receptor antibody positive; CI, confidence interval; LS, least squares; NR, not reported; SE, standard error

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

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

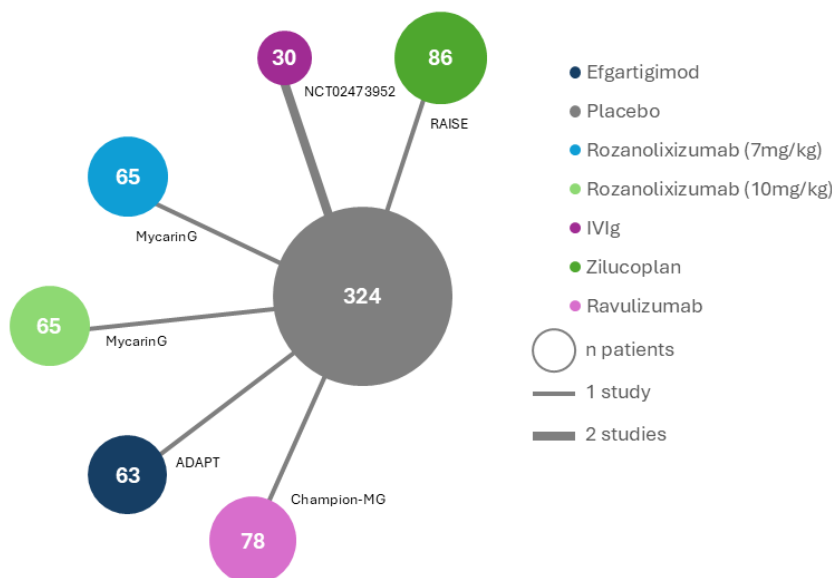
- 6.36 Treatment with efgartigimod was associated with a statistically significant improvement in Revised Myasthenia Gravis Quality of Life (MG-QoL15r) scores compared to placebo at Week 4 in the first treatment cycle. Analyses of change over time in MG-QoL15r scores showed that treatment with efgartigimod was associated with rapid improvements, with the maximum difference between treatment arms observed at Week 5. The treatment difference was sustained up to Week 8, after which there was no observable difference between treatment arms.
- 6.37 The trial report did not provide any statistical analysis of EQ-5D-5L data. However, EQ-5D-5L data from the ADAPT trial were used to inform an ad hoc analysis of the association between MG-ADL scores and change in EQ-5D utility scores over time in the economic model.
- 6.38 The submission did not provide any data on baseline corticosteroid use or changes in corticosteroid use over time from the ADAPT trial and extension. It is unclear whether efgartigimod is steroid-sparing as there are no comparative data on corticosteroid use with or without efgartigimod.
- 6.39 Exacerbations or myasthenic crisis events were not captured as efficacy outcomes in the ADAPT studies. Results from a post hoc analysis of hospitalisations and exacerbations during the ADAPT trial were supportive of numerically lower rates of all-cause hospitalisations and exacerbations in the efgartigimod arm compared to placebo. However, the results should be interpreted with caution given the uncontrolled nature of the analysis and limited reporting in the poster publications.
- 6.40 Treatment exposure data in the ADAPT trial and extension study were analysed based on a total cycle duration analysis (i.e. time from the first dose of the previous treatment cycle to the first dose of the subsequent treatment cycle). In the ADAPT trial, the median total cycle duration was approximately 10 weeks for the first two treatment cycles, with a median treatment-free interval of approximately 7 weeks. In the extension study, the median total cycle duration was approximately 10 weeks for the first treatment cycle, decreasing to 7 weeks by the thirteenth treatment cycle in Part B of the extension. This corresponded to a median treatment-free interval of 7

weeks between the first two treatment cycles decreasing to 4 weeks by the thirteenth treatment cycle.

**Network meta-analysis**

- 6.41 The submission presented a Bayesian network meta-analysis (NMA) comparing efgartigimod (ADAPT) with chronic IVIg (Bril 2024, Wolfe 2002), ravulizumab (CHAMPION-MG), rozanolixizumab (MycarinG) and zilucoplan (RAISE) using placebo as a common reference arm.
- 6.42 The transitivity between the IVIg, complement inhibitor and FcRn blocker trials was highly uncertain, with major differences in study designs and patient populations. In particular the FcRn blockers (efgartigimod, rozanolixizumab) are administered as cyclical therapies with on/off treatment periods with endpoints assessed at peak efficacy (4-6 weeks, at the end of a treatment cycle) which does not account for the treatment effects waning over time during the off-treatment period.
- 6.43 The inclusion of the Wolfe 2002 study was inadequately justified given concerns with the robustness of the trial that was prematurely terminated, had a very small sample size and presented results that indicated numerically inferior efficacy for IVIg versus placebo which appeared counter-intuitive to the broader evidence base supporting the use of IVIg in practice. Sensitivity analyses with the exclusion of the Wolfe 2002 study were considered more relevant and were presented as primary analyses during the evaluation.
- 6.44 The network diagram for MG-ADL and QMG assessments excluding the Wolfe 2002 study is presented in Figure 2.

**Figure 2: Network diagram for change in MG-ADL and QMG**



Source: Figures 5.7 and 5.8, Attachment CLN 2.1 of the submission

Note: There was only 1 study (Bril 2024, labelled as NCT02473952) informing the IVIg and placebo connection (not 2 studies as indicated by the thicker line)

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- 6.45 The network was sparsely populated with no connections between treatment arms. Global inconsistency analyses assessing the consistency of the direct and indirect evidence could not be performed due to the lack of independent closed loops in the network.
- 6.46 The submission noted that the Brill 2024 trial did not report change in MG-ADL outcomes. Therefore, the MG-ADL results were imputed based on the study’s QMG results at the same timepoint. The submission’s imputation approach appeared to be based on assumptions of surrogacy between the MG-ADL and QMG instruments. The surrogacy model assumes a linear relationship in both scales which was inadequately justified in the submission, particularly given the known floor and ceiling effects for MG-ADL scores. It may be more appropriate to conduct comparisons based on other outcomes such as change in MGC which was captured in Brill 2024.
- 6.47 The results of the fixed effects NMA for change in MG-ADL (excluding the Wolfe 2002 study) are presented in Figure 3.

Figure 3: Results of fixed effects NMA for change in MG-ADL (excluding the Wolfe 2002 study)

<b>Efgartigimod</b>						
-0.25 (-1.88, 1.45)	<b>Rozanolixizumab 10 mg/kg</b>					
-0.27 (-1.94, 1.44)	-0.02 (-1.39, 1.31)	<b>Rozanolixizumab 7mg/kg</b>				
-0.78 (-2.36, 0.84)	-0.54 (-2.39, 1.30)	-0.50 (-2.35, 1.35)	<b>Zilucoplan</b>			
-1.17 (-2.60, 0.25)	-0.93 (-2.63, 0.76)	-0.91 (-2.60, 0.83)	-0.39 (-2.02, 1.22)	<b>Ravulizumab</b>		
<b>-1.83 (-3.50, -0.13)</b>	-1.58 (-3.46, 0.34)	-1.55 (-3.46, 0.38)	-1.05 (-2.92, 0.83)	-0.65 (-2.38, 1.04)	<b>IVIg</b>	
<b>-2.86 (-3.84, -1.87)</b>	<b>-2.62 (-3.97, -1.29)</b>	<b>-2.60 (-3.95, -1.22)</b>	<b>-2.08 (-3.36, -0.83)</b>	<b>-1.69 (-2.74, -0.64)</b>	-1.04 (-2.41, 0.33)	<b>Placebo</b>

Source: Figure 5.1, Attachment CLN 2.1 of the submission

Abbreviations: IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living

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

Note: Results are presented as mean difference with 95% credible intervals. Mean differences less than zero favour the column-defined intervention compared to the row-defined intervention.

**Bolded results are statistically significant**

- 6.48 All treatments except for IVIg were associated with statistically significant reductions in MG ADL score compared to placebo. The results also indicated that efgartigimod was associated with a statistically significant improvement in MG-ADL compared to IVIg. There were no statistically significant differences between efgartigimod, rozanolixizumab, zilucoplan and ravulizumab; although the results numerically favoured efgartigimod, the differences were modest and may not be clinically important.
- 6.49 Any comparisons with IVIg should be interpreted with caution given the estimates were imputed in the submission and may not reflect actual estimates from the Brill 2024 trial.

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6.50 The results of the fixed effects NMA for change in QMG (excluding the Wolfe 2002 study) are presented in Figure 4.

Figure 4: Results of fixed effects NMA for change in QMG (excluding the Wolfe 2002 study)

<b>Efgartigimod</b>						
-0.48 (-2.90, 2.02)	<b>Rozanolixizumab 10 mg/kg</b>					
-1.73 (-4.20, 0.77)	-1.26 (-3.18, 0.61)	<b>Rozanolixizumab 7mg/kg</b>				
<b>-2.29</b> <b>(-4.50, -0.04)</b>	-1.82 (-4.27, 0.61)	-0.54 (-3.01, 1.89)	<b>Zilucoplan</b>			
<b>-3.33</b> <b>(-6.58, -0.05)</b>	-2.86 (-6.19, 0.55)	-1.61 (-5.03, 1.83)	-1.07 (-4.31, 2.55)	<b>IVIg</b>		
<b>-3.22</b> <b>(-5.24, -1.23)</b>	<b>-2.76</b> <b>(-5.02, -0.51)</b>	-1.51 (-3.75, 0.81)	-0.94 (-2.96, 1.05)	0.11 (-3.01, 3.22)	<b>Ravulizumab</b>	
<b>-5.22</b> <b>(-6.80, -3.60)</b>	<b>-4.74</b> <b>(-6.64, -2.89)</b>	<b>-3.49</b> <b>(-5.37, -1.58)</b>	<b>-2.93</b> <b>(-4.52, -1.37)</b>	-1.88 (-4.77, 0.95)	<b>-1.99</b> <b>(-3.27, -0.71)</b>	<b>Placebo</b>

Source: Figure 5.10, Attachment CLN 2.1 of the submission

Abbreviations: IVIg, intravenous immunoglobulin; QMG, Quantitative Myasthenia Gravis

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

Note: Results are presented as mean difference with 95% credible intervals. Mean differences less than zero favour the column-defined intervention compared to the row-defined intervention.

**Bolded results are statistically significant**

- 6.51 All treatments except for IVIg were associated with statistically significant reductions in QMG score compared to placebo. The result for IVIg versus placebo appeared consistent with direct evidence from the Brill 2024 study. The Brill 2024 study authors noted that it was a small study (N=62) which may not have been sufficiently powered to show a statistically significant difference.
- 6.52 The results also indicated that efgartigimod was associated with a statistically significant improvement in QMG score compared to zilucoplan, IVIg and ravulizumab, although the wide credible intervals cannot exclude the potential for smaller differences that may not be clinically important.
- 6.53 There were no statistically significant differences between efgartigimod and rozanolixizumab; although the results numerically favoured efgartigimod, the differences were modest and may not be clinically important.
- 6.54 Overall, the ESC and the PBAC considered that the results from the network meta-analyses should be interpreted with caution given various methodological concerns. In particular, there were differences between treatments administered with fixed dosing intervals (IVIg, ravulizumab, zilucoplan; endpoints assessed at 12-24 weeks) compared to treatments administered as on/off treatment cycles (efgartigimod, rozanolixizumab; endpoints assessed at 4-6 weeks, representing peak efficacy at the end of a treatment cycle) that do not account for the treatment effects waning over time during the off-treatment period. Comparisons between different classes of treatment were challenging due to these differences.

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- 6.55 In particular, for the comparison versus IVIg (based on Brill 2024), there were substantial differences between the placebo arms of the two trials, with the ADAPT trial reporting that 19.3% of patients in the placebo group achieved a QMG response ( $\geq 3$ -point reduction for  $\geq 4$  consecutive weeks) versus 59.4% in the placebo arm of Brill 2024 ( $\geq 3$ -point reduction at week 24).

**Published indirect comparisons**

- 6.56 During the evaluation, seven published network meta-analyses (Chen 2023, Gu 2024, Ma 2024, Sacca 2023, Smith 2024, Zhong 2024) and one matching adjusted indirect comparison that compared efgartigimod and ravulizumab (van Steen 2024) were identified. Indirect analyses published as abstracts or posters only were not included due to limited reporting. This resulted in the exclusion of the Wolfe 2023 (poster) network meta-analysis, included in the submission, that assessed the impact of efgartigimod, ravulizumab, rozanolixizumab and zilucoplan (based on the ADAPT, CHAMPION-MG, MycarinG and RAISE trials) on health-related quality of life (mean changes from baseline in EQ-5D VAS and MG-QOL15r). The Ma 2024 study was also excluded as the analysis did not include key trials for rozanolixizumab (MycarinG) and zilucoplan (RAISE).
- 6.57 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.
- 6.58 The ESC and the PBAC considered there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod alfa and rozanolixizumab). The ESC considered that the NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 6.59 None of the published indirect treatment comparisons included IVIg or PLEX trials.

**Comparative harms**

- 6.60 A summary of key adverse events reported during each treatment cycle and follow-up (8 weeks each) in the ADAPT trial AChR antibody positive group and overall population are presented for the first treatment cycle (Table 8) and second treatment cycle (Table 9) below.

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**Table 8: Summary of key adverse events during the first treatment cycle and follow-up (8 weeks)**

	AChR+ group				Overall population			
	Efgartigimod N = 65		Placebo N = 64		Efgartigimod N = 84		Placebo N = 83	
	Events	Events/ patient-yr	Events	Events/ patient-yr	Events	Events/ patient-yr	Events	Events/ patient-yr
Any AE	128	7.89	141	8.08	182	8.39	191	8.54
Treatment-related AE	38	2.34	29	1.66	52	2.40	41	1.83
Serious AE	1	0.06	6	0.34	2	0.09	7	0.31
AE leading to treatment discontinuation	1	0.06	3	0.17	6	0.28	3	0.13
Deaths	0	0	0	0	0	0	0	0
<b>Adverse events of special interest</b>								
Infections	27	1.66	19	1.09	34	1.57	25	1.12

Source: Table 14.3.1.1.1, p4232 of the ADAPT trial report

Abbreviations: AChR+, acetylcholine receptor antibody positive; AE, adverse event; yr, year

**Table 9: Summary of key adverse events during the second treatment cycle and follow-up (8 weeks)**

	AChR+ group				Overall population			
	Efgartigimod N = 51		Placebo N = 43		Efgartigimod N = 63		Placebo N = 57	
	Events	Events/ patient-yr	Events	Events/ patient-yr	Events	Events/ patient-yr	Events	Events/ patient-yr
Any AE	49	4.95	54	6.01	62	5.04	76	6.45
Treatment-related AE	10	1.01	7	0.78	11	0.89	11	0.93
Serious adverse event	2	0.20	3	0.33	2	0.16	3	0.25
AE leading to treatment discontinuation	1	0.10	0	0	1	0.08	0	0
Deaths	0	0	0	0	0	0	0	0
<b>Adverse event of special interest</b>								
Infections	16	1.62	10	1.11	22	1.79	16	1.36

Source: Table 14.3.1.1.2, p4237 of the ADAPT trial report

Abbreviations: AChR+, acetylcholine receptor antibody positive; AE, adverse event; yr, year

- 6.61 The most frequently reported adverse events ( $\geq 10\%$  of patients) in either treatment group of the overall population were headache, nasopharyngitis, upper respiratory tract infection, nausea and diarrhoea.
- 6.62 In particular, ESC noted that treatment with efgartigimod was associated with a higher rate of treatment-related adverse events compared to placebo during the first treatment cycle, with similar numbers of events between arms during the second treatment cycle. For adverse events of special interest, efgartigimod was associated with a higher rate of infections (most commonly upper respiratory infections, urinary tract infections and bronchitis) compared to placebo. One serious event of thrombocytosis was considered possibly related to efgartigimod. No deaths were reported during the trial.
- 6.63 Overall, the frequency of adverse events was greater during the first treatment cycle compared to the second treatment cycle. The rate of adverse events in the AChR antibody positive group appeared similar to the overall population.

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- 6.64 There was no apparent association between the development of antibodies and observed clinical outcomes during the trial period.
- 6.65 Data from the ADAPT+ extension study (mean duration of follow-up 1.6 years) indicated declining adverse event rates with each treatment cycle. The most frequently reported adverse events were headache, nasopharyngitis and COVID-19. Adverse events leading to treatment discontinuation occurred in 8.3% of patients. One serious adverse event of infusion-related reaction was considered probably related to efgartigimod. Five deaths were reported during the study, and none were considered related to efgartigimod. No new immunogenicity signals were identified.
- 6.66 The submission provided additional data from the Periodic Benefit-Risk Evaluation Report (PBRER; 17 December 2023 to 16 June 2024). The only important identified risk of efgartigimod is hypersensitivity reactions and infusion-related reactions. Important potential risks include serious infections and malignancies. Missing information includes use during pregnancy and lactation, use with live/attenuated vaccines, use with monoclonal antibodies, use in renal impairment, long-term safety of efgartigimod treatment and use in immunocompromised patients. One new potential signal of pulmonary mass was identified during the reporting period and was undergoing evaluation at the time of reporting.
- 6.67 During the reporting interval, the sponsor received reports of inappropriate dosing of efgartigimod, given every 2 weeks and was commonly referred to as ‘2 weeks on, 2 weeks off’ and an ‘every-other-week’ schedule. It was noted that the physicians’ intention behind this deviation from the approved dosing regimen (once weekly for 4 weeks with a minimum 4-week gap) is to accommodate patients’ needs by providing an evenly distributed dosing and to reduce the treatment-free period between treatment cycles for patients with generalised myasthenia gravis. The PBRER stated that other dosing regimens (weekly and every 2 weeks) are being evaluated in clinical studies and the analysis of these cases has not shown any safety concerns.
- 6.68 For IVIg, the submission presented an overview of adverse events reported in the Brill 2024 trial and Wolfe 2002 study. The submission stated that limited safety data were captured in the Wolfe 2002 study which was prematurely terminated and had a very small sample size. The submission noted that few serious adverse events occurred during the Brill 2024 trial but there was a lack of detailed information available to determine whether the events were treatment-related or not.

***Benefits/harms***

- 6.69 As outlined in paragraph 6.71, the ESC considered the evidence did not support the claim of superior efficacy versus chronic IVIg or PLEX, thus benefits and harms statements have not been presented.

**Clinical claim**

- 6.70 The submission claimed that despite the limited evidence base available for chronic IVIg, efgartigimod administered over 3 treatment cycles is superior in terms of efficacy and non-inferior in terms of safety compared to chronic IVIg.
- 6.71 While the results of the submission's network meta-analysis indicated that efgartigimod was associated with a statistically significant improvement in QMG score compared to IVIg, the ESC considered the analysis was not reliable as: it did not account for the treatment effects of efgartigimod waning over time during the off-treatment period; there were substantial other transitivity issues including differences in study designs and patient populations (including large difference between outcomes in the placebo arms of the Brill 2024 and ADAPT trials in terms of QMG response); and there were limitations with the IVIg evidence informing the analysis. In particular, only 54.8% of patients in Brill 2024 were on an NS-IST at baseline. Subgroup analyses suggested that IVIg may be associated with a greater incremental treatment effect in patients on an NS-IST at baseline (in the subgroup of patients on an NS-IST at baseline the average change from baseline in QMG score at Week 24 was -5.1 in the IVIg arm and -1.7 in the placebo arm; while in the overall study population the average change was -5.1 and -3.1 in the IVIg and placebo arms, respectively). Overall, the ESC and the PBAC acknowledged the limitations of the available evidence for chronic IVIg but considered the claim that efgartigimod is superior in terms of efficacy compared to chronic IVIg was not adequately supported.
- 6.72 The pre-PBAC response stated that the "weak evidence base for human blood products and strong evidence for efgartigimod indicates that there is a superior clinical benefit for efgartigimod" and stated that the sponsor does "not and cannot agree with a cost-minimisation approach (vs. IVIg)".
- 6.73 No clinical claim was made against PLEX.
- 6.74 The submission described efgartigimod as potentially superior in terms of efficacy compared to its near market comparators (zilucoplan, ravulizumab, rozanolixizumab). No clinical claim was made in terms of safety. The ESC and the PBAC considered that the claim of superior efficacy versus zilucoplan, ravulizumab and rozanolixizumab was not adequately supported due to the substantial limitations of the indirect comparison and poor transitivity between the included trials in terms of study duration, disease characteristics and baseline therapies. In particular, the ESC noted the lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 6.75 The evaluation considered that the following issues should be considered:
- There are no comparative data beyond two cycles of treatment in the 26-week ADAPT trial. Longer-term data from the extension study suggest that a reduction in symptoms can be maintained while patients are on therapy, but the gap between treatment cycles reduces over time.

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- The applicability of the efgartigimod trial evidence to the Australian PBS population is unclear given potential differences in baseline functional impairment and measures of response based on MGC thresholds.
- Longer term data from the extension study indicated maintenance of treatment effect in subsequent treatment cycles, however, this was associated with decreasing treatment-free intervals over time (to a minimum of 4 weeks). There are limited data regarding the circumstances of use of efgartigimod in clinical practice and available data indicate a direct relationship between time on treatment and maintenance of treatment effect.
- There are limited long-term safety data beyond a mean follow-up of 1.6 years in the extension study, with 70% of patients discontinuing prematurely, mainly due to roll-over to another observational study (43%).

6.76 The PBAC considered that, while the submission’s network meta-analysis indicated that efgartigimod was associated with a statistically significant improvement in QMG score compared to IVIg, this analysis was unreliable as it did not account for the treatment effects of efgartigimod waning over time during the off-treatment period. Overall, based on the totality of the evidence presented across the four submissions for new gMG therapies, the PBAC considered that efgartigimod has non-inferior comparative effectiveness and safety versus chronic IVIg and also against ravulizumab, rozanolixizumab and zilucoplan.

***Economic analysis***

6.77 The submission presented a stepped economic evaluation of efgartigimod in combination with standard therapy compared to chronic IVIg in combination with standard therapy for the treatment of AChR antibody positive generalised myasthenia gravis who remain symptomatic despite standard therapy. The economic evaluation was based on a placebo-controlled trial (ADAPT) and extension study with additional modelled data. The economic evaluation was presented as a cost-utility analysis.

6.78 Key components of the economic evaluations are summarised in Table 10.

**Table 10: Summary of model structure, key inputs and rationale**

<b>Component</b>	<b>Summary</b>
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years
Time horizon	Lifetime horizon (33 years)
Methods used to generate results	Markov cohort state transition model with tunnel states
Treatments	Efgartigimod and chronic IVIg in combination with standard therapy (consisting of anticholinesterases, corticosteroids and other non-steroidal immunosuppressive therapies). Patients who discontinue therapy (non-response or other reasons) were assumed to remain on standard therapy alone.
Health states	6 health states: MG-ADL < 5, MG-ADL 5-7, MG-ADL 8-9, MG-ADL ≥10, myasthenic crisis, death.
Cycle length	4 weeks with half-cycle correction
Patient characteristics	Age was assumed based on published estimates. Sex, mean weight, distribution across weight categories, baseline distribution across MG-ADL score categories, the proportion of patients on corticosteroids and distribution of use across doses of corticosteroids were based on data from the combined treatment arms of the ADAPT trial.

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Component	Summary
Circumstances of use	<p>The model assumed that all patients would be fully adherent to standard therapy (consisting of anticholinesterases, corticosteroids and other non-steroidal immunosuppressive agents).</p> <p>The model assumed that patients treated with efgartigimod would be fully adherent in each cycle of therapy (i.e. all patients received 4 infusions at the recommended dose). The submission modelled cyclical use of efgartigimod based on the assumption that patients in the MG-ADL &lt; 5 health state would not receive treatment, as well as a minimum 4-week gap between treatment cycles.</p> <p>The submission assumed that patients who remained on IVIg treatment in the MG-ADL &lt; 5 health state would not receive IVIg therapy while patients in MG-ADL ≥5 health states would receive ongoing therapy.</p> <p>Patients who discontinued efgartigimod or IVIg were assumed to receive standard therapies (anticholinesterase, corticosteroids and non-steroidal immunosuppressants) as per baseline use in the ADAPT trial.</p>
Transition probabilities	<p>Efgartigimod response and non-response rates were based on patient-level ADAPT trial data, applied once at the start of the model. Patients who were non-responders were assumed to discontinue treatment permanently. A constant treatment discontinuation rate was also applied to efgartigimod responders based on ADAPT trial data.</p> <p>A one-off treatment discontinuation rate was applied to patients on chronic IVIg based on adverse event data from the Wolfe 2002 study. All other patients were assumed to continue treatment.</p> <p>Efgartigimod responders were attributed separate transition probabilities between the MG-ADL health states depending on the model cycle (first and subsequent), treatment status (on- or off-treatment tracked based on time from entry into tunnel states) and disease status (MG-ADL &lt; 5 or ≥ 5). The transition probabilities were derived using patient-level ADAPT trial and ADAPT+ extension study data.</p> <p>Patients on chronic IVIg were attributed separate transition probabilities between the MG-ADL health states depending on the model cycle (first and subsequent). Transition probabilities for the first model cycle were synthesised using the inverse of comparative treatment effects between efgartigimod and IVIg from the submission’s indirect comparison, applied to data from the efgartigimod arm of the ADAPT trial. In subsequent cycles, patients were assumed to remain in the same health state unless they developed myasthenic crisis or died.</p> <p>Patients who permanently discontinued efgartigimod or chronic IVIg were assumed to receive standard therapies only. Separate transition probabilities were applied for the first 5 model cycles based on the placebo arm of the ADAPT trial. In subsequent cycles, patients were assumed to remain in the same health state unless they developed myasthenic crisis or died.</p> <p>Transition probabilities to the myasthenic crisis health state were based on published estimates (Ramos-Fransi 2015). Following myasthenic crises, it was assumed that patients would revert to the baseline distribution across MG-ADL health states.</p> <p>The risk of exacerbations was based on estimates obtained from the CADTH review of eculizumab for myasthenia gravis and assumptions.</p> <p>The distribution of low- and high-dose corticosteroid use was based on the ADAPT trial and assumptions.</p> <p>The incidence of adverse events for efgartigimod and chronic IVIg were based on the ADAPT trial efgartigimod and placebo arms, respectively. Adverse events were assumed to occur only during cycles of treatment.</p> <p>Transition probabilities for general mortality were based on Australian life tables.</p> <p>Hazard ratios for increased mortality associated with low- and high-dose corticosteroid use were based on published estimates from multiple studies (Ajegnova 2013, Mebrahtu 2019, Wilson 2017, Movahedi 2016, Schols 2001).</p>

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Component	Summary
	The probability of myasthenic crisis-related death were based on published estimates from multiple studies (Neumann 2020, Alsheklee 2009, Mandawat 2010, Liu 2019, Liu 2017, Spillane 2014, Soleimani 2004).
Utility values	<p>MG-ADL health state utility values were estimated using a regression model derived from an <i>ad hoc</i> analysis of ADAPT trial data (unpublished).</p> <p>The myasthenic crisis health state utility value was assumed based on the modelled utility value for the MG-ADL <math>\geq 10</math> health state.</p> <p>The exacerbation disutility value was based on published estimates from multiple studies.</p> <p>Corticosteroid-related disutility values were based on published estimates from two studies (Bexelius 2013, Sullivan 2017).</p> <p>Adverse event disutility values were derived from a catalogue of EQ-5D index scores for ICD-9 and CCC conditions (Sullivan 2011).</p>
Costs	<p>Drug costs were based on proposed or current PBS items, published information from the National Blood Authority and dosing information from various published sources. Administration costs were based on hospital costs for non-admitted services.</p> <p>Disease monitoring costs were based on MBS items, hospital costs for non-admitted services, data from a sponsor-commissioned study and expert opinion.</p> <p>Costs associated with exacerbations and myasthenic crises were calculated assuming all patients are hospitalised. The cost of exacerbations was based on AR-DRG B07B and length of stay based on multiple published studies; estimated using the NWAU 2024-25 calculator. The cost of myasthenic crises was based on AR-DRG B42A; estimated using the NWAU 2024-25 calculator.</p> <p>Corticosteroid-related complication costs were estimated for low- and high-dose corticosteroid use using published data (Bexelius 2013, Voorham 2018).</p> <p>Adverse event costs were based on various AR-DRG items (D63A, D43A, F60A, C62A, I66A, B77A) assuming same day admissions using the NWAU 2024-25 calculator.</p> <p>Terminal care costs were based on the published cost of health services in the last year of life (AIHW 2022).</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel 365

Source: Section 3, pp105-157 of the submission

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Groups; CCC, Clinical Classification Categories; ICD-9, International Classification of Diseases, Ninth Revision; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; NWAU, National Weighted Activity Unit

6.79 All patients entered the model distributed across the MG-ADL 5-7, MG-ADL 8-9 and MG-ADL  $\geq 10$  health states. A one-off discontinuation due to non-response was applied to efgartigimod at the start of the model, separating the responder from the non-responder cohort. A constant discontinuation rate was also applied to patients remaining on efgartigimod treatment over the model duration. A one-off discontinuation due to adverse events was also applied to patients in the chronic IVIg arm, applied in the second model cycle with no other discontinuations occurring throughout the model.

6.80 Patients who remained on efgartigimod could then transition to other MG-ADL health states, develop myasthenic crisis or die during each 4-week cycle. In the first model cycle, patients on chronic IVIg could transition to other MG-ADL health states, develop

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- myasthenic crisis or die but in subsequent cycles they were assumed to remain in the same health state unless they developed myasthenic crisis or died.
- 6.81 Patients who discontinued treatment for any reason during the first 5 model cycles could transition to other MG-ADL health states, develop myasthenic crisis or die. In subsequent cycles, patients who discontinued treatment were assumed to remain in the same health state unless they developed myasthenic crisis or died.
  - 6.82 Patients who experienced myasthenic crisis were assumed to remain in that state for one cycle, after which they transitioned to the MG-ADL 5-7, MG-ADL 8-9 or MG-ADL  $\geq 10$  health states (based on the baseline distribution across these categories) or died.
  - 6.83 The model structure assumed that patients would not re-initiate efgartigimod or chronic IVIg therapy after discontinuation.
  - 6.84 The submission did not adequately justify the assumed age of 60 years which differed to the average age of 47 years in the AChR antibody positive subgroup in the trial. The evaluation and the ESC considered that this approach was inappropriate given the known relationship of age with other characteristics including sex distribution and weight. In addition, utility estimates in the model were derived from the younger trial population that are unlikely to be representative of the assumed age of the modelled population. The PSCR argued that the assumed age of 60 years reflected the reported average age of patients with myasthenia gravis (63 years) and noted that sensitivity analyses assuming an age of 47 years resulted in a lower ICER/QALY.
  - 6.85 The submission did not adequately address the impact of potential differences in baseline functional impairment between the trial and PBS population including the assumed equivalence of an MG-ADL threshold of  $\geq 5$  (with at least 50% of the total score due to non-ocular symptoms) and an MGC threshold of  $\geq 10$ . Prior treatment criteria in the proposed restriction and trial were broad and it was unclear whether the utilisation of these treatments in the trial would be applicable to the proposed PBS population.
  - 6.86 Key drivers of the economic model are summarised in Table 11.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	The submission nominated a 33-year time horizon for the economic analysis, reflecting a lifetime horizon for the modelled population with an assumed baseline age of 60 years. The submission noted that other published models in myasthenia gravis have used time horizons ranging from 2 years to lifetime. A shorter time horizon may be appropriate given the high degree of uncertainty associated with long-term treatment effects. The ESC considered that a ten-year time horizon may be more appropriate given the uncertain long-term extrapolations e.g. due to the lack of long-term data around outcomes and treatment/remission durations.	High, favours efgartigimod

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Description	Method/Value	Impact
Model structure	<p>The model structure in the submission was most similar to the efgartigimod CADTH model.</p> <p>While there are no established MG-ADL thresholds to define levels of disease activity, the submission claimed that expert opinion supports the use of MG-ADL &lt;5 as a state of controlled disease. The submission also claimed that the MG-ADL categories of 5-7, 8-9 and ≥10 were consistent with subgroup analysis conducted for the ADAPT trial, and that a clustering analysis was used to identify appropriate categorical groupings based on MG-ADL score and health-related quality of life (EQ-5D and MG-QoL15). These claims could not be verified as the analysis was not provided in the submission. The submission noted that there was data sparseness among the subgroup with MG-ADL ≥10, which limited the ability to provide further granularity.</p> <p>The model included tunnel states in the efgartigimod arm (tracking time from entry into MG-ADL health states) in order to implement cyclical use of efgartigimod. The use of tunnel states to implement treatment costs (dependent on both treatment and disease status) was complex and difficult to track using the submission's model structure. The evaluation stated that a microsimulation may have been more informative as it would have greater ability to track these changes over time. However, the ESC considered the limited available data would make such an approach problematic and considered that a simplified model structure with fewer health states may be more suitable (e.g. use of 'response' and 'non-response' health states).</p>	Unclear, favours efgartigimod
Transition probabilities	<p>The derivation and implementation of the transition probabilities were complex and difficult to trace or validate due to poor labelling and inadequate description in the submission. The approach hindered the ability to validate the modelled transitions against trial-based outcomes and test alternative assumptions in sensitivity analyses.</p> <p>Model outputs at 6 months (coinciding with the maximum duration of the ADAPT trial) show more than 50% of patients in the efgartigimod arm were in the MG-ADL &lt; 5 health state while the ADAPT+ extension study indicated that less than 1% of patients were in this MG-ADL category at baseline of the extension study.</p> <p>The sponsor claimed that it was challenging to produce trial data that would directly mimic the modelled approach given the way in which the health state transition probabilities were derived.</p>	High, favours efgartigimod

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Description	Method/Value	Impact
Circumstances of use for efgartigimod (including discontinuation assumptions)	<p>The submission assumed a one-off discontinuation (18.5%) in patients who do not achieve response to efgartigimod after 2 treatment cycles, based on MG-ADL response in the trial. Trial-based definitions of response were inconsistent with continuation criteria in the proposed restriction.</p> <p>A constant discontinuation rate for efgartigimod was assumed based on an ad hoc analysis based on pooled ADAPT trial and extension data, extrapolated over the model duration. The validity of the ad hoc analysis could not be determined due to insufficient information in the sources provided. The ESC considered that the premature discontinuation rates in ADAPT were high (70%) and may not be applicable to clinical practice, as a substantial proportion (43%) of patients discontinued prematurely due to rollover to another extension study.</p> <p>The assumption that patients treated with efgartigimod would be fully adherent in each cycle of therapy was inconsistent with trial data indicating imperfect compliance.</p> <p>The submission modelled cyclical use of efgartigimod based on the assumption that patients in the MG-ADL &lt; 5 health state would not receive treatment, with a minimum 4-week gap between treatment cycles. This appeared inconsistent with the proposed continuing (requires yearly demonstration of continued response; without functional impairment criteria) and re-initiating (requires demonstration of functional impairment based on MG-ADL ≥5 with &gt;50% of the score due to non-ocular symptoms OR MGC score ≥10) restrictions.</p> <p>Patients who discontinued efgartigimod were assumed to receive standard therapies (anticholinesterase, corticosteroids and non-steroidal immunosuppressants) as per baseline use in the ADAPT trial. The evaluation and the ESC considered that the assumption that patients would be using standard therapies without treatment escalation or use of other therapies such as rituximab or IVIg/PLEX was clinically implausible.</p>	High, favours efgartigimod
Circumstances of use for chronic IVIg	<p>The submission assumed a one-off treatment discontinuation of 33% due to adverse events for patients on IVIg and no further discontinuations. The evaluation and the ESC considered that the use of this estimate was inappropriate given concerns with the robustness of the analysis in the source publication. The submission did not adequately justify limiting treatment discontinuations to adverse events alone, which is unlikely to be applicable to clinical practice.</p> <p>The submission assumed that patients who remained on IVIg treatment in the MG-ADL &lt; 5 health state would not receive IVIg therapy while patients in MG-ADL ≥5 health states would receive ongoing therapy. The submission acknowledged that the assumed discontinuation of treatment in patients with MG-ADL &lt; 5 was inconsistent with market research that indicated that patients would remain on IVIg treatment consistently. The assumed use of IVIg 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. The assumption that patients who continue to have significant symptoms would remain on treatment without any clinical benefit was implausible.</p> <p>Patients who discontinued chronic IVIg were assumed to receive standard therapies (anticholinesterase, corticosteroids and non-steroidal immunosuppressants) as per baseline use in the ADAPT trial. The assumption that patients would be using standard therapies without treatment escalation or use of other therapies such as rituximab or PLEX was clinically implausible.</p>	High, favours efgartigimod

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Description	Method/Value	Impact
Chronic IVIg treatment effects	<p>The submission synthesised the transition probabilities for chronic IVIg (in the first model cycle only) based on the inverse of the estimated treatment difference between efgartigimod and IVIg from the indirect comparison, applied to patient-level MG-ADL scores in patients in the efgartigimod arm who received the first treatment cycle in the ADAPT trial. The analysis could not be validated during the evaluation due to inadequate documentation. The comparative efficacy of efgartigimod versus IVIg is uncertain given methodological concerns with the indirect comparison.</p> <p>In subsequent model cycles, the submission assumed that patients on chronic IVIg would remain in the same health state unless they developed myasthenic crisis or died. The assumption that patients who continue to have significant symptoms would remain on chronic IVIg indefinitely without any clinical benefit was not plausible and inconsistent with the National Blood Authority treatment criteria.</p>	High, favours efgartigimod
MG-ADL health state utility values	<p>The submission estimated MG-ADL health state utility values based on an <i>ad hoc</i> analysis of ADAPT trial data, assessing the relationship between MG-ADL score categories (&lt; 5, 5-7, 8-9 and ≥10) and EQ-5D-5L utility values. The submission valued the EQ-5D-5L health states based on an Australian utility study (Norman 2023). The validity of this approach could not be determined due to inadequate documentation in the submission.</p> <p>A mixed model with fixed and random effects was used with the intercept representing the utility value for MG-ADL &lt; 5 and coefficients for MG-ADL 5-7, MG-ADL 8-9, MG-ADL ≥10 and treatment allocation (placebo). The submission claimed the statistical significance of the placebo coefficient supports the use of treatment-specific utility values as MG-ADL scores are not fully capturing treatment benefits associated with efgartigimod. The submission claimed that a published <i>post hoc</i> analysis of MG-ADL scores and EQ-5D-5L utility values in the ADAPT trial (Dewilde 2023) was supportive of the included MG-ADL and treatment coefficients. The Dewilde 2023 study authors noted limitations with the study including substantial variation in the change estimate and that patients with the same total MG-ADL score may have very different clinical profiles. The study authors also noted that the regression model assumed that any unit improvement in an MG-ADL item has the same utility impact, which may not be reasonable.</p> <p>While it may be reasonable to assume additional utility benefits not captured through the MG-ADL score, the modelled magnitude of benefit associated with efgartigimod treatment was large (0.1291 utility gain) in addition to MG-ADL improvements and other quality of life benefits associated with reduced corticosteroid use, exacerbations and myasthenic crises. The ESC considered the magnitude of this additional utility benefit appeared implausible.</p> <p>The submission assumed that utility values based on the placebo arm of the trial could be used as a proxy for patients on chronic IVIg. This assumption was inadequately justified given the lack of direct comparative data against chronic IVIg and favoured efgartigimod given the use of treatment-specific utility values.</p> <p>Patients who discontinued efgartigimod or chronic IVIg were attributed utility values for standard therapy alone. No justification was provided for the assumption that patients who failed efgartigimod or chronic IVIg who have MG-ADL &lt; 5 would have the same utility as patients on efgartigimod. This assumption favoured efgartigimod given the accumulating proportion of patients who discontinued efgartigimod but remained in the MG-ADL &lt; 5 health state over time.</p> <p>The submission did not address the appropriateness of using EQ-5D-5L utility values from the trial population with a mean age of 47 years to the modelled population aged 60 years at baseline to 93 years at the end of the model.</p>	High, favours efgartigimod

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Description	Method/Value	Impact
Exacerbations	<p>The submission estimated the underlying risk of exacerbations based on estimates obtained from the CADTH review of eculizumab for myasthenia gravis. The use of external data was inadequately justified given the availability of potentially relevant data from the ADAPT trial.</p> <p>The submission claimed that the economic model only incorporated exacerbations that required hospitalisation as non-hospitalised events are expected to have minimal impact on costs and quality of life. This was inconsistent with the use of exacerbation rates from the REGAIN trial that included non-hospitalised events. A published analysis of exacerbations in the REGAIN trial indicated a total of 27 exacerbation events in the placebo arm, of which 24 events required rescue therapy, and 18 events required hospitalisation.</p> <p>Modelled reductions in exacerbations led to reduced costs associated with managing exacerbations (based on hospitalisation costs) and reduced QALY losses due to exacerbation events (based on an event disutility that was poorly justified). There are no data supporting reductions in exacerbations in patients treated with efgartigimod compared to chronic IVIg.</p>	Moderate, favours efgartigimod
Corticosteroid use	<p>The submission claimed that efgartigimod use is associated with reductions in corticosteroid use based on an observational study of US claims data (Kassardjian poster, no date). The results should be interpreted with caution due to limited reporting.</p> <p>The submission claimed that prednisolone 10 mg daily was considered a high dose based on Australian expert opinion. The proposed high dose threshold is at the lower end of recommended doses in published guidelines for myasthenia gravis (Sanders 2016) and was also lower than the mean daily dose of 21.26 mg based on the ad hoc subgroup analysis of patients on <math>\geq 10</math> mg per day of prednisolone in the trial.</p> <p>To model the benefit of reduced corticosteroid use associated with efgartigimod, the submission assumed only low-dose corticosteroid use among patients with MG-ADL &lt; 5, and the majority of patients on corticosteroids who have MG-ADL <math>\geq 5</math> would be on high-dose corticosteroids. The modelled difference in corticosteroid use favoured efgartigimod given greater time spent with MG-ADL &lt; 5 compared to chronic IVIg, which led to reduced costs associated with corticosteroid-related complications, improved life expectancy and reduced QALY losses due to corticosteroid use.</p> <p>The modelled benefits were poorly justified in the submission given no data were provided to support the assumed relationship between MG-ADL scores and corticosteroid doses. Additionally, there are no data to support reductions in corticosteroid use with efgartigimod compared to chronic IVIg.</p>	High, favours efgartigimod
Mortality	<p>The submission assumed that treatment with efgartigimod would be associated with mortality benefits due to reduced incidence of myasthenic crises and reduced use of low- and high-dose corticosteroids. There are no available data supporting the assumed reductions in myasthenic crises and steroid-sparing effects of efgartigimod as well as mortality benefits compared to chronic IVIg.</p>	Low, favours efgartigimod <sup>a</sup>

Source: Constructed during the evaluation

<sup>a</sup> Mortality associated with the myasthenic crises health state had limited impact due to low incidence of myasthenic crisis in the economic model. Mortality associated with corticosteroid use had limited impact due to interacting factors between life expectancy in the model and time spent on treatment with efgartigimod and chronic IVIg.

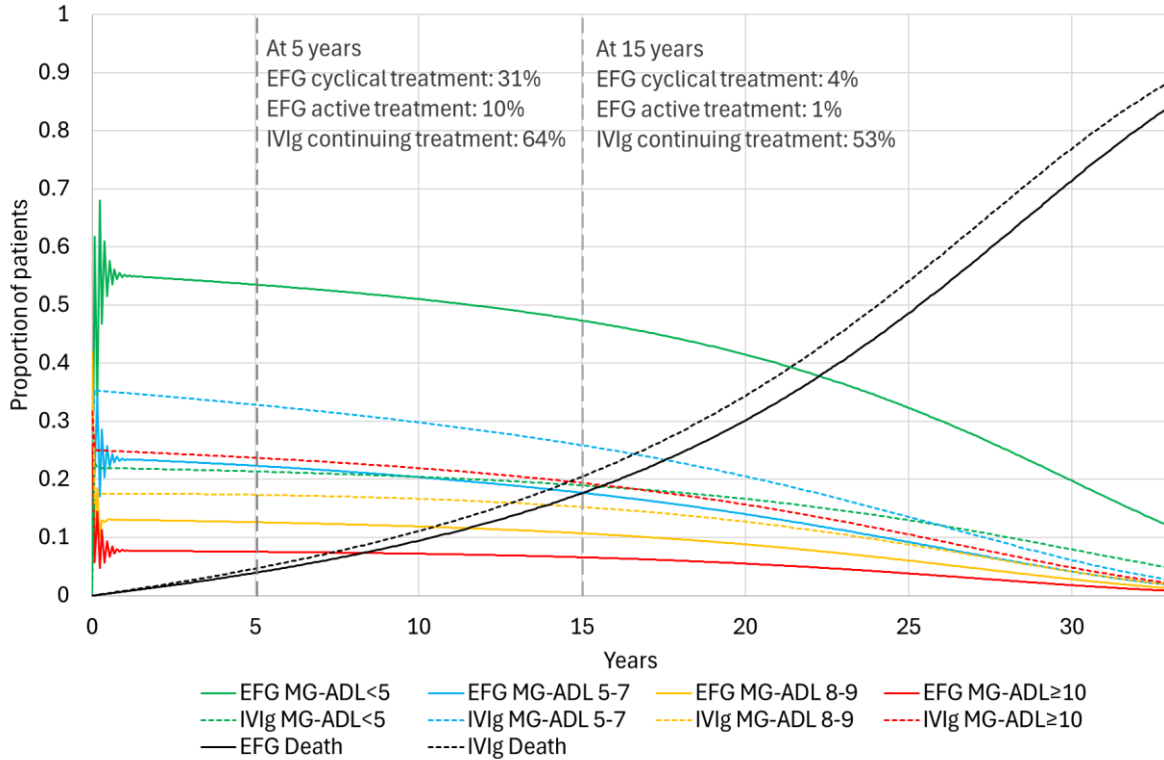
6.87 The ESC considered the reliability of the economic model was limited due to the lack of long-term data available and the complex nature of the condition. Specifically, the ESC considered:

- It was unclear whether the modelled population that was largely based on the ADAPT trial can be generalised to the PBS population due to potential differences in baseline functional impairment, response definitions and re-treatment criteria.

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- The circumstances of use of efgartigimod and chronic IVIg may not be representative of clinical practice, which were both modelled assuming patients with MG-ADL < 5 would not receive treatment.
  - Discontinuation assumptions were highly uncertain and poorly justified, which resulted in an increasing proportion of patients in the efgartigimod arm who were off treatment but maintained improved functional capacity while the majority of patients in the chronic IVIg arm remained on treatment with no changes to functional capacity over time.
  - The assumption that patients who discontinue efgartigimod or chronic IVIg therapy would only remain on standard therapies without any modifications or use of subsequent therapies such as rituximab was unlikely to reflect clinical practice.
  - The relative efficacy of chronic IVIg was synthesised based on results from the submission's network meta-analysis that was highly uncertain due to methodological concerns. Additionally, treatment effects were only modelled for the first model cycle assuming no change in subsequent cycles.
  - The MG-ADL health state utility values were highly uncertain and could not be validated due to inadequate documentation. The submission applied treatment-specific utilities and the ESC considered that the modelled utility gain associated with allocation to efgartigimod treatment was large (0.1291 utility gain) and appeared implausible. Further, the ESC noted this was applied in addition to modelled improvements in MG-ADL score and other quality of life benefits associated with reduced corticosteroid use, exacerbations and myasthenic crises.
  - Assumptions leading to reductions in exacerbations, myasthenic crises, corticosteroid use and mortality were inappropriate and inadequately supported by the available evidence.
  - The ESC considered that the modelled time horizon of 33 years was long when considering the modelled population had an assumed baseline age of 60 years. The ESC considered that a ten-year time horizon may be more appropriate given the uncertain long-term extrapolations e.g. due to the lack of long-term data around outcomes and treatment/remission durations.
- 6.88 Figure 5 presents Markov traces of the proportion of patients in each health state over time.

Figure 5: Markov traces of health state occupancy over time



Source: Constructed during the evaluation using the Section 3 economic model of the submission

Abbreviations: EFG, efgartigimod; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living

Note: The proportion of patients in the myasthenic crises health state is not shown due to low occupancy over time (< 0.1% in each arm)

- 6.89 The Markov traces show a clear separation in the distribution of patients across the MG-ADL health states, primarily due to more patients in the efgartigimod arm spending time in the MG-ADL < 5 health state compared to chronic IVIg.
- 6.90 The curves indicated significant fluctuations in the proportions occupying each health state in the efgartigimod arm at the start of the model, while the proportions of patients in each health state in the chronic IVIg arm were relatively stable over time. This is reflective of the complex implementation of different sets of transition probabilities for efgartigimod, particularly for responders that differed based on cyclical use of treatment, while chronic IVIg transitions were only possible in the first model cycle and in subsequent cycles all patients were assumed to remain in the same health state unless they developed myasthenic crisis or died.
- 6.91 The traces also demonstrate mortality benefits for efgartigimod, primarily associated with reduced corticosteroid use. At the end of the model, 16% of patients were alive in the efgartigimod arm while 11.7% remained alive in the chronic IVIg arm.
- 6.92 The traces indicate that efgartigimod treatment benefits were maintained over time despite declining proportions of patients receiving therapy. This was in contrast to the disease trajectory for patients on chronic IVIg therapy who mostly remain on treatment despite ongoing functional impairments.

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

Table 12: Results of the stepped economic evaluation

Step and component	Efgartigimod	IVIg	Increment
<b>Step 1: Modelled outcomes to Week 26 including response, treatment discontinuation, myasthenic crisis, adverse events and deaths using health state utility values, myasthenic crisis disutility values, adverse event disutility values and corticosteroid disutility values; and using drug costs (efgartigimod and IVIg) and standard therapy drug costs (anticholinesterase, corticosteroid, non-steroidal immunosuppressant)</b>			
Costs		\$28,515	
QALYs	0.3019	0.2211	0.0809
<b>Incremental cost per QALY gained</b>			<b>1</b>
<b>Step 2: Extrapolate to 2 years</b>			
Costs		\$71,564	
QALYs	1.3119	0.9627	0.3492
<b>Incremental cost per QALY gained</b>			<b>1</b>
<b>Step 3: Include exacerbation events using exacerbation disutility values and exacerbation treatment costs; add drug administration costs, disease monitoring costs, corticosteroid-related complication costs, myasthenic crises costs, adverse events costs and terminal care costs; discounting (5%) included</b>			
Costs		\$154,054	
QALYs	1.2743	0.9272	0.3471
<b>Incremental cost per QALY gained</b>			<b>1</b>
<b>Step 4: Extrapolate to 33 years</b>			
Costs		\$940,972	
QALYs	8.8054	6.4176	2.3879
<b>Incremental cost per QALY gained</b>			<b>2</b>

Source: Table 3.48, and the Section 3 economic model of the submission

Abbreviations: IVIg, intravenous immunoglobulin; QALY, quality-adjusted life year

Italicised estimates were calculated during the evaluation due to multiple errors identified in the calculation of the submission's estimates (outcomes for trial duration calculated over 2 years instead of 26 weeks, inconsistent use of discounted and undiscounted estimates between treatment arms, QALY losses due to exacerbations were inverted into QALY gains).

The redacted values correspond to the following ranges:

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

<sup>2</sup> \$255,000 to < \$355,000

6.94 Based on the economic model, treatment with efgartigimod in combination with standard therapy was associated with an incremental cost per QALY gained of \$255,000 to < \$355,000 compared to chronic IVIg in combination with standard therapy for the treatment of generalised myasthenia gravis.

6.95 During the evaluation, it was noted that 96.6% of incremental QALYs and 78.4% of incremental costs in the model are accrued in the extrapolated period beyond 26 weeks.

6.96 For every 100 patients treated with efgartigimod versus chronic IVIg and followed up for 33 years, the economic evaluation (based on undiscounted values) estimated that there would be:

- Increased time spent with higher functional capacity, with an average of 8.2 years with an MG-ADL score of less than 5.
- A reduction in clinical events (752 fewer exacerbation events and 7 fewer myasthenic crises events).

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- An average increase in life expectancy of 1 year, primarily due to reduced mortality associated with corticosteroids.
- Additional efgartigimod drug acquisition costs of \$1 million and administration costs of \$5.2 million.
- A decrease in IVIg drug acquisition costs of \$59.7 million and a decrease in administration costs of \$10.2 million.
- A decrease in exacerbation management costs of \$25.5 million.
- A decrease in the costs of disease monitoring, management of myasthenic crises and corticosteroid-related complications of \$4.1 million.

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

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Table 13: Sensitivity analyses

Analysis	Incremental cost (\$)	Incremental QALY	ICER	Change from base case ICER
<b>Base case</b>		2.3879	<sup>1</sup>	-
<b>Adverse event disutilities (base case not included) <sup>a</sup></b>				
Include adverse event disutilities		2.3872	<sup>1</sup>	-%
<b>Discount rate (base case 5% for benefits and costs)</b>				
3.5% discount rate		2.7782	<sup>1</sup>	-%
0% discount rate		4.2454	<sup>2</sup>	-%
<b>Time horizon (base case 33 years)</b>				
20 years		2.0166	<sup>3</sup>	+-%
10 years		1.3248	<sup>4</sup>	+-%
2 years		0.3471	<sup>5</sup>	+-%
<b>Patient characteristics (base case age 60 years at baseline)</b>				
47 years based on AChR+ subgroup in ADAPT		2.5932	<sup>1</sup>	-%
<b>Treatment discontinuations (base case efgartigimod: one-off 18.46% at the start due to non-response and 1.41% every 4 weeks for other reasons, chronic IVIg one-off 33% due to adverse events in the second model cycle only)</b>				
Efgartigimod non-response rate is doubled		1.9649	<sup>1</sup>	-%
Efgartigimod non-response rate is halved		2.5993	<sup>1</sup>	+-%
Efgartigimod discontinuation for other reasons is doubled		2.2800	<sup>6</sup>	-%
Efgartigimod discontinuation for other reasons is halved		2.4927	<sup>7</sup>	+-%
Chronic IVIg discontinuation due to adverse events is doubled		2.2991	<sup>3</sup>	+-%
Chronic IVIg discontinuation due to adverse events is halved		2.4322	<sup>1</sup>	-%
Discontinuation for other reasons in both arms is halved		2.5371	<sup>8</sup>	+-%
Discontinuation for other reasons in both arms is doubled		2.1912	<sup>9</sup>	-%
No difference in treatment discontinuations between arms (chronic IVIg assumed equivalent to efgartigimod)		2.1877	<sup>3</sup>	+-%
<b>Circumstances of use in patients who do not discontinue treatment (base case efgartigimod: 100% adherence, cyclical therapy (MG-ADL &lt; 5 off-treatment and MG-ADL ≥5 on-treatment with minimum 4-week gap between treatment cycles); chronic IVIg: 100% adherence for induction dose and imperfect adherence for maintenance doses, cyclical therapy (MG-ADL &lt; 5 off-treatment and MG-ADL ≥5 on-treatment with no minimum gap between treatment cycles); standard therapy: 100% adherence, ongoing use)</b>				
Efgartigimod based on 4.72 treatment cycles per year in all MG-ADL health states		2.3879	<sup>1</sup>	+-%
Chronic IVIg based on ongoing use in all MG-ADL health states		2.3879	<sup>1</sup>	-%
Disassociate treatment costs from MG-ADL status in both arms (efgartigimod based on 4.72 treatment cycles per year, chronic IVIg based on ongoing treatment)		2.3879	<sup>1</sup>	-%
<b>Corticosteroid use (base case 75.2% of all patients are on corticosteroids; high dose corticosteroids defined as ≥10 mg; MG-ADL &lt; 5: 100% on low dose corticosteroids, MG-ADL ≥5: 26.8% on low dose and 73.2% on high dose corticosteroids)</b>				
High dose corticosteroids defined as ≥5 mg (affects cost of corticosteroids, cost of corticosteroid-related complications and corticosteroid-related mortality but not corticosteroid disutilities)		2.4227	<sup>1</sup>	-%
High dose corticosteroids defined as ≥15 mg (affects cost of corticosteroids, cost of corticosteroid-related complications and corticosteroid-related mortality but not corticosteroid disutilities)		2.2474	<sup>1</sup>	+-%
Patients with MG-ADL < 5 are not on corticosteroids		2.6761	<sup>1</sup>	-%
No change in corticosteroid use based on MG-ADL score (low and high dose use based on MG-ADL ≥5 for all states)		1.8683	<sup>3</sup>	+-%

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Analysis	Incremental cost (\$)	Incremental QALY	ICER	Change from base case ICER
<b>Base case</b>		<b>2.3879</b>	<b>1</b>	-
<b>Exacerbation events and myasthenic crises (base case exacerbation rates based on the CADTH eculizumab model for myasthenia gravis for any exacerbation event, myasthenic crises transition probabilities based on Ramos-Fransi 2015)</b>				
Increase exacerbation risk by 50%		2.4085	1	- %
Decrease exacerbation risk by 50%		2.3672	1	+ %
<b>Health state utilities (base case derived from ADAPT trial data, treatment specific for efgartigimod and chronic IVIg; standard therapy assumed based on efgartigimod for MG-ADL &lt; 5 and chronic IVIg for MG-ADL 5-7, 8-9 and ≥10; myasthenic crises assumed the same as MG-ADL ≥10 for chronic IVIg)</b>				
ADAPT trial data, pooled health state utilities (same values applied between treatments) <sup>b</sup>		1.3674	8	+ %
MyRealWorldMG observational study <sup>c</sup>		1.8457	3	+ %
MG-ADL <5 for standard therapy assumed based on chronic IVIg utility value		1.7858	3	+ %
<b>Costs (base case resource use and unit costs based on various sources)</b>				
Efgartigimod administration costs based on MBS item 116		2.3879	1	- %
Chronic IVIg administration costs based on MBS item 14245		2.3879	1	+ %
Halve exacerbation event costs		2.3879	1	+ %
Double exacerbation event costs		2.3879	9	- %

Source: Section 3A.9, pp172-180 of the submission

Abbreviations: AChR+, acetylcholine receptor antibody positive; HR, hazard ratio; ICER, incremental cost effectiveness ratio; IVIg, intravenous immunoglobulin; MBS, Medicare Benefits Schedule; MG-ADL, Myasthenia Gravis Activities of Daily Living; PLEX, plasma exchange; QALY, quality adjusted life year

<sup>a</sup> Due to an error in the model, adverse event disutilities were not applied. This was not corrected during the evaluation due to minimal impact on the cost-effectiveness estimate

<sup>b</sup> Same utility values applied between treatments (MG-ADL < 5: 0.767, MG-ADL 5-7: 0.691, MG-ADL 8-9: 0.601, MG-ADL ≥10: 0.499, myasthenic crises: 0.499)

<sup>c</sup> Same utility values applied between treatments (MG-ADL < 5: 0.776, MG-ADL 5-7: 0.611, MG-ADL 8-9: 0.530, MG-ADL ≥10: 0.373, myasthenic crises: 0.373)

The redacted values correspond to the following ranges:

<sup>1</sup> \$255,000 to < \$355,000

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

<sup>3</sup> \$355,000 to < \$455,000

<sup>4</sup> \$655,000 to < \$755,000

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

<sup>6</sup> \$75,000 to < \$95,000

<sup>7</sup> \$555,000 to < \$655,000

<sup>8</sup> \$455,000 to < \$555,000

<sup>9</sup> \$155,000 to < \$255,000

6.98 The results of the sensitivity analyses indicate that the model is most sensitive to time horizon, treatment discontinuation rates and circumstances of use in patients who are persistent to therapy, MG-ADL health state utility values, corticosteroid use (primarily dose reductions in patients with MG-ADL < 5) and exacerbation rate (primarily due to event costs).

6.99 However, due to 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), response definitions (MGC ≥ 3 reduction), treatment benefits associated with efgartigimod and chronic IVIg and the disease trajectory following discontinuation of these treatments.

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- 6.100 Overall, 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/course and year***

- 6.101 The submission estimated the drug cost for efgartigimod per treatment cycle would be \$| (based on the proposed effective AEMP \$| per vial, 2.4 vials per infusion assuming the same distribution of patients across weight categories in the ADAPT trial and 4 infusions per cycle assuming perfect compliance). The submission's proposed cost per vial was \$| in the financial estimates assuming 50:50 split between private and public hospital settings. The number of vials per infusion in the financial estimates was consistent with the economic analysis.
- 6.102 The submission estimated the drug cost for efgartigimod in the first year of treatment in the economic model would be \$| (based on efgartigimod costs of \$| per treatment cycle, yielding an estimated 4.04 treatment cycles in the first year of treatment accounting for discontinuations and modelled time off-treatment in patients with MG-ADL < 5 and a minimum 4-week gap between treatment cycles). In the economic model, the efgartigimod drug costs declined substantially in subsequent years of therapy primarily due to the accumulating proportion of patients who discontinued therapy over time (i.e. the number of cycles per patient decreased from 4.04 cycles in Year 1, to 2.7 cycles in Year 2, 2.2 cycles in Year 3, 1.8 cycles in Year 4 and 1.5 cycles in Year 5). The PBAC noted that the evaluation and the ESC had considered the discontinuation assumptions in the economic model were highly uncertain and poorly justified (paragraph 6.87). Estimated costs in the economic analysis were lower than applied in the financial section, which were based on 4.72 treatment cycles per patient per year (\$| per year).
- 6.103 The efgartigimod costs applied in the submission were based on cyclical use of efgartigimod (with strict re-treatment criteria applied ADAPT and ADAPT+ Part A), however the ESC considered that the efgartigimod drug costs would substantially increase if it were used without strict re-treatment criteria. For example, a fixed cycle regimen of 4 once-weekly infusions with a 4-week intertreatment period (as evaluated in ADAPT-NXT) would result in 7 cycles of efgartigimod in Year 1, rather than 4.04 cycles as assumed in the economic model. Further, a sponsor-commissioned utilisation study in the United States indicated that the most common treatment-free interval between cycles was 4-6 weeks (Bhavaraju-Sanka 2024). DUSC commented that the difference between the submission and real world estimates indicates that the number of cycles and vials would be greater than estimated. DUSC considered that

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- the real-world estimate from Bhavaraju-Sanka (2024) of treatment-free interval between cycles (4-6 weeks) could be used instead of the ADAPT interval.
- 6.104 As outlined in Section 7, the ESC advised that, for the new gMG therapies, the average amount of drug per patient would need to be determined and for the FcRn blockers should account for the likely decreasing treatment-free intervals over time seen in the extension trials. As outlined in paragraph 6.40, the median treatment-free interval was 7 weeks between Cycles 1 and 2, and decreased to 4 weeks by the thirteenth treatment cycle.
- 6.105 The submission estimated the drug cost of the induction dose of IVIg was \$16,500. The cost was estimated based on an assumed cost of \$100 per gram of IVIg, yielding an assumed cost per vial of Intagram 10 (2.5 g/25 mL) of \$250. The submission also estimated the number of vials based on an estimated dose of 164 g and an assumed dose of 2 g/kg and the mean weight of patients in the ADAPT trial. The estimated total cost for induction was calculated as \$250 x 66 vials.
- 6.106 The estimated drug cost of the maintenance dose of IVIg was \$4,000. The cost was based on estimated annual IVIg use of 514 g per patient with myasthenia gravis (derived from the NBA 2021-22 report) and the proportion of IVIg use for maintenance therapy (80.1% of patients using 90% of total IVIg volume) in myasthenia gravis patients in 2017/2018 (MSAC Assessment Report 1566; April 2020 MSAC meeting). The submission assumed a total number of administrations per year of 13.04, yielding a dose per administration of 39.42 g. The submission estimated a total of 16 vials of Intagram 10 (2.5 g/25 mL) for each dose at an assumed cost of \$250 per vial. The estimated cost per maintenance dose was calculated as \$250 x 16 vials.
- 6.107 The estimated drug cost for IVIg in the first year of treatment in the economic model was \$42,089 (based on the cost of induction of \$16,500 and \$4,000 for maintenance doses, yielding an estimated 7.4 x 4-week treatment cycles in the first year of treatment accounting for discontinuations and modelled time off-treatment in patients with MG-ADL < 5). IVIg costs declined marginally in subsequent years as there were no further discontinuations to therapy except due to myasthenic crises and death. Estimated costs in the economic analysis were lower than applied in the financial section that was based on an assumed cost of \$100 per gram of IVIg and 514 g of IVIg dispensed per patient per year (\$51,400 per year).
- 6.108 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 gMG 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).
- 6.109 The estimated drug cost for standard therapy (anticholinesterases, corticosteroids and other immunosuppressive agents) in the first year of treatment was \$1,591 for the efgartigimod arm and \$1,613 for the chronic IVIg arm. The marginal difference was

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due to differences in the use of low- and high-dose corticosteroids based on MG-ADL health state occupancy in the model. The submission estimated cost offsets associated with reduced use of corticosteroids in the financial estimates. The estimates could not be validated due to inadequate documentation in the submission.

Cost-comparison

**Table 14: Comparison of the annual drug cost or dose of efgartigimod and IVIg**

Treatment	Annual cost or dose	Source
<b>Efgartigimod</b>		
Efgartigimod economic model	15,534 mg in Year 1	2.4 vials per infusion (assuming the same distribution of patients across weight categories in the ADAPT trial (40.3% of patients weight >80kg and thus require 3 vials; remainder require 2 vials), 4 infusions per cycle (perfect compliance), 4.04 cycles per year (accounting for discontinuations and modelled time off-treatment in patients with MG-ADL < 5 and a minimum 4-week gap between treatment cycles). This equates to a treatment-free interval of 8.9 weeks between cycles.
Efgartigimod: minimum treatment-free interval	26,915 mg	As above, but with 7 cycles per year. This equates to a treatment-free interval of 4 weeks between cycles.
Efgartigimod: financial estimates	18,148 mg	As above, but with 4.72 cycles per year based on a <i>post hoc</i> analysis of the average cycles per year in AChR+ patients with ≥ 1 year of follow-up in the ADAPT trial and extensions (Howard 2024). This equates to a treatment-free interval of 7.0 weeks between cycles.
Efgartigimod: 6 weeks between cycles	19,994 mg	As above, but with 6 weeks between cycles based on Bhavaraju-Sanka (2024) (paragraph 6.103)
<b>IVIg costing scenarios</b>		
ESC: IVIg (average grams dispensed per maintenance MG patient)	541 g \$█	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). 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.
Submission economic model: IVIg	678 g \$42,089	Induction dose: 164 g (2g/kg); Maintenance dose: 514 g per patient per year based on the 2021-22 NBA Report. See paragraphs 6.105 and 6.107
<b>IVIg costing scenarios: sensitivity analyses</b>		
Average IVIg dose per NBA data plus IVIg price based on MSAC review	\$32,688	The MSAC review of 'Immunoglobulin therapy for Myasthenia Gravis' from April 2020 <sup>b</sup> used a price of \$60.41 per gram in the base case based on NBA data from 2017-18 i.e. this was the cost at which the cost-effectiveness of IVIg was assessed. Average IVIg dose of 541 grams per patient per year based on data received from the NBA for 2023-24
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 Public Summary Document (PSR)

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

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

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

6.110 The evaluation and the ESC considered that costing scenarios based on the maximum recommended dose of IVIg were not plausible as these estimates substantially exceeded the quantities of IVIg dispensed by the NBA. Based on the average amount of IVIg dispensed per patient as maintenance therapy for myasthenia gravis, the cost of IVIg was approximately \$ [REDACTED] per year, which the ESC considered was more plausible.

Cost-per-responder

6.111 The PBAC noted that, at the price proposed by the sponsor, the incremental cost-per-responder versus placebo would be \$255,000 to < \$355,000 (based on 30.6% difference in the proportion of patients with ≥2 point reduction in MG-ADL at 4 weeks, and a cost of \$ [REDACTED] for 4 weeks of therapy). The PBAC advised that this was unacceptably high in the context of previous cost-per-responder analyses.

6.112 The PBAC noted that, at a cost per patient per year of \$ [REDACTED], and assuming the average of the incremental difference in response rates across the four gMG trials (24% at 12 weeks, based on a simple mean of the proportion of patients with ≥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**

6.113 This submission was considered by DUSC.

6.114 The submission used a mixed market share/epidemiological approach to estimate the utilisation and financial impacts of listing efgartigimod as a treatment for generalised myasthenia gravis. Key inputs used in the submission are summarised in Table 15.

**Table 15: Key inputs for financial estimates**

Data	Value applied and source	Comment
<b>Eligible population</b>		
Myasthenia gravis patients using IVIg	<p>Increasing from [REDACTED] in Year 1 to [REDACTED] in Year 6. Based on extrapolated estimates from 2019/2020 to 2023/2024 from the MSAC assessment of IVIg use for myasthenia gravis (MSAC Assessment Report 1566; April 2020 MSAC meeting) using NBA data on all myasthenia gravis indications between 2011/2012 and 2017/2018.</p> <p>The submission presented a supportive analysis of actual data from 2019/2020 to 2021/2022 which indicated that extrapolated estimates were broadly consistent with post-COVID actual utilisation.</p> <p>The submission continued to extrapolate estimates to 2031 using a linear function consistent with the MSAC report.</p>	<p>DUSC noted that NBA data was provided by the department giving total IVIg patient counts for the years 2019-20 to 2023-24.</p> <p>DUSC commented that the submission should be updated with the new data.</p>

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Data	Value applied and source	Comment
Proportion who are AChR+	85%. Assumption. The submission claimed that this was consistent with the general consensus from the published literature.	DUSC agreed with the commentary that this assumption appears reasonable.
Proportion with MG-ADL ≥ 5	59.3%. Based on data from the MyRealWorld-MG patient registry (DeWilde 2023). Estimates were derived from transforming reported mean MG-ADL scores and standard deviations in patients with generalised symptoms (MGFA II-IV) to Z-scores and then converting these scores to proportions with MG-ADL ≥ 5.	Calculated estimates could not be validated due to inadequate documentation of methodology.  DUSC noted that the calculated estimate for the proportion with MG-ADL ≥ 5 were based on the full population of MGFA II-IV, not those using IVIg, who would be expected to have worse symptoms and agreed with the commentary that this was probably underestimated.
Combined newer agents uptake rate	Assumed to increase from █████% in Year 1 to █████% in Year 6. The submission claimed that this was consistent with Australian market research which indicated that at least █████% of chronic IVIg users meeting the eligibility criteria would switch to efgartigimod over a six-year time horizon. The submission assumes the same uptake rates in new and established IVIg users.	The market research was based on efgartigimod utilisation rather than the broader market for newer agents.  Additionally, the uptake estimates were based on patients with ongoing functional impairment (MGC ≥ 4 and/or MG-ADL ≥ 5) despite IVIg/PLEX therapy rather than all patients eligible for IVIg.  The assumption of the same uptake rates in new and established IVIg users was not adequately justified.  DUSC considered feedback from clinicians and patients indicates high awareness of the new drugs and considered the combined uptake of the newer agents was likely underestimated. DUSC considered that new IVIg users and existing users with ongoing functional impairment will likely have much greater uptake. However the pre-PBAC response noted that some IVIg patients may not wish to transition to a new therapy if they are satisfied with IVIg treatment.
FcRn blocker market share of newer agents	Assumed █████%. The submission claimed that FcRn blockers would have greater market share than complement inhibitors (assumed █████%) due to the targeted mechanism of action, fast response and favourable safety profile.	DUSC considered that the assumed market share of FcRn blockers was highly uncertain.
Efgartigimod market share of FcRn blockers	Assumed █████%. The submission claimed that efgartigimod would have greater market share than rozanolixizumab (assumed █████%) due to a superior benefit/risk profile.	DUSC considered that the assumed market share of efgartigimod was highly uncertain.
Grandfathered patients	It was estimated that approximately █████ <sup>2</sup> patients would initiate efgartigimod under the sponsor's expanded access program (which is aligned with the proposed PBS restriction) in 2025.	This estimate could not be validated. The model assumed that all grandfathered patients would remain on therapy for the full six-year forecast period.

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Data	Value applied and source	Comment
<b>Treatment utilisation</b>		
Patient years of efgartigimod treatment	Increasing from [redacted] <sup>2</sup> in Year 1 to [redacted] <sup>2</sup> in Year 6. Patient years of therapy were estimated by assuming all grandfathered patients start therapy in the first month while the uptake of all patients initiating efgartigimod was distributed equally across the year ([redacted]% per month). All patients continuing therapy beyond the first year are assumed to have a full year of treatment with no discontinuations.	The assumption of part-year utilisation of efgartigimod was inconsistent with other estimates used in the budget model which were based on total patients receiving treatment using full calendar years.  The assumption of no treatment discontinuations was not adequately supported.
Vials dispensed per patient year	18.88 infusions per year and 45.4 vials per year.	Treatment patterns reported in a tightly regulated clinical study setting (equating to a treatment-free interval between cycles of approximately 8 weeks) may not be representative of clinical practice.
Efgartigimod infusions per year	Based on a <i>post hoc</i> analysis of the average cycles per year (4.72) in AChR+ patients with ≥ 1 year of follow-up in the ADAPT trial and extension (Howard 2024) × recommended number of infusions per cycle (4 infusions per cycle) × the baseline weight distribution of patients from the ADAPT trial (60% < 80 kg using 2 vials per infusion; 40% ≥ 80 kg using 3 vials per infusion)	A sponsor-commissioned utilisation study in the United States indicated that the most common treatment-free interval between cycles was 4-6 weeks (Bhavaraju-Sanka 2024). DUSC noted that the estimates were based on the trial data (cycles of 8 weeks), which differed to real-world data (cycles between 4-6 weeks). DUSC commented this difference indicates that the amount of cycles and vials would be greater than estimated. The PBAC further noted this assumption was inconsistent with assumptions applied in the economics.
Dispensed IVIg per patient	514 g per year. Based on the total IVIg grams dispensed for myasthenia gravis in 2021/2022 (NBA Annual Report 2022) × proportion of IVIg use for maintenance therapy (80.1% of patients using 90% of total IVIg volume) in myasthenia gravis patients in 2017/2018 (MSAC Assessment Report 1566; April 2020 MSAC meeting)	NBA data shows the average amount of IVIg was 541.1 grams per patient per year in 2023-24 (specific to the myasthenia gravis maintenance setting).
<b>Costs</b>		
Efgartigimod cost	\$[redacted] per vial. Proposed effective DPMQ assuming 50% of use will be in the public hospital setting (\$[redacted] per vial) and 50% of use will be in the private hospital setting (\$[redacted] per vial).	The assumption of a 50:50 split between private and public hospital settings was not adequately justified.
IVIg cost	Assumed \$100 per gram. Based on the total IVIg grams dispensed in 2021/2022 (8.054 million grams) / total cost of IVIg in 2021/2022 (\$810.4 million) (NBA Annual Report 2022).	NBA data shows the average cost per gram of IVIg (across all indications on the NBA) was \$[redacted]

Source: Table 4-1, pp182-184; Table 4-3, p187; Figure 4-1, p189; Table 4-7, p192 of the submission

Abbreviations: AChR+, acetylcholine receptor antibody positive; DPMQ, dispensed price for maximum quantity; GP, general practitioner; IV, intravenous; IVIg, intravenous immunoglobulin; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite score; MGFA, Myasthenia Gravis Foundation of America classification; MSAC, Medicare Services Advisory Committee; NBA, National Blood Authority; PBS, Pharmaceutical Benefits Scheme;

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

6.115 Table 16 summarises the estimated eligible population, scripts dispensed and net cost to government of listing efgartigimod presented in the submission.

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**Table 16: Estimated use and financial implications of listing efgartigimod (as estimated in the submission)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible patient population	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Market uptake rate for newer agents <sup>a</sup>	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %	█ <sup>2</sup> %
Patients using newer agents	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Market uptake for FcRn blockers (█ <sup>2</sup> %)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
- Treated with efgartigimod (█ <sup>2</sup> %)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Grandfathered patients using efgartigimod	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Total patients treated with efgartigimod	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Patient years of treatment (adjusted for uptake throughout year) <sup>b</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Vials dispensed per patient year (45.4 vials)	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Total PBS/RPBS cost less copay</b>	█ <sup>5</sup>	█ <sup>6</sup>	█ <sup>7</sup>	█ <sup>8</sup>	█ <sup>9</sup>	█ <sup>10</sup>
Cost to the PBS (reduced corticosteroid use)	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>
Cost to the MBS (disease management) <sup>c</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>
Cost to NBA (substituted IVIg)	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>
Cost to State/Territory hospitals (infusion and exacerbation costs) <sup>d</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>	█ <sup>11</sup>
<b>Net cost to government</b>	█ <sup>5</sup>	█ <sup>12</sup>	█ <sup>13</sup>	█ <sup>7</sup>	█ <sup>8</sup>	█ <sup>8</sup>

Source: Table 4-6, p190; Table 4-8, p193; Table 4-10, p195; Table 4-12, p197; Table 4-13, p198; Table 4-14, p199; Table 4-15, p199; Table 4-19, p202; Table 4-22, p205; Table 4-24, p207; Table 4-25, p209; Table 4-28, p211 of the submission

Abbreviations: AChR+, acetylcholine receptor antibody positive; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; NBA, National Blood Authority; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

<sup>a</sup> Includes efgartigimod, rozanolixizumab, ravulizumab and zilucoplan

<sup>b</sup> Assumes uptake in initiating patients in a year would be equally distributed across each month and monthly patient numbers rounded up

<sup>c</sup> Based on GP visit Level C

<sup>d</sup> Infusion administration costs were based on non-admitted hospital costs and would be substantially lower if based on MBS costs

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

<sup>3</sup> 5,000 to < 10,000

<sup>4</sup> 10,000 to < 20,000

<sup>5</sup> \$20 million to < \$30 million

<sup>6</sup> \$40 million to < \$50 million

<sup>7</sup> \$60 million to < \$70 million

<sup>8</sup> \$80 million to < \$90 million

<sup>9</sup> \$90 million to < \$100 million

<sup>10</sup> \$100 million to < \$200 million

<sup>11</sup> net cost saving

<sup>12</sup> \$30 million to < \$40 million

<sup>13</sup> \$50 million to < \$60 million

6.116 The submission estimated the cost to the PBS/RPBS of listing efgartigimod for generalised myasthenia gravis was \$20 million to < \$30 million in Year 1, increasing to \$100 million to < \$200 million in Year 6, a total cost of \$400 million to < \$500 million over the first six years of listing. The net cost to the PBS/RBS including cost offsets due to substituted use of corticosteroids was similar.

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- 6.117 The submission estimated the net cost to government was \$20 million to < \$30 million in Year 1, increasing to \$80 million to < \$90 million in Year 6, a total cost of \$300 million to < \$400 million over the first six years of listing. The estimated net cost to government excluding State/Territory costs was \$20 million to < \$30 million in Year 1, increasing to \$80 million to < \$90 million in Year 6, a total cost of \$300 million to < \$400 million over the first six years of listing.
- 6.118 The evaluation considered that the estimated cost to the PBS/RPBS was uncertain due to the following reasons:
- The mixed market share/epidemiological approach used in the submission assumed that there would be no substantial differences in patterns of use between IVIg and newer therapies despite differences in initiation rules, dosing intervals (cyclical, continuous), continuation rules and stopping rules. This approach also assumed that newer therapies will not grow the market despite potentially offering another line of therapy (i.e. in patients intolerant or inadequately responsive to IVIg/PLEX).
  - The estimated proportion of patients with MG-ADL  $\geq 5$  was based on all generalised myasthenia gravis patients rather than the subset of patients using IVIg who are required to have an MGC score  $\geq 4$ . It is likely that a substantially higher proportion of patients using IVIg will meet the MG-ADL criterion compared to the overall myasthenia gravis population.
  - The assumption of similar uptake rates from established users and new users was not adequately justified given that many patients may be adequately managed with their existing IVIg treatment.
  - The assumed market dynamics were uncertain given the potential entry of multiple new therapies for myasthenia gravis, with different modes of action, method and frequency of administration and different adverse event profiles.
  - Estimates of utilisation for efgartigimod were based on patient-years of therapy assuming uptake was equally distributed across the year. This was not consistent with other estimates included in the budget impact model which were based on total patients using full calendar years of treatment (particularly IVIg cost offsets).
  - It was unclear whether the efgartigimod utilisation estimates from the ADAPT trial and extension (observed in a tightly regulated clinical study setting with specific rules regarding re-treatment) would be representative of Australian clinical practice.
- 6.119 DUSC considered the estimates presented in the submission to be underestimated, and that the main issues were:
- DUSC commented that the estimates were highly sensitive to the treatment uptake rate and market share.

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- DUSC noted that the submission has estimated a higher number of IVIg users when compared to the updated NBA data. DUSC considered that using the updated NBA data would lower the financial estimate for this input.
  - DUSC considered that some changes to highly sensitive assumptions would result in more reliable estimates, that are higher than the submission's base case estimates. DUSC noted that the:
    - Sponsor's assumed proportion of patients using IVIg for maintenance therapy rate (80%) was lower than compared to the updated NBA data (mean 87%). DUSC commented that the sponsor could update these estimates with the newer NBA data.
    - predicted uptake among eligible patients is probably low, due to the poor evidence base for current options, and difficulties in access and likely patient demand.
    - there is potential for uptake higher up in the treatment cascade by patients who are not currently eligible for IVIg, given the current wording of the proposed restriction.
    - annual number of treatment cycles estimate is low, DUSC considered that the real-world estimate from Bhavaraju-Sanka (2024) of treatment-free interval between cycles (4-6 weeks) could be used instead of the ADAPT interval (8 weeks).
  - DUSC agreed with the commentary that the estimated proportion of patients with MG-ADL  $\geq 5$  was based on all gMG patients rather than the subset of patients using IVIg who are required to have an MGC score  $\geq 4$ . It is likely that a substantially higher proportion of patients using IVIg will meet the MG-ADL criterion compared to the overall myasthenia gravis population.
- 6.120 As outlined in Section 7, the ESC considered that the use of IVIg as maintenance therapy, from the NBA data, may be a more appropriate starting point to estimate the use of new gMG therapies.
- 6.121 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.

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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 █ 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 80% are responding (i.e. █% * █% = █/█%). Total uptake of █% in █% of the market. Total market uptake of █% in Year 1 (i.e. █ <sup>1</sup> patients in Year 1).
Increase in uptake over time	█ percentage points each year for the first six years of listing (i.e. █ <sup>2</sup> patients in Year 6)

Source: Compiled during preparation of the PSD  
 The redacted values correspond to the following ranges:  
<sup>1</sup> < 500  
<sup>2</sup> 500 to < 5,000

6.122 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).

**Quality Use of Medicines**

6.123 The submission claimed that there are no quality use of medicine issues associated with using efgartigimod.

**Financial Management – Risk Sharing Arrangements**

6.124 The submission proposed a risk sharing arrangement (RSA) consisting of an expenditure cap based on the utilisation estimates with a █% rebate for all use beyond these estimates. The ESC noted the submission’s proposed RSA was based on an average of █ treatment cycles (█ vials) per patient per year, which was higher than assumed in the economic model (4.04 treatment cycles in Year 1, then reducing substantially in subsequent years).

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- 6.125 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.*

## **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 alfa and rozanolixizumab):

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

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

- 7.2 The ESC recalled advice from the clinicians present at the gMG stakeholder meeting (May 2024)<sup>1</sup> 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 trialled at least three months of combination therapy with all three of: an NS-IST; plus an anti-cholinesterase; plus a corticosteroid. The restriction should require these therapies to have been used at optimised dosing (though specific doses should not be outlined in the PBS restriction, to enable clinician judgement), unless contraindicated or severely intolerant. As such, the ESC considered that the timing of initiation of the new therapy should be based on a minimum of three months having elapsed since initiation of the NS-IST. Further, the ESC considered that the intention would be for

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<sup>1</sup> Myasthenia Gravis Stakeholder Meeting (May 2024) Outcome Statement, Available at: <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/stakeholder-meetings>

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the NS-IST to be continued concurrently with the new gMG therapy (unless contraindicated or severely intolerant). Refer to paragraphs 8.6 to 8.13 for the PBAC's advice regarding the restriction criteria.

- 7.5 The ESC considered that a key issue in the bridging setting would be the potential for ongoing use of the new therapies in patients who would have responded to standard therapy, or whose condition would have improved over time (given the potential for recovery of receptors in gMG). As such, the ESC reiterated the advice from the stakeholder meeting that there should be robust stopping rules to prevent ongoing use.
- 7.6 The ESC considered that, overall, the primary literature suggests that most patients generally respond to NS-ISTs within 12 months, with many patients responding within the first one to six months.<sup>2,3</sup> The ESC considered that any PBS restriction for bridging therapy should require the patient to cease the new therapy after around six months of treatment (acknowledging that variations in treatment duration between therapies may be required to align with treatment courses). After three months of therapy cessation (i.e. a total of at least 12 months since NS-IST initiation), patients whose condition remains uncontrolled may recommence under the refractory listing. Overall, the maximum treatment duration in the bridging setting would be around six months.
- 7.7 The ESC considered that another key issue in the bridging setting was the lower level of certainty in the incremental benefit versus optimisation of existing therapies given the availability of therapies that are effective for many patients, and that this would impact on the cost-effectiveness of the new therapies. The ESC considered that it was unclear whether these concerns would be adequately addressed by limiting use in this setting to a maximum duration of six months, along with a combined risk sharing arrangement (RSA) for any recommended drugs across both setting.

Refractory setting

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

Both settings

- 7.9 The ESC considered that restrictions should be consistent across any new gMG therapies recommended for listing.
- 7.10 Across both settings, the following aspects of the restrictions would need to be determined:

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<sup>2</sup> Hehir, M.K., Burns, T.M., Alpers, J., Conaway, M.R., Sawa, M. and Sanders, D.B. (2010), Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: Outcomes in 102 patients†. *Muscle Nerve*, 41: 593-598. <https://doi.org/10.1002/mus.21640>, Accessed at <https://pubmed.ncbi.nlm.nih.gov/20405499/>

<sup>3</sup> Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Myasthenia Gravis Study Group. Neurology*. 1998 Jun;50(6):1778-83. doi: 10.1212/wnl.50.6.1778. PMID: 9633727.

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- functional impairment criteria;
  - response criteria;
  - requirements around prior and concomitant treatments; and
  - restriction structure around: balance of supply; grandfather arrangements (where applicable); a transition pathway between the bridging and refractory settings; any allowance for switching between the newer therapies; and recommencement in the refractory setting (if ceased for reasons other than loss of response or exceeding the six month duration in the bridging setting).
- 7.11 The ESC noted that the NBA qualifying criteria for IVIg<sup>4</sup> specifies that the patient has a Myasthenic Gravis Composite (MGC) of at least 4 points; and at least 2 other treatments are ineffective, contraindicated, unavailable or caused intolerable side effects. The ESC considered this was broad as the other treatments could comprise two of: an anti-cholinesterase; a corticosteroid; or thymectomy (i.e. there is no requirement for the patient to have trialed 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 (although use of IVIg prior to surgery or in a myasthenic crisis should be permitted);
  - there should be no requirement for the patient to have trialed prior IVIg (or PLEX); and
  - amendments to the prescribing criteria for IVIg may be required, along with systems to ensure that the anticipated reductions in IVIg use are realised.

***ESC’s view on the comparator***

- 7.14 At its July 2024 meeting, the PBAC considered “for the non-refractory group, the comparator should be optimisation of existing therapies. For refractory patients and those who are unable to use or not responding to existing therapies, the PBAC acknowledged that there are variations in access to IVIg/PLEX and that any clinical

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<sup>4</sup> Criteria for Clinical Use of Immunoglobulin in Australia, accessed at: <https://www.criteria.blood.gov.au/MedicalCondition/View/2681>

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comparisons may be limited by the lack of evidence for IVIg/PLEX. As such, the PBAC considered that placebo may be a reasonable comparator in this group. However, the PBAC considered that chronic IVIg/PLEX remained a relevant comparator for providing a frame of reference for interpreting the cost per patient of ravulizumab in the refractory setting” (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).

- 7.15 As such, the ESC reiterated the PBAC’s previous advice that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost per patient of the newer gMG therapies in the refractory setting.
- 7.16 The ESC considered that the four gMG therapies considered at the March 2025 meeting (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.

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

- 7.17 The ESC noted the PBAC’s previous advice that “for the non-refractory group, the comparator should be optimisation of existing therapies”, but that none of the trials for the new therapies required baseline therapies to have been optimised.
- 7.18 The ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod alfa and rozanolixizumab). The ESC considered that the published NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 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]
<b>Data below is specific to the myasthenia gravis maintenance setting</b>	
Average number of 'dispensing events' per patient in 2023-24	15.7 per patient per year
Average total annual dose in 2023-24 <sup>a</sup>	541.0625 grams
Average grams per 'dispensing event'	34.4 grams
Average cost per patient per year of IVIg for maintenance <sup>a</sup>	\$ [REDACTED]
Total number of patients treated with IVIg for maintenance in 2023-24	1,324 patients
Annual growth in the number of patients using IVIg for maintenance (from 2019-20 to 2023-24) <sup>d</sup>	3.3%
Of the patients who were treated with IVIg for maintenance in 2023-24, the percent who:	
commenced more than 7 years ago	28.5%
commenced 7 years ago	4.1%
commenced 6 years ago	5.2%
commenced 5 years ago	6.9%
commenced 4 years ago	7.6%
commenced 3 years ago	8.2%
commenced 2 years ago	10.9%
commenced 1 years ago	12.1%
commenced within the last full year of data (2023-24)	16.6%
<b>Context of IVIg use for gMG <sup>b</sup></b>	
Proportion of all IVIg use in Australia that is for myasthenia gravis maintenance (2022-23)	7.3%
Total spend on IVIg for gMG maintenance in 2023-24	\$ [REDACTED]
% of IVIg use in gMG that is in the maintenance setting (2023-24) <sup>c</sup>	91%

Overall notes:

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

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

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

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

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

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

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

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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 Pharmaceutical Benefits Scheme.
- 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.

**8 PBAC Outcome**

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

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to support the claim that efgartigimod was superior in terms of efficacy or safety compared with the other three therapies considered at the March 2025 meeting for the treatment of gMG (zilucoplan, ravulizumab and rozanolixizumab). Overall, the PBAC advised that the four treatments should be considered as non-inferior with each other and with IVIg.

- 8.2 The recommendation was made on the basis of the totality of the evidence presented across all four of the submissions for new gMG therapies.
- 8.3 The PBAC noted the strong consumer and clinician support for the new gMG therapies received via the Consumer Comments facility on the PBS website. The PBAC appreciated the input provided by patients, carers and clinicians and found the comments very informative for understanding the high and unmet clinical need for new effective treatments and the potential use of the new therapies in practice. The comments outlined the significant impact that gMG can have on quality of life, including the impact on patients' families. The comments also described the limitations of currently available treatment options including adverse events and lengthy administration times. Consumers outlined that the new therapies represent a substantial improvement in administration time compared with IVIg, and also shorter travel distances for patients outside metropolitan areas. The comments described a hope that the new therapies will reduce gMG symptoms quickly, reduce the need for other medications and associated side-effects, and reduce hospital visits, contributing to an overall improved quality of life. The PBAC noted the strong support for access to both complement inhibitors (ravulizumab and zilucoplan) and FcRn blockers (efgartigimod and rozanolixizumab) across both the bridging and refractory settings.
- 8.4 The PBAC advised that the restrictions were complex and further work would be required to finalise the restrictions including further consultation with expert neurologists and immunologists before listing can proceed.
- 8.5 The PBAC acknowledged the key trials of the new therapies were not designed to specifically assess efficacy in the bridging setting, but considered the new gMG therapies (both complement inhibitors and FcRn blockers) should be listed in both the bridging and refractory settings given the high unmet need, clinical rationale and strong clinician support (both through the stakeholder meeting and the consumer comments) for broad listings that allow clinician discretion in the choice as to which agent to use in a particular patient.
- 8.6 As such, the PBAC considered the four new therapies for gMG should be listed in three settings, consistent with the advice provided by clinicians at the stakeholder meeting and in the consumer comments:
  - Immediate access for patients whose condition is acute and severe, and who are at high risk of rapid deterioration. The PBAC advised that the restriction in this setting should require patients to be treated with concomitant corticosteroid and NS-IST therapy with the flexibility that NS-IST can be commenced within two weeks of initiation of the new therapy. A maximum time on treatment of 3-

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months would apply for this setting.

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

- 8.7 The PBAC considered the restriction in the bridging setting should provide access for patients whose condition is moderate-to-severe, and who have trialled at least three months of therapy with remission-inducing intent. The PBAC advised this should be defined as two of the following three: NS-IST; a corticosteroid; thymectomy. The NS-IST and/or corticosteroid should have been administered at optimised dosing (definition of optimised doses not specified and will be up to the treating physician to determine). The PBAC advised the initiation criteria in this setting should require patients to meet a disease severity threshold similar to most of the key trials, e.g. around MG-ADL  $\geq 6$  (consistent with two of the four trials of the new therapies for gMG). The PBAC agreed with the clinician correspondence which expressed a preference for also including a clinician-reported component i.e. using the MGC instrument (with a threshold to be determined based on consultation with expert neurologists and immunologists) in addition to the MG-ADL (paragraph 6.5b).
- 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  $\geq 2$  (plus a corresponding MGC level to be determined based on consultation with expert neurologists and immunologists), achieved at 2 to 16 weeks, per the clinician correspondence (paragraph 6.5e).
- 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 bridging therapy. The PBAC also advised it would be

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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. Therefore, for the FcRn inhibitors, the PBAC advised that repeat cycles should be permitted, noting the strict re-treatment criteria in some of the FcRn trials may be difficult to implement in practice.

- 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. In particular, the PBAC noted that FcRn blockers should not be administered concomitantly with IVIg or PLEX given FcRn blockers remove circulating immunoglobulin;
  - 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 three 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 insufficient evidence to support superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab). The PBAC further considered that the published

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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 considered that, while the submission’s network meta-analysis indicated that efgartigimod was associated with a statistically significant improvement in QMG score compared to IVIg, this analysis was unreliable as it did not account for the treatment effects of efgartigimod waning over time during the off-treatment period. The PBAC noted that at least one of the submissions for a new gMG therapy claimed non-inferior efficacy and safety versus IVIg based on an indirection comparison versus NCT02473952 (later published as Brill 2024) which found no statistically significant differences in functional outcomes or serious adverse events between the new therapy and IVIg. The PBAC acknowledged the limitations of the available evidence for chronic IVIg however, based on the totality of the evidence presented across the four submissions, the PBAC considered that there was insufficient evidence to support superior efficacy or safety of any of the four new gMG therapies versus chronic IVIg or PLEX.
- 8.19 Overall, the PBAC considered that efgartigimod has non-inferior comparative effectiveness and safety versus chronic IVIg and also against zilucoplan, ravulizumab and rozanolixizumab.
- 8.20 The PBAC agreed with ESC that the cost-utility analysis submitted was limited by the lack of long-term data available and the complex nature of the condition. As such, the PBAC considered the uncertainty in the ICER was unlikely to be adequately resolved with further revisions to the model structure and reiterated that the cost-per-patient of IVIg could provide a frame of reference for the newer gMG therapies in a cost-comparison approach.
- 8.21 To determine the average IVIg dose per patient per year, the PBAC considered it would not be practical to use the dose recommended in the Product Information (induction dose: 1-2g/kg and maintenance dose: 0.4-1 g/kg every 4 to 6 weeks)<sup>5</sup> given the wide dose range specified which could result in annual doses from 352g to 1,172g per patient (using an average patient weight of 83.7 kg per Brill 2024). Further, in Brill 2024 (one of the key studies of chronic IVIg in gMG), IVIg was administered every 3 weeks which does not align with the Product Information (dosing every 4 to 6 weeks).
- 8.22 The PBAC acknowledged the NBA data was based on the average dose across all severity levels and thus included patients with less severe disease than the threshold for initiation of the new therapies. Further, use of the 2023-24 NBA data would not account for the varying cost per gram of IVIg (which depends on the proportion of imported IVIg, with the cost in 2023-24 being higher than previous years).

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<sup>5</sup> Australian Product Information for Privigen and Intragam  
<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2020-PI-01935-1&d=20250321172310101>;  
<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2014-PI-03087-1>

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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 noted that a key uncertainty in the estimation of the average annual dose of efgartigimod was the treatment-free interval between cycles (refer to paragraphs 6.104 to 6.107). Overall, the PBAC considered the estimated number of cycles per year derived from the economic model (4.04 in Year 1) was not reliable given the evaluation and the ESC had considered that the discontinuation assumptions in the model were highly uncertain and poorly justified (paragraph 6.89). The PBAC further considered the financial estimates, which had assumed 4.72 cycles per year (based on a *post hoc* of the ADAPT trial and extensions) may also have underestimated the number of infusions in clinical practice given longer-term data from the extension studies and real world data indicated decreasing treatment-free intervals over time, and also given the strict retreatment criteria applied in the trial (refer to paragraph 6.114). However, overall, the PBAC considered this latter data was likely the best information available, and that the risk of additional cycles should be managed through the RSA.
- 8.24 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 efgartigimod dose recommended in the product information assuming the same weight distribution as patients in the trial (i.e. 2.4 vials per infusion and 4 infusions per cycle) with the number of cycles per patient per year based on the *post hoc* analysis of the average cycles per year (4.72) in AChR+ patients with  $\geq 1$  year of follow-up in the ADAPT trial and extension, as used in the submission's financial estimates. Based on these assumptions the average annual dose of efgartigimod would be: 18,148 mg per year.
  - 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.
- 8.25 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 6.112). 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.
- 8.26 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

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applied: market growth (of around 4% per year, based on the last five years of IVIg data); and the proportion of patients whose gMG is AChR+ (of around 86%, based on the pooled estimates provided in one of the submissions, noting this is similar to the submission's estimate of 85%).

- 8.27 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. 33.3% 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 |%).
- 8.28 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 |% in Year 1 (i.e. |% 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.
- 8.29 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 |percentage points each year for the first six years of listing.
- 8.30 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 8.24).
- 8.31 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.
- 8.32 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).

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- 8.33 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.
- 8.34 The PBAC acknowledged the financial estimates as outlined in paragraphs 8.26 to 8.30 were associated with some uncertainty and considered that it may be reasonable for the risk of use outside the intended restriction to be managed through a RSA – with the [ ] based on the financial estimates outlined by the PBAC (e.g. with the AChR+ proportion and uptake rates applied as outlined in paragraphs 8.26 to 8.30 and Table 17) with a rebate of less than [ ]%, then a [ ] based on the total number of patients using IVIg for maintenance gMG with a rebate of [ ]%.
- 8.35 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).
- 8.36 The PBAC advised that efgartigimod is not suitable for prescribing by nurse practitioners.
- 8.37 Efgartigimod 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 efgartigimod 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 efgartigimod:
- 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**

Argenx is delighted that the PBAC recognises the high clinical need for new therapies to treat generalised myasthenia gravis (gMG), and welcomes the PBAC's intent to list efgartigimod for the treatment of this condition. The PBAC is to be commended for its recognition of the significant impact that gMG can have on the quality of life of patients and their families, as outlined in the comments from patients, carers and clinicians. Argenx is committed to improving the lives of patients and believes that efgartigimod will deliver significant additional benefits over the current standard of care for gMG. For this reason, Argenx is disappointed that the PBAC's recommendation doesn't reflect the true value of efgartigimod and the company is unable to accept the conditions of the recommendation. Recognising the urgency to deliver life-changing immunology solutions to patients, Argenx is eager to work with the PBAC to co-create solutions to resolve this issue.