

An addendum to this Public Summary Document has been included at the end of the document.

**5.14 ROZANOLIXIZUMAB,
Solution for subcutaneous infusion,
280 mg in 2 mL (140 mg per mL),
Rystiggo[®],
UCB Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 1 submission requested Section 100 (Highly Specialised Drugs Program) Authority Required (Written) listing for rozanolixizumab for the treatment of adult patients with generalised myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive.
- 1.2 Current disease-modifying treatment options for AChR-positive generalised myasthenia gravis such as corticosteroids and non-steroidal immunosuppressants (NS-ISTs) can take up to 2 years to induce remission, with the ESC considering that overall, the primary literature suggests that patients generally respond to NS-ISTs within 12 months, with many patients responding within the first one to six months (refer to paragraph 7.6). Bridging therapies may provide relief from symptoms while remission induction occurs, with the only currently available therapies being intravenous immunoglobulin (IVIg) and plasma exchange (PLEX). The submission claimed that current demand for IVIg exceeds domestic supply, and there is also a global shortage of IVIg, with long production lead times and reliance on blood donations for production meaning that clinical need cannot be addressed in the short term. PLEX is associated with bleeding risk and hypotension and is not widely available outside of metropolitan centres.
- 1.3 The submission positioned rozanolixizumab as an alternative to IVIg and PLEX as a bridging therapy for the management of disease symptoms while remission induction occurs with NS-ISTs, though the Pre-Sub-Committee Response (PSCR) proposed a potentially broader place that was in line with the use of IVIg in current clinical practice.
- 1.4 Listing was requested on the basis of a cost-minimisation approach versus IVIg.

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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 considered for additional treatment such as IVIg or PLEX.
Intervention	Rozanolixizumab by SC infusion (weight-based dosing, 280 mg – 840 mg) once a week, 6-week treatment cycle, with subsequent symptom-driven cycles as required; in combination with standard care.
Comparator	Main comparator: IVIg Supplementary comparator: PLEX Near market comparator: efgartigimod 10 mg/kg once weekly for 4 weeks, with subsequent symptom-driven cycles as required
Outcomes	Reduction in functional impairments, improvements in quality of life, safety.
Clinical claim	In adult patients with AChR-positive generalised myasthenia gravis: <ul style="list-style-type: none"> • Rozanolixizumab is superior in terms of efficacy and non-inferior in terms of safety compared to current standard of care. • The poor evidence base for IVIg precluded any robust clinical conclusion for the comparative efficacy and safety of rozanolixizumab versus IVIg, but it is likely at least non-inferior in terms of efficacy and safety. • Rozanolixizumab is likely to be at least non-inferior in terms of efficacy and safety to PLEX, based on MSAC's previous conclusion that PLEX is non-inferior in terms of efficacy and safety compared with IVIg. • Rozanolixizumab is non-inferior to efgartigimod for efficacy, based on the proportion of MG-ADL responders, and safety, based on serious adverse events and discontinuation due to adverse events.

Source: Table 1.1-1, pp9-10 of the submission.

Abbreviations: AChR, acetylcholine receptor; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; PLEX, plasma exchange; SC, subcutaneous

2 Background

Registration status

- 2.1 Rozanolixizumab was registered by the TGA on 7 February 2025 as 'an add-on to standard therapy for the treatment of gMG in adult patients who are AChR or anti-muscle-specific tyrosine kinase (MuSK) antibody positive'.
- 2.2 The TGA Delegate's overview was received on 5 November 2024, and rozanolixizumab was considered at the December 2024 Advisory Committee on Medicines (ACM) meeting.
- 2.3 The TGA Delegate noted a need for further investigation of the long-term efficacy and safety of rozanolixizumab, and that frequent dose switching in the MG0007 extension trial prevented evaluation regarding efficacy and safety of the respective doses and the assessment of dosing effects.

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty		Max. qty packs	Max. qty units	No. of Rpts	Available brands
	Published price	Effective price				
ROZANOLIXIZUMAB						
Rozanolixizumab, SC infusion, solution, 140 mg/mL, 2 mL, 1 vial	Public hospital: \$ Private hospital: \$	Public hospital: \$ Private hospital: \$	1*	1*	0	Rystiggo
Category / Program: Section 100 – Highly Specialised Drugs Program						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)						
Authority type: Complex Authority Required (CAR)						
Indication: Generalised myasthenia gravis						
Treatment Phase: Episodic treatment						
Clinical criteria:						
Patient must be ≥ 18 years of age						
AND						
Clinical criteria:						
Patient must have a diagnosis of Myasthenia Gravis Foundation of America (MGFA) Disease Class II to IVa						
AND						
Clinical criteria:						
Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies						
AND						
Clinical criteria:						
Patient must be receiving concomitant treatment with at least one of the following: (i) azathioprine, (ii) methotrexate, (iii) cyclophosphamide (iv) ciclosporin (v) mycophenolate						
AND						
Clinical criteria:						
Myasthenia gravis composite (MGC) score of at least 4 points						
AND						
Clinical criteria:						
Treatment must not be in combination with intravenous immunoglobulin (IVIg) or plasma exchange (PLEX)						
Treatment criteria:						
Must be treated with a neurologist						
Prescribing Instructions:						
The myasthenia gravis composite (MGC) reference in this restriction is described in the following literature publication: Burns, T. M., Conaway, M. Sanders, D. B. 2010. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. Neurology, 74, 1434-40.						
Administrative Advice:						
The authority application must be made in writing and must include: (1) A completed authority prescription form; and (2) A completed authority application form relevant to the treatment phased; and (3) A detailed cover letter from the prescriber; and At the time of the authority applications, details (result and date of result) of the following monitoring requirements must be provided: Baseline MGC score						

*Prescriber should request a sufficient quantity based on patient weight for 6 weeks of treatment.

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- 3.1 The submission proposed a special pricing arrangement for rozanolixizumab with an effective price representing a rebate of approximately $\frac{1}{3}$ % of the published DPMQ per script.
- 3.2 The submission indicated that the intended place in therapy was as a bridging therapy, however the PSCR stated the proposed place is 'in line with the use of IVIg in current clinical practice' with the proposed PBS restriction being broadly based on the National Blood Authority (NBA) criteria for IVIg¹. The ESC noted that the NBA qualifying criteria for IVIg 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. As outlined in Section 7, 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. The pre-PBAC response stated rozanolixizumab is administered in treatment cycles of 6 weeks, with subsequent cycles administered based on symptoms recurrence (i.e. a patient has worsening symptoms). Hence the pre-PBAC response argued that rozanolixizumab is ideally suited as an alternative bridging therapy to IVIg and PLEX, and more broadly as an IVIg replacement (consistent with the proposed PBS restriction). Refer to paragraph 8.6 for the PBAC's advice regarding the place in therapy.
- 3.3 As outlined in Section 7, the ESC noted that there are two key, distinct places in therapy which may be feasible for PBS-listing of the new therapies for gMG:
- 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.
- 3.4 The ESC recalled advice from the clinicians present at the gMG stakeholder meeting (May 2024)² that the complement inhibitors should be available in both these settings.
- 3.5 The proposed PBS restriction was narrower than the draft TGA indication due to additional clinical criteria for AChR binding autoantibodies, functional impairment and co-administered therapies.
- 3.6 The requested restriction for patients with AChR-positive generalised myasthenia gravis with MGFA class of II-IVa was consistent with the inclusion criteria for the key

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

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

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- clinical trial (MycarinG). The trial also included a small number of patients with muscle-specific kinase (MuSK) autoantibodies.
- 3.7 The requested restriction included the Myasthenia Gravis Composite (MGC) instrument to assess functional impairment, in line with the current NBA listing for maintenance therapy with IVIg (MGC score ≥ 4 points). This was inconsistent with the eligibility criteria for the MycarinG trial, which required patients to have functional impairment on the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale of ≥ 3 (for non-ocular symptoms) and Quantitative Myasthenia Gravis (QMG) scale of ≥ 11 . The submission argued that the mean baseline MGC score of 16 in the MycarinG trial indicated that almost all patients had an MGC score ≥ 4 points. The submission did not provide a distribution of baseline MGC scores, and the evaluation considered it was unclear whether the proposed MGC threshold would be equivalent to the eligibility criteria in the MycarinG trial. The ESC previously considered that the degree of correlation between the two instruments [MGC and MG-ADL] was unclear (para 3.9, Zilucoplan Public Summary Document [PSD] July 2024 PBAC meeting). Refer to paragraphs 8.7 to 8.8 for the PBAC's advice regarding initiation criteria.
- 3.8 Treatment with rozanolixizumab is episodic, based on symptoms being sufficiently severe to require another treatment cycle of 6 weeks. The submission argued that there is no continuation restriction because patients initiate a subsequent treatment cycle with rozanolixizumab only if they worsen and meet the PBS restriction for initial treatment again. Using the same absolute functional impairment threshold for initial and subsequent cycles would allow patients who have shown no response to treatment (and who maintained their original MGC score) to receive subsequent cycles of rozanolixizumab treatment. The requested restriction was inconsistent with the MG0007 extension study criteria for initiation of subsequent treatment cycles, which was dependent on patients demonstrating symptom worsening (e.g., an increase of ≥ 2 -points on the MG-ADL scale or ≥ 3 -points on the QMG scale) between assessments. The ESC commented that the submission's proposed 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 Cycle 12 (refer to Table 8). Refer to paragraph 8.11 for the PBAC's advice regarding re-treatment criteria for the FcRn blockers.
- 3.9 The proposed restriction did not specify a minimum time between treatment cycles. The Product Information states that the safety of initiating subsequent cycles of rozanolixizumab sooner than 4 weeks from the last infusion of the previous treatment cycle has not been established.
- 3.10 The proposed PBS restriction did not specify requirements for prior therapy but did require concomitant treatment with at least 1 NS-IST. The requirement for concomitant treatment with an NS-IST was not reflected in the baseline characteristics of patients in the MycarinG trial, with only 51.5% taking

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immunosuppressants at baseline (and only 34.5% of participants taking the nominated immunosuppressants in the submission's proposed restriction). The proposed restriction did not require concomitant therapies at initiation to have been optimised and ineffective prior to commencing treatment with rozanolixizumab, meaning patients could be treated with rozanolixizumab immediately after initiating treatment with an NS-IST.

- 3.11 As outlined in Section 7, the ESC considered that any PBS restriction for bridging therapy should require the patient to have trialled at least three months of combination therapy with all three of: an NS-IST; plus an anti-cholinesterase; plus a corticosteroid. The restriction should require these therapies to have been used at optimised dosing (though specific doses should not be outlined in the PBS restriction, to enable clinician judgement), unless contraindicated or severely intolerant. As such, the ESC considered that the timing of initiation of the new therapy should be based on a minimum of three months having elapsed since initiation of the NS-IST concurrently with the new gMG therapy (unless contraindicated or severely intolerant). Refer to paragraphs 8.7 to 8.9 for the PBAC's advice regarding prior therapy requirements for initiation of the new gMG therapies. Further, the ESC considered that the intention would be for the NS-IST to be continued.
- 3.12 It was unclear whether the sponsor intended for combination therapy of rozanolixizumab and zilucoplan to be permitted under the proposed restriction. Without specific criteria in the restriction, there is a risk of combination use of a complement inhibitor (ravulizumab or zilucoplan) with rozanolixizumab.
- 3.13 The requested restriction does not include requirements for assessment of response. The Product Information states treatment must be discontinued in patients who have not demonstrated a response within 3, 6-week treatment cycles (a response is defined as a decrease of ≥ 2 points on the MG-ADL scale from baseline). The NBA listing for IVIg states that IVIg should be used for 4 months (induction plus 3 maintenance cycles) before determining whether the patient has responded, and if there is no benefit, the treatment should be abandoned. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy (improvement in fatiguability and weakness as measured by the MGC score of at least 3-points less than the qualifying score, or the patient with severe disease continues to report improvement in symptoms and disability post-infusion, with end-of-cycle deterioration). In the included rozanolixizumab studies, response was assessed at Day 43 (after 6 weeks of treatment) with successful response to rozanolixizumab based on a ≥ 2 -point improvement from baseline in MG-ADL scores or a ≥ 3 -point improvement in MGC or QMG scores.
- 3.14 The requested restriction does not specify a maximum treatment duration or stopping rule (such as a 2-year stopping rule considered at the myasthenia gravis stakeholder meeting). As outlined in Section 7, the ESC considered that one of the key issues with PBS-listing of the new therapies in the bridging setting would be the potential for on-going use in patients who would have responded to standard

therapy, or whose condition would have improved over time (given the potential for recovery of receptors with gMG). As such, the ESC reiterated the advice from the stakeholder meeting that there should be robust stopping rules to prevent ongoing use in the bridging setting. Refer to Section 7 for ESC Advice relevant to stopping rules.

- 3.15 The submission argued that it is appropriate to have a Section 100 listing for initial treatment (to allow for dispensing at a hospital pharmacy). The submission noted that in the short term (at least 1 months for each patient), the sponsor would provide and fund a home infusion program (as it is administered as a one-hour subcutaneous infusion), but in the longer term, the Section 100 listing would allow for outpatient treatment with infusion pumps that allow for subcutaneous infusions. There is potential for the change of administration location after 1 months (from home to hospital outpatient) to impact the ongoing utilisation of rozanolixizumab.
- 3.16 The submission stated that there will be patients that will require grandfathering from the sponsor's patient access program. The submission did not propose a grandfathering restriction, stating that patients should qualify under the proposed restriction for episodic treatment. Given the episodic nature of treatment with rozanolixizumab, this was reasonable.

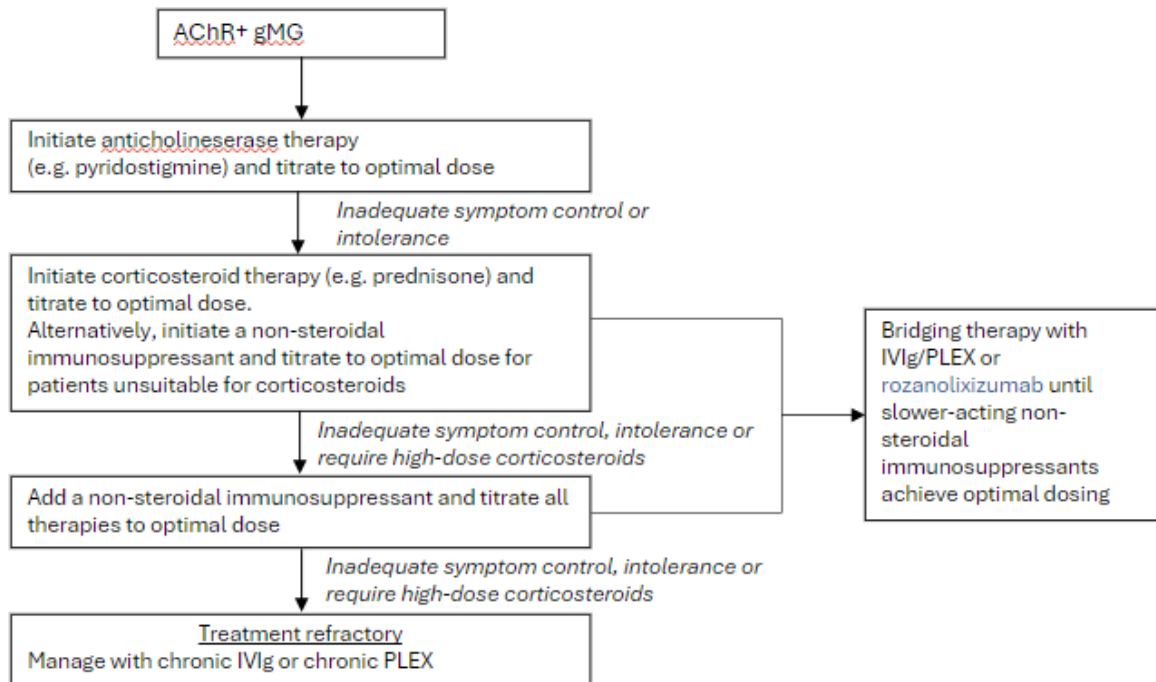
For more detail on PBAC's view, see section 8 PBAC outcome.

4 Population and disease

- 4.1 Myasthenia gravis is a rare, chronic, heterogenous autoimmune disorder caused by antibodies attacking components of the neuromuscular junction leading to impaired signal transmission between nerves and muscles. Patients with myasthenia gravis can be classified into subgroups based on the antibodies involved in the disease process, 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.
- 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 resulting 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 (Sciancalepore 2024) of myasthenia gravis epidemiology studies 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 Current treatment guidelines (Sanders 2016 updated in Narayanaswami 2021) recommend the use of anticholinesterase inhibitors in most patients with AChR positive generalised myasthenia gravis. However, the guidelines note that the majority of patients will also require immunosuppressive therapy, with corticosteroids used as the main first-line treatment option. The guidelines state that other immunosuppressive agents such as mycophenolate mofetil, azathioprine, methotrexate, tacrolimus and ciclosporin may also be used as monotherapies (for patients who refuse corticosteroids or who are contraindicated to corticosteroids) or in combination with corticosteroids (for patients with an inadequate response, for patients with significant steroid side-effects or who require high corticosteroid doses that cannot be tapered down). The guidelines note that chronic IVIg/PLEX can be used as bridging therapies while patients adjust to other slower-acting immunosuppressive agents. Patients with treatment-refractory disease (variable definitions in the literature) can receive treatment with chronic PLEX/IVIg, 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.
- 4.6 Rozanolixizumab is a fully humanised, chimeric IgG4 monoclonal antibody that targets the neonatal Fc receptor (FcRn blocker). Blocking of this receptor accelerates the removal of circulating immunoglobulin (IgG), including pathogenic IgG autoantibodies, via the natural lysosomal degradation pathway. Rozanolixizumab is administered as a subcutaneous infusion once a week in a treatment cycle of 6 weeks. Subsequent treatment cycles are administered based on clinical evaluation of symptom recurrence.
- 4.7 The proposed clinical management algorithm is presented in Figure 1.

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



Source: Figure 1.2-2, p32 of the submission

Abbreviations: AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IVIg, intravenous immunoglobulin; NBA, National Blood Authority; NS-IST, non-steroidal immunosuppressive therapy; PLEX, plasma exchange

Note: Not shown in the treatment algorithm are thymectomy and IVIg or PLEX for myasthenic crisis. While maintenance/chronic treatment is permitted by the NBA criteria for IVIg maintenance therapy, the international treatment guidelines only recommend short-term treatment in non-refractory patients.

- 4.8 The submission positioned rozanolixizumab as an alternative bridging therapy to short term treatment with IVIg or PLEX for patients with AChR-positive generalised myasthenia gravis, stating that this was aligned with the key criterion in the MycarinG trial that patients must be considered for treatment with additional therapy such as IVIg or PLEX. The submission argued that rozanolixizumab is most likely to substitute for short-term IVIg and PLEX because of its short 6-week treatment cycle, with subsequent cycles administered based on clinical evaluation of symptom recurrence. The submission noted that patients in myasthenic crisis (MGFA class V) would not be eligible for treatment with rozanolixizumab based on the requested restriction. However, the PSCR stated 'the proposed place in therapy for rozanolixizumab is in line with the use of IVIg in current clinical practice', which the ESC noted also includes the refractory setting.
- 4.9 The evaluation considered that the clinical place in therapy for rozanolixizumab is currently unclear, particularly as the use of newer agents such as complement inhibitors (zilucoplan, ravulizumab) and FcRn blockers (rozanolixizumab, efgartigimod) have yet to be incorporated into most treatment guidelines.
- 4.10 The PBAC previously noted that clinicians and consumers had stated that the newer agents have rapid onsets of action and could be used as bridging therapy while

waiting for NS-ISTs to induce remission. However, the PBAC noted that no evidence had been presented to specifically demonstrate the difference in onset of action between these newer agents (ravulizumab, zilucoplan) and NS-ISTs (para 7.12, ravulizumab PSD, July 2024 PBAC meeting; para 7.12, zilucoplan PSD, July 2024 PBAC meeting).

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

5 Comparator

- 5.1 The submission nominated IVIg as the main comparator, with PLEX as a supplementary comparator. The main argument in support of this nomination was that IVIg and PLEX are both treatments used as short-term bridging therapies for symptom management until the onset of effect of immunosuppressive therapies. IVIg was nominated as the main comparator as it is more commonly used than PLEX (Sansoni 2023), with PLEX available mostly in metropolitan hospitals across Australia (Myasthenia gravis stakeholder meeting). The evaluation and the ESC considered that IVIg and PLEX were appropriate comparators, and that IVIg was an appropriate main comparator.
- 5.2 International treatment guidelines state that IVIg or PLEX may be used as short-term treatments in non-refractory patients when other treatments are insufficiently effective, and prior to beginning corticosteroids if deemed necessary to prevent or minimise exacerbations. IVIg and PLEX are also nominated in guidelines as add-on treatments to corticosteroids and/or NS-ISTs in refractory patients (Sanders 2016). The submission noted that chronic IVIg use is associated with a high risk of thromboembolism, anaphylaxis, acute kidney damage, reduction in haematocrit and renal function; and PLEX is associated with bleeding risk and hypotension (Gajdos 2012, Pinto 2023, Ammann 2016, Kapoor 2020). Further, a proportion of patients do not respond satisfactorily to IVIg or PLEX.
- 5.3 The submission noted that efgartigimod was under evaluation by the TGA and has a similar mechanism of action to rozanolixizumab in that both act by reducing pathogenic IgG autoantibody levels, and has a short 4-week treatment cycle, similar to the 6-week cycles for rozanolixizumab. Efgartigimod was appropriately nominated as a near market comparator in the submission.
- 5.4 Zilucoplan and ravulizumab are both complement inhibitors with TGA indications as an add-on to standard therapy for the treatment of adults with AChR-positive generalised myasthenia gravis. Zilucoplan and ravulizumab had previously been considered at the March 2025 meeting. Zilucoplan shares the same sponsor as rozanolixizumab. The ESC considered that the four gMG therapies being considered at the March 2025 meeting (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The sponsor outlined the clinical positioning of its two agents for gMG (zilucoplan and rozanolixizumab). Zilucoplan was proposed for use in the refractory setting given the PBAC's previous advice to target patients with the highest clinical need, and because the trial was not specifically designed to assess efficacy in the bridging setting. On the other hand, the sponsor targeted rozanolixizumab at the bridging setting because it is a symptom-led treatment that was designed as an IVIg replacement. Further, the sponsor outlined that the key trial for zilucoplan enrolled a population who had more severe disease at baseline and who were more heavily pre-treated compared with the patients in the rozanolixizumab trial.
- 6.2 The sponsor reiterated its request for a price premium over IVIg.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (17), health care professionals (9 individual health care professionals plus a group of 11 neurologists) and an organisation (Myasthenia Alliance Australia (MAA)) via the Consumer Comments facility on the PBS website. The comments described the high unmet need for new therapies to treat gMG. The comments outlined the significant impact that gMG can have on quality of life such as an inability to perform daily tasks, work, study, drive or participate in social activities. The comments also described the impact on family, along with the financial burden associated with the condition. The comments also described the limitations of currently available treatment options including adverse events and lengthy administration times. The comments also described a hope that the new therapies will reduce gMG symptoms, reduce the need for other medications and associated side-effects and reduce hospital visits, contributing to an overall improved quality of life.
- 6.4 The comments noted the efficacy associated with rozanolixizumab and its rapid onset of action. One clinician outlined that FcRn blockers provide an alternative to IVIg and PLEX in that they can provide rapid improvement in patients who have significant weakness, which is important as some patients are unresponsive or intolerant to IVIg, and PLEX is not available at all centres. Many clinicians stated that the FcRn blockers have a mild or favourable adverse effect profile.
- 6.5 Advice from MAA stated its aim is for each patient to have equitable and timely access to the best available treatment that most benefits them. MAA supported access to the new therapies across the disease severities and settings including early upfront access and also in patients with refractory disease, noting that refractory patients have a higher unmet need. MAA strongly supported access to a broad range of treatment options. The input received from MAA, and from individual consumers, indicated that the mode of administration is important to consumers, with 63% of

participants in a recent survey indicating they are seeking a more manageable or flexible treatment option. MAA outlined that the new therapies represent a substantial improvement in administration time compared with IVIg, and also shorter travel distances for patients outside metropolitan areas. MAA highlighted that continuous and reliable treatments are important for patients and that a meaningful response would comprise well-controlled symptoms within a reasonably quick timeframe. The comments outlined that even a small improvement in the MG-ADL score can be meaningful for patients e.g. it may represent a capacity to perform a daily activity the patient was previously unable to perform.

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

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- 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

- 6.7 The submission was primarily based on one head-to-head randomised trial comparing rozanolixizumab to placebo in patients with generalised myasthenia gravis (MycarinG). The submission also presented results of two open-label extension studies of patients previously enrolled in MycarinG (MG0004, with patients receiving continuous rozanolixizumab treatment for 52 weeks; and MG0007, with a fixed initial 6-week cycle followed by symptom-driven cycles as required) as supportive data. The submission presented results from an interim report for MG0007, with a data cut off on 8 July 2022. During the evaluation the final study report for MG0007 (July 2024) was provided.
- 6.8 In the MycarinG trial, patients were randomised 1:1:1 to one of two rozanolixizumab dose tiers (7 mg/kg or 10 mg/kg), or matched placebo. The rozanolixizumab arms did not represent actual dose strengths, but approximate doses (with actual doses received based on patient bodyweight category and are therefore referred to as ~7 mg/kg and ~10 mg/kg. The submission stated that the rozanolixizumab ~7 mg/kg dose strength is the same as recommended in the draft TGA Product Information.
- 6.9 The rozanolixizumab MG0004 and MG0007 extension studies re-randomised patients to either ~7 mg/kg or ~10 mg/kg dose tiers, using the same fixed doses by bodyweight as in the MycarinG trial. However, in both studies, patients were permitted to swap dose tiers from ~7 mg/kg to ~10 mg/kg or vice versa at the beginning of the treatment cycles for tolerability and efficacy reasons at the

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investigator's discretion. The TGA Delegate's overview noted that the frequent dose switches across both dosing groups in MG0007 caused inconsistent drug exposure which was not fully captured in the efficacy outcomes (group comparisons according to first dose in study, most recent dose for all cycle analyses and dose in the respective cycles for individual cycle analyses).

- 6.10 It is unclear whether the availability of the ~10 mg/kg dose strength in the MG0007 study may have affected treatment compliance, as well as longer-term measures of efficacy and safety. The ~10 mg/kg dose in MG0007 was higher than the recommended dose in the draft Product Information.
- 6.11 The submission presented a series of indirect comparisons versus IVIg (NCT02473952 published during the evaluation as Brill 2024, Wolfe 2002, Zinman 2007) and efgartigimod (ADAPT, Howard 2019). The indirect comparisons were conducted using the ITT population from MycarinG as well as the subgroup of AChR-positive patients (approximately 80% of the whole trial population). The submission stated that results of the indirect comparisons using the AChR-positive subgroup from MycarinG were consistent with the overall MycarinG ITT population. Results of the indirect comparison utilising the ITT population of MycarinG are presented below.
- 6.12 The submission did not identify any trials that would allow for an indirect comparison of rozanolixizumab with PLEX.
- 6.13 Details of the included trials are presented in the submission are provided in Table 2.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Rozanolixizumab trials		
MycarinG (MG0003)	A phase 3, randomized, double-blind, placebo-controlled study evaluating efficacy and safety of rozanolixizumab in adult patients with generalized myasthenia gravis. Bril et al. Safety and efficacy of rozanolixizumab in patients with generalized myasthenia gravis (MycarinG): A randomised, double-blind, placebo-controlled, adaptive phase 3 study.	Clinical Study Report, 19 April 2022 Lancet Neurol. 2023; 22(5):383-394
MG0004	A randomized, open-label extension study to investigate the long-term safety, tolerability and efficacy of rozanolixizumab in adult patients with generalised myasthenia gravis.	Clinical Study Report, 19 April 2022
MG0007	An open-label extension study to evaluate rozanolixizumab in study participants with generalised myasthenia gravis.	Interim Clinical Study Report, 17 August 2022 Final Clinical Study Report, 12 June 2024
IVIg trials		
Bril 2024	A study to evaluate the efficacy and safety of IGIV-C in symptomatic subjects with generalized myasthenia gravis; NCT02473952 Bril V, Berkowicz T, Szczudlik A, et al. Efficacy and safety of maintenance intravenous immunoglobulin in generalized myasthenia gravis patients with acetylcholine receptor antibodies: A multicenter, double-blind, placebo-controlled trial.	Clinicaltrials.gov Muscle and Nerve 2024; 1-12
Wolfe 2002	Wolfe GI, Barohn RJ, Foster BM, et al. Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis.	Muscle and Nerve 2002; October: 549-552
Zinman 2007	Zinman L, Ng E, Bril V. IV immunoglobulin in patients with myasthenia gravis: A randomized controlled trial.	Neurology 2007;68: 837-841
Efgartigimod trials		
ADAPT	Howard JF, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled phase 3 trial.	Lancet Neurol 2021; 20(7):526-536
ADAPT+	Howard JF, Bril V, Vu T, et al. 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.	Front Neurol 2024; 14:1284444.
Howard 2019	Howard JF, Bril V, Burns TM, et al. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis.	Neurology 2019; 92: e2661-e2673.

Source: Table 2.2-1, pp52-53 of the submission; Table 2.2.1, p7, Appendix 10 of the submission.

Abbreviations: IVIg, intravenous immunoglobulin

6.14 The key features of the included trials are summarised in Table 3.

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Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Key Outcomes
Rozanolixizumab versus placebo					
MycarinG	200	MC, R, DB, PC, 6 weeks duration	Low	Adults with AChR+ or MuSK+ gMG with MGFA class II to IVa, MG-ADL \geq 3 and QMG \geq 11 with stable background therapy permitted	Primary: Change in MG-ADL score at Day 43. Other outcomes: Change in MGC and QMG; MG-ADL, MGC, QMG responders; quality of life (EQ-5D-5L, MG-QoL15r), safety
IVIg versus placebo					
Bril 2024	62	R, DB, PC 24 weeks duration	Low	Adults with AChR+ gMG, MGFA class II to IVa, QMG score \geq 10 with stable background therapy	Primary: Change in QMG at Week 24 Other: % with clinical improvement based on QMG, MGC, MG-ADL
Wolfe 2002	15	R, DB, PC 6 weeks duration	Unclear	Aged >15 years with mild or moderate gMG, never received corticosteroids or immunotherapy OR persistent symptoms despite corticosteroids	Primary: Change in QMG at day 42 Other: % decrease from baseline in MG-ADL
Zinman 2007	52	R, DB, PC 4 weeks duration	Low	Adults with myasthenia gravis and worsening weakness	Primary: Change in QMG at Day 14 Other: Change in QMG at Day 28, and from day 14 to 28
Efgartigimod versus placebo					
ADAPT	167	MC, DB, R, PC 26 weeks duration	Low	Adults with gMG (regardless of AChR antibody status) with MGFA class II to IV disease and MG-ADL \geq 5 with > 50% of the score due to non-ocular symptoms, with at least one stable background therapy	Primary: % MG-ADL responders in AChR+ (\geq 2-point reduction in MG-ADL sustained for at least 4 consecutive weeks) in cycle 1. Other: QMG responders (\geq 3-point improvement) in the AChR+ subgroup, MG-ADL responders in the overall population
Howard 2019	24	Phase 2, MC, DB, R, PC 11 weeks duration	Low	Adults with AChR+ gMG with MGFA class II to IVa disease and MG-ADL \geq 5 with > 50% of the score due to non-ocular symptoms, with at least one stable background therapy	Exploratory outcomes only: Primary: safety Other: Change in MG-ADL, QMG, and MGC at Week 11, change in quality of life (MG-QoL15r)

Source: Table 2.3-1, p56; Section 2.3, pp59-60 of the submission; Table 2.4-13, p80 of the submission; Table 2.3.1, Appendix 10 of the submission; Howard 2021 (ADAPT); Howard 2019.

Abbreviation: AChR+, anti-acetylcholine receptor antibody positive; DB, double-blind; gMG, generalised myasthenia gravis; MC, multicentre; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, myasthenia gravis composite score; MGFA Myasthenia Gravis Foundation of America; MG-QoL15r, revised Myasthenia Gravis Quality of Life; PC, placebo-controlled; QMG, Quantitative Myasthenia Gravis score; R, randomised; wks, weeks.

Comparative effectiveness

Rozanolixizumab versus placebo, and extension studies

6.15 Results from MycarinG for the primary outcome of change in MG-ADL score from baseline to Day 43, and key secondary outcomes of change in QMG and MGC scores from baseline to Day 43, are summarised in Table 4.

Table 4: Mean change in MG-ADL from baseline at day 43, MycarinG trial (ITT population)

	RLZ ~7 mg/kg N = 66	RLZ ~10 mg/kg N = 67	Placebo N = 67
Mean change from baseline to day 43, MG-ADL score			
Baseline Mean (SD)	8.4 (3.8)	8.1 (2.9)	8.4 (3.4)
Day 43 Mean (SD)	n = 64 5.1 (3.8)	n = 62 4.8 (3.6)	n = 64 7.8 (3.6)
LSM change at Day 43 (SE)	-3.37 (0.49)	-3.40 (0.49)	-0.78 (0.49)
LSM difference vs placebo (95% CI)	-2.59 (-4.09, -1.25)	-2.62 (-3.99, -1.16)	-
Mean change from baseline to day 43, QMG score			
Baseline Mean (SD)	15.4 (3.7)	15.6 (3.7)	15.8 (3.5)
Day 43 Mean (SD)	11.2 (5.5)	10.0 (5.2)	14.9 (5.1)
LSM change at Day 43 (SE)	-5.40 (0.68)	-6.67 (0.69)	-1.92 (0.68)
LSM difference vs placebo (95% CI)	-3.48 (-5.61, -1.58)	-4.76 (-6.82, -2.86)	-
Mean change from baseline to day 43, MGC score			
Baseline Mean (SD)	15.9 (6.5)	16.4 (5.7)	15.6 (6.5)
Day 43 Mean (SD)	10.8 (7.0)	9.0 (6.1)	14.2 (7.8)
LSM change at Day 43 (SE)	-5.93 (0.92)	-7.55 (0.93)	-2.03 (0.92)
LSM difference vs placebo (95% CI)	-3.90 (-6.63, -1.25)	-5.53 (-8.30, -2.97)	-

Source: Table 2.5-1, p99; Table 2.5-5, p103; Table 2.5-3, p101 of the submission.

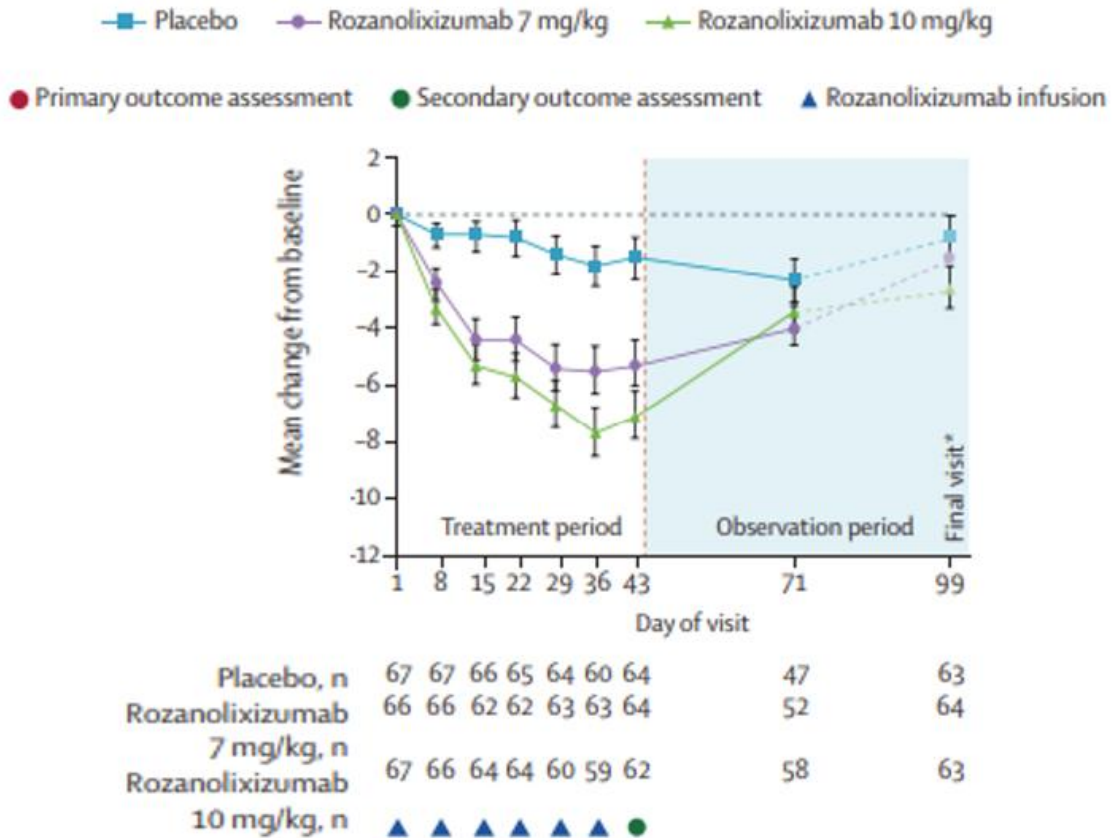
Abbreviations: CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; MG-ADL, myasthenia gravis activities of daily living; MGC, myasthenia gravis composite; QMG, quantitative myasthenia gravis; RLZ, rozanolixizumab; SD, standard deviation; SE, standard error

Bold indicates statistically significant results

6.16 Rozanolixizumab demonstrated statistically significantly greater improvements from baseline to Day 43 in MG-ADL, QMG and MGC scores, compared to placebo.

6.17 Figure 2 illustrates the change over time in MG-ADL scores from baseline through the treatment and observation period of the MycarinG trial.

Figure 2: Change in MG-ADL scores, MycarinG trial (ITT population)



Source: Figure 2.5.1, p100 of the submission

Abbreviations: ITT, intent-to-treat; MG-ADL, myasthenia gravis activities of daily living

- 6.18 While treatment with rozanolixizumab led to a rapid improvement in MG-ADL by Week 2 of treatment, which increased up until the end of the treatment period on Day 43, MG-ADL scores then worsened throughout the observation period, returning to baseline levels by the final visit. Similar patterns observed of rapid improvement then worsening towards baseline during the observation period were observed for the QMG and MGC scale outcomes.
- 6.19 In the MG0004 extension study, changes in MG-ADL, QMG and MGC scores from the first cycle of the extension study baseline to Day 43 were assessed as secondary outcomes. The submission noted that mean changes in these scores exceeded the minimal clinically important difference (2-points reduction in MG-ADL, 3-point reduction in QMG or MGC) from the first visit (Week 5) during the treatment period and were maintained until the start of the observation period (Week 52), at which point scores returned towards baseline. Low patient numbers towards the end of the MG0004 study (only 17 patients remained enrolled at Week 37) limit the usefulness of these results.
- 6.20 In the MG0007 extension study, improvements in MG-ADL, QMG and MGC scores were observed from Day 8 of each cycle and continued through Day 43 in both rozanolixizumab treatment groups. The study report noted that clinically relevant

reductions were consistently observed with repeated cyclic treatment. There was no clear pattern of increased or reduced treatment effect with subsequent cycles.

6.21 Table 5 summarises the proportion of MG-ADL, QMG and MGC responders at Day 43.

Table 5: MG-ADL, QMG and MGC responders at day 43, MycarinG trial (ITT population)

	RLZ ~7 mg/kg N = 66	RLZ ~10 mg/kg N = 67	Placebo N = 67
MG-ADL responders at day 43 (≥2-point reduction from baseline)			
Responders, n (%)	46 (69.7)	43 (64.2)	20 (29.9)
RLZ vs placebo, OR (95% CI)	5.40 (2.58, 11.34)	4.21 (2.04, 8.68)	-
QMG responders at day 43 (≥3-point reduction from baseline)			
Responders, n (%)	35 (53.0)	45 (67.2)	25 (37.3)
RLZ vs placebo, OR (95% CI)	1.90 (0.95, 3.79)	3.44 (1.69, 6.99)	-
MGC responders at day 43 (≥3-point reduction from baseline)			
Responders, n (%)	39 (59.1)	46 (68.7)	26 (38.8)
RLZ vs placebo, OR (95% CI)	2.28 (1.14, 4.56)	3.45 (1.69, 7.04)	-
Minimal symptom expression at any time during treatment and observation periods (MG-ADL score of 0 or 1)			
Yes, n (%)	17 (25.8)	19 (28.4)	2 (3.0)

Source: Table 2.5-2, p101; Table 2.5-6, pp104-105 of the submission; Table 8-10, p138 MycarinG clinical study report.

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; MG-ADL, myasthenia gravis activities of daily living; MGC, myasthenia gravis composite; OR, odds ratio; QMG, quantitative myasthenia gravis; RLZ, rozanolixizumab; SD, standard deviation; SE, standard error

Bold indicates statistically significant results

Note: MG-ADL response was defined as at least a 2-point reduction from baseline, while QMG and MGC response were defined as at least a 3-point reduction from baseline.

6.22 Statistically significantly greater proportions of patients treated with rozanolixizumab achieved an MG-ADL and MGC response at Day 43 compared to placebo. A statistically significantly greater proportion of patients treated with rozanolixizumab ~10 mg/kg achieved a QMG response at Day 43 compared to placebo. However, the difference between the ~7 mg/kg arm and placebo did not reach statistical significance.

6.23 Divergent bar plots of improvement in MG-ADL and QMG at Day 43 showed that regardless of more stringent thresholds applied to define meaningful change for the MG-ADL or QMG scale, there was consistently a higher percentage of patients in the rozanolixizumab treatment arms who reported improvement compared to patients in the placebo arm.

6.24 Just over a quarter of patients treated with rozanolixizumab in the MycarinG trial achieved minimal symptom expression at any time during the trial (measured as MG-ADL scores of 0 or 1), compared to 3% of placebo treated patients. In the MG0007 extension study, minimal symptom expression (score of 0 or 1 on MG-ADL scale at any time during the treatment or 16-week observation period for each cycle) was achieved across cycles ranging from 27.8% in Cycle 2 to 40.8% in Cycle 7, with no clear pattern of increased or reduced minimal symptom expression with subsequent cycles.

6.25 Observed results and change from baseline to Day 43 in quality-of-life measures (MG-QoL15r and EQ-5D-5L VAS scales) in the MycarinG trial are summarised in Table 6.

Table 6: Mean change from baseline in quality-of-life outcomes, MycarinG trial (ITT population)

	RLZ ~7 mg/kg N = 66	RLZ ~10 mg/kg N = 67	Placebo N = 67
MG-QoL15r			
Baseline Mean (SD)	15.7 (7.7)	15.5 (6.6)	15.0 (6.4)
Day 43 Mean (SD)	11.7 (8.0)	10.0 (7.3)	13.7 (6.6)
Mean change at Day 43 (SD)	-4.0 (6.1)	-5.3 (5.9)	-1.3 (4.3)
EQ-5D-5L VAS			
Baseline Mean (SD)	57.8 (16.5)	56.8 (17.2)	54.4 (19.2)
Day 43 Mean (SD)	70.2 (19.9)	68.5 (19.4)	60.0 (18.5)
Mean change at Day 43 (SD)	12.2 (19.9)	11.4 (16.8)	6.1 (18.2)

Source: Table 7.3.19, pp1670-1672; Table 7.3.21, pp1683-1685, MG0003 Tables, MycarinG clinical study report.

Abbreviations: VAS, visual analogue scale; MG-QoL15r, Myasthenia Gravis Quality of Life 15 item scale revised; SD, standard deviation
 Note: Lower scores on the MG-QoL15r scale indicate better quality of life, while higher scores on the EQ-5D-5L VAS scale indicate better quality of life. Quality of life outcomes were exploratory only in the MycarinG trial.

- 6.26 There was a higher mean improvement from baseline in MG-QoL15r and EQ-5D-5L VAS scores at Day 43 in the MycarinG trial for both rozanolixizumab groups compared with placebo.
- 6.27 The MG0007 study report noted that patient-reported outcomes including EQ-5D-5L and MG-QoL15r supported the consistent benefit of rozanolixizumab in patients with myasthenia gravis. Improvements MG-QoL-15r and EQ-5D-5L VAS scores from baseline to Day 43 were observed for both rozanolixizumab treatment groups with a consistent response observed with repeated cyclic treatment.
- 6.28 Treatment exposure in study MG0007 is summarised in Table 7.

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Table 7: Study cycles and time in study, MG0007 extension study

	Rozanolixizumab total N=157
Total Study Cycles	962
Cycles per patient, mean (SD)	6.1 (4.4)
Cycles per patient, median (range)	6.0 (1, 17)
Number of cycles per participant year	3.59
Total Study Infusions	5,333
Infusions per patient, mean (SD)	34.0 (25.2)
Infusions per patient, median (range)	33.0 (1, 98)
Infusions per patient per cycle, mean (SD)	5.4
Infusions per patient per cycle, median (range)	6.0 (1, 6)
Total time in study (months)	3,263.1
Total time in study (days)	97,893
Annualised cycles per patient (962 / (97,893/365.25))	3.59
Annualised infusions per patient (5,333 / (97,893/365.25))	19.90
Mean (SD)	20.78 (9.31)
Median	24.20
Min, max	0.1, 34.6
Time in study, n (%)	
< 3 months	10 (6.4)
≥ 3 to < 6 months	8 (5.1)
≥ 6 to < 9 months	10 (6.4)
≥ 9 to < 12 months	4 (2.5)
≥ 12 to < 18 months	14 (8.9)
≥ 18 to < 24 months	31 (19.7)
≥ 24 to < 30 months	65 (41.4)
≥ 30 months	15 (9.6)

Source: Table 8-1, p101 MG0007 clinical study report, July 2024; Table 5.1.3, p291, MG0007 tables, MG0007 clinical study report, July 2024

Abbreviations: SD, standard deviation

- 6.29 The median time in the MG0007 study was 24.2 months (range 0.2 to 34.6 months), with 79.6% of the 157 patients enrolled for a year or more and 51% enrolled for 2 or more years. Overall, patients enrolled in MG0007 underwent 962 treatment cycles, with a median 6.0 (range 1 to 17) cycles, or 3.59 cycles per patient year. Patients received an average of 34 infusions during the study, with the majority of patients (75.2%) receiving all 6 infusions per cycle (mean 5.4 infusions per cycle per patient).
- 6.30 No measure of time between cycles was available in the MycarinG trial as patients were treated for only one 6-week cycle followed by an 8-week observation period. Treatment-free intervals (time from last dose of previous cycle to first dose of subsequent cycle) were measured in the MG0007 extension study and are summarised in Table 8 for all patients (n=157).

Table 8: Survival analysis of treatment-free interval (Safety Set, MG0007 extension study)

Between Cycles	n	Median (days)	95% CI	% Censored
1 to 2	157	64.0	50.0, 71.0	19.7
2 to 3	126	51.0	43.0, 66.0	16.7
3 to 4	105	43.0	38.0, 53.0	9.5
4 to 5	95	43.0	37.0, 50.0	8.4
5 to 6	87	44.0	37.0, 50.0	5.7
6 to 7	82	43.0	36.0, 49.0	13.4
7 to 8	71	41.0	36.0, 43.0	11.3
8 to 9	63	37.0	35.0, 40.0	17.5
9 to 10	52	31.0	29.0, 36.0	21.2
10 to 11	41	31.0	28.0, 36.0	26.8
11 to 12	30	29.0	22.0, 34.0	26.7

Source: Table 9-10, p177 MG0007 clinical study report, July 2024
 Abbreviations: CI, confidence interval

- 6.31 The median treatment-free interval was approximately 9 weeks between Cycles 1 and 2, and approximately 7 to 9 weeks between Cycles 2 and 3. Over subsequent cycles, the median treatment-free interval gradually decreased from approximately 6 weeks to approximately 4 weeks by Cycle 12.
- 6.32 Three (4.5%) placebo-treated patients received rescue therapy during the MycarinG treatment period, with one of these patients requiring additional rescue therapy during the observation period. One patient (1.5%) in the rozanolixizumab ~7 mg/kg arm and 2 patients (3%) in the ~10 mg/kg arm required rescue therapy during the observation period. All patients received IVIg as rescue medication. Additional patients who required rescue therapy during the observation period of MycarinG opted to roll over to the MG0004 (10.5% of total study population) or MG0007 (12.5%) extension studies to receive further treatment with rozanolixizumab. During the MG0007 extension study, 15.9% of patients received rescue therapy (IVIg, PLEX or intravenous steroids). The median time to rescue therapy was not reached in the rozanolixizumab ~7 mg/kg arm and was 969 days in the ~10 mg/kg treatment arm. Exacerbations or myasthenic crisis events were not captured as clinical outcomes in the rozanolixizumab studies.

Rozanolixizumab versus IVIg

- 6.33 The submission noted that there were several differences across the IVIg trials including dose regimens, timepoints for outcome assessments and disease characteristics that precluded a pooled analysis of outcomes and therefore conducted indirect comparisons between the MycarinG rozanolixizumab trial and the IVIg trials individually. No non-inferiority margins were specified, with the submission assuming non-inferiority between treatments based on a lack of statistically significant difference.
- 6.34 The submission did not describe the methods used for performing the indirect comparisons and did not provide documentation in order to verify the results of the indirect comparisons.

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- 6.35 The indirect comparison of the MycarinG trial (~7 mg/kg arm only) and Bril 2024 was the key evidence presented for the submission's claim of non-inferiority of rozanolixizumab and IVIg. The submission noted differences between the trials in terms of baseline disease severity and functional impairment. Concomitant myasthenia gravis therapies could not be compared between trials as details were not provided in Bril 2024. The submission noted that the IVIg dosing regimen used in Bril 2024 was more intensive than recommended in the Australian product information or subsidised by the NBA, which may overestimate the efficacy of IVIg at doses recommended in Australia. The PSCR argued that the full publication of Bril 2024 (which became available after lodgement of the submission) enabled a comparison of the baseline characteristics across MycarinG and Bril 2024. The PSCR stated "both trials enrolled patients of a similar age and functional impairment at baseline: a mean MG-ADL score across treatment arms of 7-8, QMG of 15-16, and MGC of 15-17. MycarinG enrolled slightly more severe patients based on the MGFA classification, but similar proportions of patients received concomitant treatment with an NS-IST at baseline across treatment arms and the studies (49-56%)."
- 6.36 The submission noted that outcomes were assessed at 24 weeks in Bril 2024 compared to 6 weeks in MycarinG and argued that IVIg results at week 24 would be a likely overestimate of the efficacy of IVIg at Week 6. The evaluation considered that this was not adequately supported, as the comparison does not take into account the differences in treatment effects over time, with waning efficacy of rozanolixizumab after each 6-week cycle compared to a constant treatment effect for IVIg. The PSCR provided the results from Bril 2024 at Week 6 (which were included in the full publication) to enable a comparison of outcomes at the same time-point.
- 6.37 Results for the indirect comparisons of MG-ADL, MGC and QMG responder rates for the MycarinG trial ITT population (~7 mg/kg arm only) and the Bril 2024 ITT population are summarised in Table 9.

Table 9: Indirect comparison of responder efficacy outcomes, rozanolixizumab (MycarinG ITT population) versus IVIg (Bril 2024)

Trial	RLZ ~7 mg/kg	Placebo	IVIg	Odds ratio (95% CI)
MG-ADL responder (≥2-point improvement): all patients (6-week data from MycarinG ~7 mg/kg arm versus 24-week data from Bril 2024)				
MycarinG	46/66 (70%)	20/67 (30%)	-	5.40 (2.58, 11.34)
Bril 2024 (24-week data)	-	13/32 (41%)	21/30 (70%)	3.41 (1.19, 9.77)
Indirect comparison of rozanolixizumab versus IVIg (results > 1 favour rozanolixizumab)				1.58 (0.44, 5.74)
MGC responder (≥3-point improvement): all patients (6-week data from MycarinG ~7 mg/kg arm versus 24-week data from Bril 2024)				
MycarinG	39/66 (59%)	26/67 (39%)	-	2.28 (1.14, 4.56)
Bril 2024 (24-week data)	-	17/32 (53%)	18/30 (60%)	1.32 (0.48, 3.63)
Indirect comparison of rozanolixizumab versus IVIg (results > 1 favour rozanolixizumab)				1.73 (0.51, 5.89)
Bril 2024 (6-week data)		17/32 (53%)	18/30 (60%)	1.32 (0.48, 3.63)
Indirect comparison of rozanolixizumab versus IVIg – 6-week data				1.73 (0.51, 5.89)
QMG responder (≥3-point improvement): all patients (6-week data from MycarinG ~7 mg/kg arm versus 24-week data from Bril 2024)				
MycarinG	35/66 (53%)	25/67 (37%)	-	1.90 (0.95, 3.79)
Bril 2024 (24-week data)	-	19/32 (59%)	21/30 (70%)	1.60 (0.56, 4.57)
Indirect comparison of rozanolixizumab versus IVIg (results > 1 favour rozanolixizumab)				1.19 (0.34, 4.17)
Bril 2024 (6-week data)		11/32 (34.4%)	16/30 (53%)	2.18 (0.78, 6.07)
Indirect comparison of rozanolixizumab versus IVIg – 6-week data				0.87 (0.25, 3.00)

Source: Table 2.6-2, p137; Table 2.6-3, p138; Table 2.6-5, p140 of the submission

Abbreviations: CI, confidence interval; ITT, intent-to-treat; IVIg, intravenous immunoglobulin; OR odds ratio; RR, relative risk; RD, risk difference; RLZ, rozanolixizumab

- 6.38 Based on the indirect analyses of responder outcomes using the MG-ADL, MGC and QMG scales, there were no statistically significant differences in functional outcomes between rozanolixizumab and IVIg. The submission suggested that inconsistencies in response rates between the placebo arms of the trials may have been due to the differences in timepoints or a difference in the patient populations of the trials.
- 6.39 The submission also presented an indirect comparison of change from baseline in QMG score, which did not identify any statistically significant differences between treatments (QMG scores mean difference -1.58, 95% CI -4.73, 0.93).
- 6.40 This indirect analysis appeared to be the most robust comparison currently available between rozanolixizumab and chronic IVIg, however the evaluation considered that its applicability to Australian clinical practice was unclear as the IVIg dosing regimen used in the Bril 2024 trial was more intensive than recommended in Australia. The comparison did not address the deterioration in clinical effects that occurs between rozanolixizumab treatment cycles.
- 6.41 The indirect comparison of MycarinG and Wolfe 2002 compared outcomes at the same 6-week time point, however there were differences between the trials in eligibility criteria. The submission noted that Wolfe 2002 was prematurely terminated with only 15 of the planned 88 patients enrolled at the time of termination and was therefore underpowered to determine a treatment difference. The submission noted that the IVIg dose received in Wolfe 2002 was 1 g/kg on days

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- 1, 2 and 22, which was at the higher end of the recommended range for induction and maintenance dosing in the TGA Product Information and NBA criteria.
- 6.42 Based on the indirect analyses, treatment with rozanolixizumab led to statistically significantly greater improvement in MG-ADL scores and QMG scores compared with IVIg (MG-ADL scores mean difference 4.89; 95% CI 7.54, 2.24; QMG scores mean difference -5.08, 95% CI -9.14, -1.02). Given the limited data, differences in baseline levels of functional impairment and small patient numbers from Wolfe 2002, results of the indirect comparison should be interpreted with caution. The Wolfe 2002 paper did not present a summary of safety outcomes, and no indirect comparison could be made.
- 6.43 The indirect comparison of MycarinG with the Zinman 2007 IVIg trial was hampered by the limited details on eligibility criteria and baseline characteristics reported in Zinman 2007, although there were differences between the trials in baseline functional impairment. Patients in Zinman 2007 received IVIg 2 g/kg in divided doses over 2 days, corresponding to the maximum dose for induction treatment recommended in the IVIg Product Information. No further maintenance doses were administered in the trial.
- 6.44 Based on the indirect comparison, there were no statistically significant differences between rozanolixizumab and IVIg for change from baseline in QMG scores at either 2 or 4 weeks. Given the paucity of data reported in Zinman 2007 and the IVIg dose limited to induction treatment only with no maintenance dose, the results of the indirect comparison should be interpreted with caution. The Zinman 2007 paper did not present a summary of safety outcomes.

Rozanolixizumab versus efgartigimod

- 6.45 The submission presented an indirect comparison of a 6-week treatment cycle of rozanolixizumab ~7 mg/kg once weekly (based on the MycarinG trial) versus a 4-week treatment cycle of efgartigimod 10 mg/kg intravenously once weekly (based on a meta-analysis of the ADAPT and Howard 2019 trials) for the treatment of adults with MGFA class II to IV AChR-positive generalised myasthenia gravis, with placebo as the common reference. The submission did not adequately justify inclusion of Howard 2019, a phase 2 exploratory study of 24 patients that was not adequately powered for hypothesis testing.
- 6.46 The submission acknowledged that there were differences between the trials in terms of trial duration, AChR antibody status, degree of functional impairment at baseline, and baseline disease severity. During the evaluation, it was also noted that there were differences between the trials in terms of prior thymectomy, and baseline corticosteroid use.
- 6.47 The MycarinG and ADAPT trials used the same definitions of response (2-point improvement from baseline in MG-ADL; 3-point improvement from baseline in QMG). However, while the proportion of responders was based on change from

baseline to day 43 (week 6) in MycarinG; in ADAPT, a responder was required to sustain the response for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the cycle. The submission acknowledged that it may be harder for patients in the ADAPT trial to achieve response compared to the MycarinG trial. The use of less rigorous response outcomes in the MycarinG trial was in favour of rozanolixizumab. In Howard 2019, the proportion of responders was based on change from baseline to day 29 or 36.

6.48 The indirect comparisons of rozanolixizumab versus efgartigimod for responder outcomes are summarised in Table 10.

Table 10: Indirect comparison of responder efficacy outcomes with rozanolixizumab and efgartigimod

Trial	Rozanolixizumab ~7 mg/kg	Placebo	Efgartigimod	Odds ratio (95% CI)
MG-ADL responder (≥2-point improvement) in cycle 1: all patients (6-week data from MycarinG versus 4-week data from ADAPT; Howard 2019)				
MycarinG ^a	46/66 (70%)	20/67 (30%)	-	5.40 (2.58, 11.34)
ADAPT ^b	-	31/83 (37%)	57/84 (68%)	3.54 (1.87, 6.70)
Howard 2019 ^c	-	5/12 (42%)	10/12 (83%)	7.00 (1.04, 46.95)
Meta-analysis of efgartigimod versus placebo (I ² =0)				3.79 (2.07, 6.95)
Indirect comparison of rozanolixizumab versus efgartigimod (results > 1 favour rozanolixizumab)				1.42 (0.55, 3.71)
MG-ADL responder (≥2-point improvement) in cycle 1: AChR-positive patients (6-week data from MycarinG versus 4-week data from ADAPT; Howard 2019)				
MycarinG ^a	41/60 (68%)	17/54 (31%)	-	4.70 (2.13, 10.36)
ADAPT ^b	-	19/64 (30%)	44/65 (68%)	4.96 (2.35, 10.47)
Howard 2019 ^c	-	5/12 (42%)	10/12 (83%)	7.00 (1.04, 46.95)
Meta-analysis of efgartigimod versus placebo (I ² =0)				5.20 (2.59, 10.41)
Indirect comparison of rozanolixizumab versus efgartigimod (results > 1 favour rozanolixizumab)				0.90 (0.32, 2.59)
QMG responder (≥3-point improvement) in cycle 1: AChR-positive patients (6-week data from MycarinG versus 4-week data from ADAPT; Howard 2019)				
MycarinG ^a	30/60 (50%)	18/54 (33%)	-	2.00 (0.94, 4.27)
ADAPT ^b	-	9/64 (14%)	41/65 (63%)	10.84 (4.18, 31.20)
Indirect comparison of rozanolixizumab versus efgartigimod (results > 1 favour rozanolixizumab)				0.19 (0.06, 0.61)

Source: Table 2.6.4, p59; Table 2.6.5, p61; Table 2.6.6, p63 of Appendix 10 of the submission

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

^a Based on patients achieving response (≥ 2-point improvement in MG-ADL or ≥ 3-point improvement in QMG) from baseline to day 43 (6 weeks).

^b Based on patients achieving sustained response (≥ 2-point improvement in MG-ADL or ≥ 3-point improvement in QMG) for at least 4 consecutive weeks, with the first improvement occurring by week 4 of the treatment cycle.

^c Based on patients achieving response (≥ 2-point improvement in MG-ADL or ≥ 3-point improvement in QMG) from baseline to day 29 (4 weeks).

6.49 The submission noted differences between trials in the proportions of responders in the placebo common reference arms, with the proportion of QMG responders in the placebo arm of MycarinG (33%) more than double the proportion of responders in ADAPT (14%). Based on the indirect comparisons for MG-ADL responders, there were no statistically significant differences between rozanolixizumab and efgartigimod based on whole trial populations and the AChR-positive subgroups. However, the indirect comparison based on QMG responders in the AChR-positive subgroups was statistically significant, in favour of efgartigimod. The submission noted that the indirect comparison may not be reliable. The results were difficult to

interpret given differences in outcome definitions between MycarinG and ADAPT and uncertainty in estimates from the exploratory Howard 2019 trial.

6.50 Indirect comparisons based on changes from baseline in MG-ADL, QMG and MGC were also presented in the submission. The submission noted differences between trials in the mean changes from baseline in functional outcomes in the placebo common reference arms. Based on the indirect analyses, there were no statistically significant differences in functional outcomes between rozanolixizumab and efgartigimod. However, the evaluation considered there were wide confidence intervals around the indirect estimates of effect.

6.51 Table 11 compares safety data from the MycarinG trial with available safety data from the efgartigimod trial publications. The submission noted that safety outcomes were reported over 6 weeks in the MycarinG trial, compared to 26 weeks in ADAPT and 11 weeks in Howard 2019. The submission stated that this may bias the outcomes in favour of rozanolixizumab. The resubmission noted differences in the incidence of adverse events across the placebo arms of the trials.

Table 11: Comparison of safety outcomes in the MycarinG, ADAPT and Howard 2019 trials (whole trial population)

Adverse event	MycarinG			ADAPT		Howard 2019	
	RLZ ~7mg/kg (N=64)	RLZ ~10 mg/kg (N=69)	Placebo (N=67)	Efgartigim od (N=84)	Placebo (N=83)	Efgartigimo d (N=12)	Placebo (N=12)
Any adverse event	52 (81%)	57 (83%)	45 (67%)	65 (77%)	70 (84%)	10 (83%)	10 (83%)
Serious adverse event	5 (8%)	7 (10%)	6 (9%)	4 (5%)	7 (8%)	0	0
Severe adverse event	3 (5%)	13 (19%)	3 (4%)	9 (11%)	8 (10%)	0	0
Any AE leading to discontinuation	2 (3%)	5 (7%)	2 (3%)	3 (4%)	3 (4%)	0	0
Any infection	10 (16%)	21 (30%)	13 (19%)	39 (46%)	31 (37%)	NR	NR
Deaths	0	0	0	0	0	0	0
Most common adverse events (reported in at least 2 trials)							
Headache	29 (45%)	26 (38%)	13 (19%)	24 (29%)	23 (28%)	4 (33%)	3 (24%)
Nasopharyngitis	1 (2%)	5 (7%)	3 (4%)	10 (12%)	15 (18%)	NR	NR
Nausea	5 (8%)	8 (12%)	5 (7%)	7 (8%)	9 (11%)	1 (8%)	1 (8%)
Diarrhoea	16 (25%)	11 (16%)	9 (13%)	6 (7%)	9 (11%)	1 (8%)	1 (8%)
Upper respiratory tract infection	2 (3%)	1 (1%)	1 (1%)	9 (11%)	4 (5%)	NR	NR
Urinary tract infection	2 (3%)	2 (3%)	4 (6%)	8 (10%)	4 (5%)	NR	NR
Abdominal pain upper	3 (5%)	2 (3%)	2 (3%)	NR	NR	1 (8%)	1 (8%)
Arthralgia	4 (6%)	5 (7%)	2 (3%)	NR	NR	0	2 (17%)
Myalgia	2 (3%)	4 (6%)	1 (1%)	NR	NR	2 (17%)	0

Source: Table 2.5-10, pp12-113 of the submission; Table 2.5.3, p46 and Table 2.5.4, p48 of Appendix 10 of the submission
Abbreviations: AE, adverse event; NR, not reported; RLZ, rozanolixizumab

6.52 The submission presented indirect comparisons of safety outcomes which did not identify statistically significant differences between rozanolixizumab and efgartigimod for serious adverse events, adverse events leading to discontinuation,

and severe adverse events. However, results based on any adverse event were statistically significant, favouring efgartigimod. The submission considered that the lower proportion of patients reporting adverse events in the placebo arm of MycarinG (67%) compared to the efgartigimod trials (83-84%) may have biased the results in favour of efgartigimod. However, rates of adverse events (e.g. events per patient-year) were not reported. A comparison of the incidence of adverse events based on different durations of follow-up is not informative.

Indirect comparisons with near market comparators

- 6.53 During the evaluation, summary details were presented of 5 published network meta-analyses that compared zilucoplan and near market comparators efgartigimod, ravulizumab, and rozanolixizumab (Chen 2023, Gu 2024, Sacca 2023, Smith 2024, Zhong 2024) and one published matching adjusted indirect comparison that compared efgartigimod and ravulizumab (van Steen 2024). A full assessment of these analyses was beyond the scope of the evaluation.
- 6.54 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.
- 6.55 The ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod alfa and rozanolixizumab). The ESC considered that the published NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 6.56 None of the indirect treatment comparisons included IVIg or PLEX trials.

Comparative harms

- 6.57 Table 12 presents an overall summary of adverse events reported in the MycarinG trial and MG0004 and MG0007 extension studies. Safety was assessed as the primary outcome in the extension studies.

Table 12: Summary of key adverse events in the MycarinG trial and extension studies

	MycarinG			MG0004	MG0007
	RLZ ~7mg/kg N = 64	RLZ ~10mg/kg N = 69	Placebo N = 67	RLZ total N=70	RLZ total N=157
Any TEAE	52 (81.3)	57 (82.6)	45 (67.2)	60 (85.7)	142 (90.4)
Serious TEAEs	5 (7.8)	7 (10.1)	6 (9.0)	9 (12.9)	45 (28.7)
Discontinuation from study due to TEAEs	2 (3.1)	5 (7.2)	2 (3.0)	4 (5.7)	26 (16.6)
Permanent discontinuation of study drug due to TEAEs	2 (3.1)	4 (5.8)	2 (3.0)	3 (4.3)	27 (17.2)
Temporary discontinuation of study drug due to TEAEs	3 (4.7)	6 (8.7)	1 (1.5)	22 (31.4)	39 (24.8)
TEAE requiring dose change	NR	NR	NR	1 (2.4)	4 (2.5)
Treatment-related TEAEs ^a	32 (50.0)	39 (56.5)	22 (32.8)	41 (58.6)	88 (56.1)
Severe TEAEs ^b	3 (4.7)	13 (18.8)	3 (4.5)	17 (24.3)	47 (29.9)
All deaths (AEs leading to deaths)	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.5)
Adverse events of interest					
Hy's Law (liver injury)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Severe headache	1 (1.6)	6 (8.7)	0 (0)	5 (7.1)	1 (0.6)
Severe diarrhoea	0 (0)	2 (2.9)	0 (0)	1 (1.4)	1 (0.6)
Severe vomiting	0 (0)	1 (1.6)	0 (0)	0 (0)	0 (0)
Opportunistic infection	0 (0)	0 (0)	0 (0)	0 (0)	4 (2.5)
Hypersensitivity reactions	7 (10.9)	4 (5.8)	1 (1.5)	12 (17.1)	21 (13.4)
Infections	10 (15.6)	21 (30.4)	13 (19.4)	22 (31.4)	90 (57.3)
Aseptic meningitis	NR	NR	NR	NR	1 (0.6)
Common TEAEs					
Headache	29 (45.3)	26 (37.7)	13 (19.4)	25 (35.7)	68 (43.3)
Diarrhoea	16 (25.0)	11 (15.9)	9 (13.4)	13 (18.6)	44 (28.0)
Pyrexia	8 (12.5)	14 (20.3)	1 (1.5)	7 (10.0)	26 (16.6)

Source: Table 2.5-10, pp112-113; Table 2.5-15, p119 of the submission; Section 8.8 pp87-94 of the MG0004 clinical study report; Table 8.1.1, Table 8.1.2, MG0004 Tables.pdf; Table 8-2, p103; Table 8-4, p109; Section 8.9, pp120-126 MG0007 clinical study report, July 2024. Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event

^a based on investigator assessment

^b Severe TEAEs are those with CTCAE Grade 3 or higher, or with intensity recorded as 'severe' by the investigator

6.58 In the MycarinG trial, the number of patients who experienced treatment emergent adverse events (TEAEs) and treatment-related TEAEs was comparable across the rozanolixizumab treatment arms but lower in the placebo arm. The most frequently reported adverse events in each treatment arm were headache, diarrhoea and pyrexia, occurring more frequently in the rozanolixizumab arms compared to placebo. No deaths were reported during the study. The number of patients reporting serious adverse events in the MycarinG trial was comparable across all groups, with the only serious events occurring in more than one patient per group being myasthenia gravis (1 patient in rozanolixizumab ~7 mg/kg arm, 2 in the ~10 mg/kg arm, and 1 patient in placebo arm) or myasthenia gravis crisis (2 patients in placebo arm). Serious TEAEs considered to be related to rozanolixizumab treatment

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were reported by 3 patients in the ~7 mg/kg arm (joint pain of moderate intensity, vomiting of severe intensity, and gastritis of mild intensity) and two patients in the ~10 mg/kg arm (chest pain of moderate intensity, headache of severe intensity). TEAEs leading to temporary or permanent treatment discontinuation or withdrawal from the study, along with severe TEAEs, occurred in more patients treated with rozanolixizumab ~10 mg/kg arm than the rozanolixizumab ~7 mg/kg arm or placebo. Safety data from MycarinG was limited to 6 weeks of treatment and 8 weeks of observation, with many patients discontinuing the trial during the observation period to roll-over to either of the MG0004 or MG0007 extension studies, limiting the usefulness of the data in determining comparative safety.

- 6.59 Safety outcomes reported in the MG0004 study were consistent with the MycarinG trial, however greater proportions of patients in MG0004 experienced adverse events given the longer duration of the study treatment (52 weeks of continuous treatment, with a median duration of exposure 22.9 weeks). Of all patients treated with rozanolixizumab, 85.7% experienced any TEAE, 12.9% a serious TEAE and 24% a severe TEAE. Only 4.3% of patients permanently discontinued treatment due to a TEAE and there were no deaths reported due to a TEAE.
- 6.60 Safety outcomes in the MG0007 study (July 2024 complete dataset) were based on patients enrolled for a median 24.2 months (maximum 34.6 months, with the majority of patients in the study for 18 to 30 months). Adverse event outcomes were grouped according to the most recent dose level of rozanolixizumab received prior to the onset of the adverse event, with the report noting a higher incidence of treatment emergent adverse events in the ~10 mg/kg arm than the ~7 mg/kg arm, including serious or treatment-related adverse events, and those leading to discontinuation from the study drug. There were 6 deaths reported in the MG0007 study: 3 due to treatment emergent adverse events (COVID-19, cardiac failure), 1 due to a combination of a treatment emergent adverse event (pneumonia) and non-treatment emergent adverse events, and one due to a non-treatment emergent adverse event (myocardial infarction). A further death occurred 804 days after the last dose of rozanolixizumab due to small cell lung cancer progressing to a fatal outcome after the study. Serious treatment emergent adverse events included myasthenia gravis (15 patients; 9.6%), myasthenia gravis crisis (4 patients; 2.5%), COVID-19 (3 patients; 1.9%) or pneumonia (2 patients; 1.3%). Approximately 16% of patients discontinued from the study, while 17% and 25% permanently or temporarily halted their study treatment respectively, with the most common reason for all discontinuations being infections and infestations. A total of 39% of MG0007 study participants discontinued from the study due to adverse events, lack of efficacy or withdrawal by subject.
- 6.61 The MG0007 study report also reported the incidence of any treatment emergent adverse event by treatment cycle. Overall, there was no increase in the incidence of treatment emergent adverse events from cycle to cycle, with the incidence of serious

adverse events or those leading to study or treatment discontinuation remaining low with repeated cyclic treatment.

- 6.62 Immunogenicity data from MG0007 were available for 121 patients over a period of at least 1 year. Prevalence of pre-existing anti-drug antibodies (ADAs) against rozanolixizumab was low (<1%). There was a general increase in ADAs observed on repeated cyclic rozanolixizumab treatment. By Cycle 1, 33.6% of participants developed treatment-emergent ADAs and 23.4% developed ADAs that were neutralising. By Cycle 12, 68.4% of participants developed treatment-emergent ADAs and 42.1% developed ADAs that were neutralising. Up to the individual last visit, 89 (58.9%) patients had developed treatment-emergent ADAs to rozanolixizumab, and 33.8% were neutralising-antibody positive. The clinical study report noted that there was no apparent impact of immunogenicity on clinical efficacy or safety.

Rozanolixizumab versus IVIg

- 6.63 The submission also presented an indirect comparison of serious adverse events which did not identify any statistically significant differences in adverse events between rozanolixizumab and IVIg. The Brill 2024 publication provided limited additional adverse event data for the IVIg trial that were not provided in the submission (see Table 13). However, rates of adverse events (e.g. events per patient-year) were not reported. The evaluation noted that the comparison of the incidence of adverse events based on different durations of follow-up was not informative.

Table 13: Adverse event outcomes from MycarinG trial ITT population and Brill 2024

	MycarinG (6 weeks)			Brill 2024 (24 weeks)	
	RLZ 7mg/kg N = 64	RLZ 10mg/kg N = 69	Placebo N = 67	IVIg N = 30	Placebo N = 32
Any TEAE	52 (81.3)	57 (82.6)	45 (67.2)	22 (73.3)	22 (68.8)
Serious TEAEs	5 (7.8)	7 (10.1)	6 (9.0)	5 (16.7)	4 (12.5)
Discontinuation from study due to TEAEs	2 (3.1)	5 (7.2)	2 (3.0)	2 (6.7)	2 (6.3)
All deaths (AEs leading to deaths)	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)
Headache	29 (45.3)	26 (37.7)	13 (19.4)	9 (30.0)	4 (12.5)
Diarrhoea	16 (25.0)	11 (15.9)	9 (13.4)	3 (10.0)	2 (6.3)

Source: Table 2.5-10, pp112-113; Table 2.5-15, p119 of the submission; Table 3, Brill 2024.

Abbreviations: AE, adverse event; CTCAE, common terminology criteria for adverse events; RLZ, rozanolixizumab; TEAE, treatment-emergent adverse event

Benefits/harms

- 6.64 A benefits/harms table was not presented as the submission made a claim of non-inferiority.

Clinical claim

- 6.65 The submission described rozanolixizumab in combination with standard of care as superior in terms of efficacy and non-inferior in terms of safety compared to standard of care alone (including anti-cholinesterase inhibitors, corticosteroids and other immunosuppressants such as mycophenolate mofetil, azathioprine,

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methotrexate, cyclophosphamide, ciclosporin). The evaluation considered this claim was reasonable in regard to efficacy and unclear in regard to safety. The evaluation considered the following issues should be considered:

- The results from the MycarinG trial do not address sustained efficacy beyond the first cycle of treatment, and no evidence of comparative efficacy or safety were available beyond 6 weeks of treatment and 8 weeks of observation.
- Available observational data from the longer-term extension studies suggest that a reduction in symptoms can be maintained while patients are on therapy, but the gap between treatment cycles reduces over time.
- The overall incidence of treatment emergent adverse events was higher in the rozanolixizumab ~7 mg/kg arm than in the placebo arm, with the submission noting a statistically significantly greater incidence of headache, pyrexia, and treatment-related adverse events in the rozanolixizumab ~7 mg/kg arm compared to placebo. However, the incidence of other adverse events, serious and severe adverse events and discontinuations due to adverse events were similar between treatment arms. Safety data from MycarinG were limited to 6 weeks of treatment and 8 weeks of observation, with many patients discontinuing the trial during the observation period to roll-over to either of the MG0004 or MG0007 extension studies, limiting the usefulness of the data in determining comparative safety. There is an important identified risk of aseptic meningitis with rozanolixizumab treatment.

6.66 The submission claimed the limited evidence base available for chronic IVIg/PLEX precludes any robust clinical conclusion on the comparative efficacy and safety of treatments. However, the submission considered that it is likely that 6 weeks of rozanolixizumab (1 treatment cycle in MycarinG trial) is at least non-inferior in terms of efficacy and safety compared to 24 weeks of IVIg/PLEX (from Bril 2024). The evaluation considered this claim was uncertain due to the limitations of the indirect analyses and the available evidence for IVIg. There were differences between the included trials in study duration and baseline disease severity and also differences in outcomes across the placebo arms of the MycarinG trial and the key IVIg evidence (Bril 2024). Additionally, the indirect comparisons did not address the deterioration in clinical effects that occurs between rozanolixizumab treatment cycles. The ESC and the PBAC acknowledged the limitations of the available evidence for chronic IVIg and agreed with the submission's claim of non-inferior efficacy and safety versus chronic IVIg and PLEX.

6.67 The submission described rozanolixizumab as non-inferior in terms of efficacy and safety compared to efgartigimod. The evaluation considered there were limitations with the indirect analyses due to differences between included trials in study duration, baseline disease characteristics, baseline therapies, and outcome definitions. The submission noted large differences in outcomes across the placebo arms of the trials; and considered that the indirect analyses were not reliable for

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some outcomes where results were statistically significantly in favour of efgartigimod (QMG responders, any adverse event). Overall, the ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab).

- 6.68 Overall, the PBAC considered that rozanolixizumab has non-inferior comparative effectiveness and safety versus chronic IVIg and also against ravulizumab, efgartigimod and zilucoplan.

Economic analysis

- 6.69 The submission claimed that one six-week treatment cycle of rozanolixizumab (6 infusions with tiered weight-based dosing) was non-inferior to six months of treatment with IVIg (2 g/kg induction dose split over 2 infusions and 7 × 1 g/kg maintenance infusions). This claim was not adequately supported by the available clinical data but was not the basis of the equi-effective doses used in the cost-minimisation approach.
- 6.70 The submission estimated equi-effective doses based on separate annualised estimates of use for both rozanolixizumab (17.80 infusions per year) and IVIg (19.26 infusions per year). This corresponded to equi-effective doses of rozanolixizumab 10,508 mg and IVIg 927 g per year.
- 6.71 The submission estimated the annualised number of rozanolixizumab infusions per year based on a *post hoc* analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension. Patients in the MycarinG trial and MG0007 study were required to meet specific thresholds for re-treatment (increase of 2.0 points on the MG-ADL or 3.0 points on the QMG scale), with a suggested minimum time of 4 weeks between cycles, which may not be representative of clinical practice. Additionally, patients in the MG0007 study could use higher doses than recommended in the product information, which may affect compliance as well as longer-term measures of efficacy and safety. Finally, the estimate used in the submission was based on interim data from the MG0007 extension study which appeared to underestimate utilisation compared to estimates from the final MG0007 study report, which reported higher numbers of average cycles and infusions per year along with decreasing time periods between later cycles. Sensitivity analyses based on utilisation data from the final MG0007 report are included in Table 15.
- 6.72 The PSCR and pre-PBAC response presented new estimates derived from a dataset which included final data from the MG0007 trial (pooled data set S2) and claimed these showed that the annualised mean cycles of rozanolixizumab had decreased from 3.4 to 2.9 cycles while the mean number of infusions had decreased from 17.8 to 16.0 per year. The ESC commented that the PSCR's calculations were poorly documented, presented as a single PowerPoint slide, and that it was unclear whether the estimates included both complete and incomplete cycles. Additionally, the reporting of the mean annualised number of cycles was inconsistent, with both 2.9 and 3.2 cycles per year reported on the same slide for the S2 Pool. Further, the

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results appeared to be inconsistent with other data (from the MG0007 study) which suggested that the frequency of treatment cycles increases with extended use of rozanolixizumab. The ESC and the PBAC considered the updated values from the PSCR and pre-PBAC response could not be verified and were not reliable for decision making.

- 6.73 Overall, the PBAC considered the submission's base case assumption of 17.80 infusions per patient per year (i.e. based on 3.4 cycles per year and 9.3 weeks between cycles) may underestimate the number of infusions in clinical practice given long term follow-up data indicated decreasing time periods between later cycles. In particular, the PBAC noted that the median time between cycles reduced from 64 days between cycles 1 and 2, to 29 days between cycles 11 and 12 (Table 8). The PBAC noted that if the minimum treatment interval of 4 weeks was used, the number of infusions would increase from 17.8 to 27.2 per year (i.e. 5.2 cycles per year), representing a 53% increase in annual dosing.
- 6.74 The PBAC considered that if re-treatment criteria in the PBS restriction were less stringent than in the trial, this may further increase the annual dose of rozanolixizumab used in clinical practice.
- 6.75 The submission estimated the annualised number of IVIg infusions per cycle based on the dosing regimen used in the Bril 2024 trial (2 g/kg loading dose split over 2 administrations and then a maintenance dose of 1 g/kg every 3 weeks; total of 24 weeks treatment). The total IVIg use per cycle was then reduced by 40% based on a sensitivity analysis included in the zilucoplan July 2024 PBAC PSD. The submission estimated the number of IVIg cycles per year based on intermittent IVIg users in the first 12 months of treatment using data from a retrospective review of US claims data (Qi 2022). The dose regimen used in the Bril 2024 trial was unlikely to be representative of Australian clinical practice (as it was inconsistent with the approved product information, exceeded the maximum subsidised dose under the NBA and was substantially higher than supported by the available Australian IVIg utilisation data) and the number of cycles estimated in the Qi (2022) study has no relevance to the estimates from the Bril 2024 trial. The PSCR argued that the IVIg dosing used in the Bril 2024 trial should form the basis of the equi-effective dose because the indirect comparison using this trial showed that rozanolixizumab was at least non-inferior to IVIg, and reducing the dose of IVIg per administration 'would likely result in a reduction of the treatment effect' even when dosing frequency is unchanged. However, in the context of the limitations of the available evidence for chronic IVIg and the frame of reference approach, the ESC considered that the equi-effective dose should be based on the average total annual dose supplied to Australian patients, as recorded in the updated NBA data of 541.1 grams.
- 6.76 Further, the evaluation noted that the estimated 40% reduction in IVIg dose used in the submission was based on an incorrect interpretation of sensitivity analyses reported in the zilucoplan July 2024 PBAC PSD, which noted that a 60% reduction (i.e. 40% of base case units) was needed to reduce the estimated dose of 1,247 g

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Table 14: Derivation of the cost-minimised price for rozanolixizumab

Variable	Value	Source
Cost of IVIg		
Total IVIg dispensed per cycle	433 g	Based on the IVIg dosing regimen used in the Bril 2024 trial and the average baseline weight of patients in the MycarinG trial (80.2 kg × 2 g/kg induction dose + 7 × 80.2 kg × 1 g/kg maintenance doses = 721 g) with an adjustment factor that reduced the total dose by 40% (721 × 0.6 = 433 g).
IVIg infusions per cycle	9	Based on the IVIg dosing regimen used in the Bril 2024 trial (induction dose split over 2 infusions and maintenance infusions every 3 weeks for 24 weeks).
Number of IVIg cycles per year	2.14	Based on a retrospective review of US claims data for IVIg intermittent users (Qi 2022)
IVIg dispensed per year	927 g	Calculation: 433 g × 2.14 The ESC considered this should be 541.06 grams based on the 2023-24 NBA data (for the IVIg myasthenia gravis 'maintenance' indication, refer to Section 7)
Cost of dispensed IVIg per year	\$█	Based on the price of Intragam 10 (2.5 g/25 mL: \$█; October 2024 NBA National Product Price List). Calculation: \$█ / g × 927 g The ESC considered this should be \$█ based on the 2023-24 NBA data (refer to Section 7). Calculation: \$█ / g × 541.06 g.
IVIg infusions per year	19.26	Calculation: 9 × 2.14 The ESC considered this should be 15.74 infusions per year based on the 2023-24 NBA data.
Cost of infusions per year	\$2,149	Based on MBS Item 14245 (\$111.60; immunomodulating agent, administration of, by intravenous infusion for at least 2 hours duration). Calculation: \$111.60 × 19.26. Using 15.74 infusions per year, the cost to the MBS would be \$1,752 per year.
Total cost of IVIg	\$█	Calculation: \$█ + \$2,149 The ESC considered this should be \$█
Cost of rozanolixizumab		
Total cost of rozanolixizumab (without premium)	\$█	Total cost of IVIg The ESC considered this should be \$█.
IV infusions per year	17.8	Based on the annualised number of rozanolixizumab infusions per year based on a post hoc analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension study.
Cost of IV infusions	\$1,986	Based on MBS Item 14245 (\$111.60; immunomodulating agent, administration of, by intravenous infusion for at least 2 hours duration). Calculation: \$111.60 × 17.8. The ESC considered this may overestimate administration costs (refer to paragraph 6.80)
Direct medicine costs of rozanolixizumab (without premium)	\$█	Calculation: \$█ – \$1,986 The ESC considered this should be \$█
Rozanolixizumab vials dispensed per infusion	2.11	Based on the recommended dosing in the draft product information and the baseline weight distribution of patients in the MycarinG trial
Vials (280 mg) dispensed per year	37.53	Calculation: 17.8 × 2.11 (i.e. 10,516 mg per year)
AEMP per vial (without premium)	\$█	Calculation: \$█ / 37.53 The ESC considered this should be \$█ per vial.
AEMP per vial (with premium)	\$█	Calculation: \$█ × █ price premium.

Source: Table 3.4-3, p175 of the submission

Abbreviations: AEMP, approved ex-manufacturer price; IV, intravenous; IVIg, IVIg, intravenous immunoglobulin; MBS, Medicare Benefits Schedule; NBA, National Blood Authority

6.79 Based on the cost minimisation approach, the submission proposed an AEMP of \$█ per vial for rozanolixizumab.

6.80 The submission used the MBS item for intravenous infusion of an immunomodulating agent for at least two hours duration (Item 14245), which may overestimate the administration costs, as the draft Product Information states that rozanolixizumab is administered as a subcutaneous infusion, delivered via a pump (refer to paragraph 3.15). The ESC considered it may be more appropriate to use the Schedule Fee of a standard MBS consultation item for a consultant physician as a proxy, per the ‘Manual of resource items and their associated unit costs’.

6.81 Table 15 presents the results of sensitivity analyses conducted during the evaluation.

Table 15: Sensitivity analyses of the cost-minimisation approach

Analyses	IVIg total cost	RLZ total cost	RLZ AEMP	% change in AEMP
Base case	\$█	\$█	\$█	-
Cost of IVIg (base case: \$█ per gram); IVIg dose adjustment factor (base case: reduction of total dose by 40%); price premium (base case: █% price premium for rozanolixizumab AEMP)				
Based on 2023-24 NBA data: - \$█ per gram - Average of 541.1 grams per year - Average of 15.7 doses per year - With █% price premium	\$█	\$█	\$█	-█%
Based on 2023-24 NBA data: - \$█ per gram - Average of 541.1 grams per year - Average of 15.7 doses per year - Without █% price premium	\$█	\$█	\$█	-█%
Annualised rozanolixizumab utilisation (base case: 17.8 infusions based on 3.4 cycles per year with 5.24 infusions cycle using post hoc analysis of the MycarinG trial and interim data from the MG0007 extension study)				
Annualised infusions from final MG0007 study report (rozanolixizumab total: 19.90 infusions)	\$█	\$█	\$█	-11%
Annualised infusions assuming 9-week treatment break between cycles (3.46 cycles; 5.24 infusions per cycle; total: 18.13 infusions)	\$█	\$█	\$█	-2%
Annualised infusions assuming 4-week treatment break between cycles (5.20 cycles; 5.24 infusions per cycle; total 27.25 infusions)	\$█	\$█	\$█	-36%
Cost of rozanolixizumab (base case: cost-minimised price versus IVIg with █% premium)				
Cost minimised price with no premium	\$█	\$█	\$█	-█%

Source: Constructed during the evaluation based on the Rystiggo (Rozanolixizumab) - gMG – CMA Excel workbook
Abbreviations: AEMP, approved ex-manufacturer price; IVIg, intravenous immunoglobulin

6.82 The cost-minimised price for rozanolixizumab was most sensitive to the estimated annualised use of IVIg, the cost per gram for IVIg, the estimated annualised use of rozanolixizumab and the inclusion of a price premium for rozanolixizumab.

6.83 The ESC considered that the cost-comparison approach should be based on the average dose per patient observed in the NBA data, without the proposed price premium. Refer to paragraph 8.23 for the PBAC’s advice regarding the cost-comparison approach.

Drug cost/patient/year

- 6.84 The calculation of rozanolixizumab drug costs was consistent between the economic and budget impact models.
- 6.85 The submission estimated that the annual drug cost for rozanolixizumab was \$ [REDACTED] (based on patients receiving 3.4 cycles × 5.24 infusions i.e. 17.8 infusions per year, assuming the same distribution of patients across weight categories as the MycarinG trial, and using the effective AEMP of \$ [REDACTED] per vial, with appropriate fees and mark-ups, assuming 74.3% public hospital and 25.7% private hospital use, and adding administration costs of \$111.60 per infusion for MBS item 14245).
- 6.86 Based on updated rozanolixizumab utilisation data from the MG0007 extension study which reported an average of 3.59 cycles × 5.24 infusions per cycle, and 19.9 infusions per year, the evaluation estimated that the annual drug cost for rozanolixizumab would be \$ [REDACTED] (based on the other estimates from the submission i.e. assuming the same distribution of patients across weight categories as the MycarinG trial and using the effective AEMP of \$ [REDACTED] per vial, with appropriate fees and mark-ups, assuming 74.3% public hospital and 25.7% private hospital use, and adding updated administration costs of \$87.30 per infusion for MBS item 116). The PBAC noted that at 6 infusions per cycle (as recommended in the product information), and 3.59 cycles per year, this would increase to 21.5 infusions per year.
- 6.87 The submission's estimated annual cost for IVIg was \$ [REDACTED] (inclusive of administration costs), based on patients receiving the IVIg dosing regimen used in the Brill 2024 trial at the average baseline weight of patients in the MycarinG trial; with an adjustment factor to reduce the total dose by 40%; and 2.14 cycles per year based on a published estimate (total 927 g per year); with IVIg costs \$ [REDACTED] per gram and administration costs of \$111.60 per infusion for MBS item 14245.
- 6.88 The ESC noted that, based on data received from the NBA on the utilisation of IVIg as maintenance therapy for Myasthenia Gravis in 2023-24, the average annual 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).

Cost-comparison

Table 16: Comparison of the annual dose and/or drug cost of rozanolixizumab and IVIg

Treatment	Annual cost or dose	Source
Rozanolixizumab		
Submission base case	10,508 mg per year	2.11 vials per infusion (assuming the same distribution of patients across weight categories in the MycarinG trial (4.2% of patients weigh ≥ 35 to < 50kg and require one vial; 80.8% weight 50 to <100kg and require two vials; 15% weigh ≥ 100 kg and require three vials). 5.24 infusions per cycle (i.e.87.3% compliance/dose intensity, the basis for this was unclear) 3.4 cycles per year based on a post hoc analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension. This equates to a treatment-free interval of 9.3 weeks between cycles. Patients in the MycarinG trial and MG0007 study were required to meet specific thresholds for re-treatment (increase of 2.0 points on the MG-ADL or 3.0 points on the QMG scale), with a suggested minimum time of 4 weeks between cycles, which may not be representative of clinical practice.
Annualised cycles from trial report and full compliance	12,711 mg per year	2.11 vials per infusion (as above), 6 infusions per cycle (full dose intensity/compliance to the number of infusions per cycle) and 3.59 cycles per year based on the annualised cycles from the final MG0007 study report (Table 7). This equates to a treatment-free interval of 8.5 weeks between cycles.
Minimum treatment-free interval and full compliance	18,415 mg per year	2.11 vials per infusion (as above), 6 infusions per cycle (full dose intensity/compliance to the number of infusions per cycle) and 5.2 cycles per year. This equates to a treatment-free interval of 4 weeks between cycles.
IVIg costing scenarios		
ESC: IVIg (average grams dispensed per maintenance MG patient)	\$ [REDACTED]	Based on an estimated cost of \$ [REDACTED] 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	\$ [REDACTED]	927 grams at \$ [REDACTED] per gram (refer to Table 14)
IVIg costing scenarios: sensitivity analyses		
Average IVIg dose per NBA data plus IVIg price based on MSAC review	\$32,688	The MSAC review of 'Immunoglobulin therapy for Myasthenia Gravis' from April 2020 ^b used a price of \$60.41 per gram in the base case based on NBA data from 2017-18 i.e. this was the cost at which the cost-effectiveness of IVIg was assessed. Average IVIg dose of 541 grams per patient per year based on data received from the NBA for 2023-24.
Maximum dose recommended in IVIg Product Info plus IVIg price based on MSAC review	\$70,788	As above for the price of IVIg. IVIg dose based on a loading dose of 2 g/kg; maintenance dose of 1 g/kg Q4W for a total of 1,172 g per year.

Source: Compiled during preparation of the Public Summary Document

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

a 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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b Based on MSAC Public Summary Document, Application No. 1566 – Review of immunoglobulin use for Myasthenia Gravis, 3 April 2020. Available at: https://www.msac.gov.au/sites/default/files/documents/1566%2520Final%2520PSD_Apr2020.pdf

- 6.89 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 through the NBA. Based on the average amount of IVIg dispensed per patient as maintenance therapy for myasthenia gravis, the cost of IVIg was approximately \$| per year, which the ESC considered was more plausible.

Cost-per-responder

- 6.90 The PBAC noted that, at a cost per patient per year of \$█, and assuming the average of the incremental difference in response rates across the four gMG trials (24% at 12 weeks, based on a simple mean of the proportion of patients with ≥2 point reduction in MG-ADL in the four key trials), the incremental cost-per-responder versus placebo would be around \$█.

Estimated PBS usage & financial implications

- 6.91 This submission was considered by DUSC.
- 6.92 The submission used an epidemiological approach to estimate the utilisation and financial impacts of listing rozanolixizumab as a bridging therapy for generalised myasthenia gravis. Key inputs used in the submission are summarised in Table 17.

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Table 17: Key inputs for financial estimates presented in the submission

Data	Value applied and source	Comment
Prevalence of myasthenia gravis	<p>22.4 per 100,000 persons.</p> <p>The submission identified a published systematic review and meta-analysis of myasthenia gravis epidemiology studies published between 1952 and 2022 (Sciancalepore 2024). The study noted that the average prevalence increased from 9.7 cases per 100,000 persons in 1952-2007 to 22.0 cases per 100,000 in 2008-2021.</p> <p>The submission also conducted a supplementary literature search to identify more-recently published studies (Ye 2024, Vissing 2024, Keovilayhong 2024, Tsai 2024, Salort-Campana 2024, Sechi 2024, Engebretsen 2024). A meta-analysis of studies published between 2014-2024 indicated a global prevalence of 22.4 cases per 100,000 persons. The submission claimed that this analysis suggested that the prevalence of the disease has stabilised over time.</p>	<p>The Sciancalepore 2024 review noted significant variation in frequencies of myasthenia gravis between and within countries because of methodological biases and complex heterogeneity of the disease characterised by several phenotypes and different clinical responses.</p> <p>The supplementary literature search and meta-analysis presented in the submission was not adequately documented (such as the exclusion of Bettini 2017 study from prevalence estimates and the selection of a sensitivity analyses over the main analysis in the Antonini 2023 study).</p> <p>Published prevalence estimates presented in the submission varied widely from 0.9 to 55.3 cases per 100,000 persons in the last 10 years.</p> <p>In regard to changes over time, the average prevalence from studies published in the last 5 years (27.9 per 100,000 persons) suggests that prevalence may still be increasing over time.</p> <p>DUSC considered that the figure of 22.4 per 100,000 persons was low and suggested using the estimate from studies published in the last 5 years (27.9 per 100,000 persons).</p>
Proportion of patients with gMG who are AChR-positive	<p>85.57% based on a pooled estimate derived from 12 studies identified in a literature search conducted for the submission. Estimates ranged from 42.1% to 98.2% across the studies.</p>	<p>DUSC considered that this estimate was reasonable.</p>
Proportion of AChR-positive generalised myasthenia gravis patients with MGC score ≥ 4	<p>56.43%. Based on the weighted average estimate reported from two studies:</p> <p>59% (516/871) based on an observational study comparing outcome measurement tools in myasthenia gravis patients recruited from a single Chinese hospital (Luo 2021).</p> <p>45% (76/168) based on an observational study assessing the severity, coping style and social support of myasthenia gravis patients recruited from a single Chinese hospital (Miao 2023).</p>	<p>The estimates were not specific to the proposed target population as both studies included substantial proportions of patients with AChR-negative disease as well as patients with ocular myasthenia gravis. In particular, patients with ocular myasthenia gravis are likely to have less functional impairment than generalised myasthenia gravis patients.</p> <p>Additionally, the studies did not report background therapies which is likely to affect the proportion of patients with an MGC score ≥4.</p> <p>The estimate from Miao 2023 could not be matched with information from the publication. DUSC considered that this was probably an underestimate as it is based on broader gMG populations, including AChR-negative disease as well as patients with ocular myasthenia gravis.</p>
Rozanolixizumab uptake rate	<p>Estimates were derived based on assumed uptake rates of █%, █%, █%, █%, █% and █% in eligible patients who had not previously been treated with rozanolixizumab.</p>	<p>The submission did not justify the assumed uptake rates.</p>

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Data	Value applied and source	Comment
Rozanolixizumab persistence	<p>Yr 1 to 2: 73%; Yr 2 to 3: 92%; Yr 3 to 4: 94%; Yr 4 to 5: 95%; Yr 5 to 6: 96%.</p> <p>Extrapolated using a log-logistic function fitted to Kaplan-Meier estimates of the time to all-cause treatment discontinuation in the interim analysis of the MG0007 extension study.</p>	<p>The persistence estimate used in the submission did not appear to account for patients who discontinued after 1 cycle in the MycarinG trial.</p> <p>There were very limited follow-up data beyond 1 year and it was unclear whether persistence estimates were representative of use in later years.</p> <p>Additionally, treatment discontinuation estimates reported in a tightly regulated clinical study setting may not be representative of clinical practice.</p>
Rozanolixizumab scripts	<p>17.8 infusions per year (i.e. 3.4 cycles per year; 5.24 infusions per cycle). Based on a post hoc analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension study using data from all patients who had received ≥ 1 rozanolixizumab treatment cycle (including partial cycles) and had ≥ 8-week post-treatment follow-up (S2 dataset).</p>	<p>The post hoc dataset used to inform utilisation estimates was not consistent with the datasets used to inform longer-term treatment efficacy or time to treatment discontinuation (e.g. the number of cycles per year was 4.31 based on the interim MG0007 analysis, or 3.59 based on the annualised number of cycles per year from the final MG0007 study report).</p> <p>The evaluation considered the number of scripts per year was likely underestimated as patients in the MycarinG trial and MG0007 study were required to meet specific thresholds for retreatment (increase of 2.0 points on the MG-ADL or 3.0 points on the QMG scale) with a suggested minimum time of 4 weeks between cycles, which may not be representative of clinical practice.</p> <p>Median follow-up of patients in the S2 dataset was 368 days and it was unclear whether the estimated number of cycles and infusions were representative of use in later years.</p>
Chronic IVIg/PLEX response rate	<p>60%. Based on the proportion of patients achieving ≥ 3-point reduction in MGC score from baseline with IVIg treatment at 6 months in the Brill 2024 trial.</p>	<p>The evaluation and DUSC considered this was not appropriate. The dosing regimen used in the Brill 2024 trial is unlikely to reflect Australian clinical practice as it is inconsistent with the approved product information, exceeds the maximum subsidised dose under the NBA and is substantially higher than supported by the available Australian IVIg utilisation data.</p> <p>Additionally, the assessment for response for ongoing subsidised treatment under the NBA typically occurs at 4 months but includes other factors such as having clinical benefit with end-of-cycle deterioration.</p>
Chronic IVIg/PLEX persistence	<p>Assumed to be the same as for rozanolixizumab.</p>	<p>The evaluation considered this assumption was not adequately justified given the different patterns of treatment between these therapies.</p>

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Data	Value applied and source	Comment
Dispensed IVIg per patient	<p>Responder: 927 g; non-responder: 463 g. Dose per cycle estimated based on the dosing regimen used in the Brill 2024 trial (2 g/kg loading dose split over 2 administrations and then a maintenance dose of 1 g/kg every 3 weeks; total of 24 weeks treatment).</p> <p>The submission claimed that estimated doses were reduced by 40% based on feedback from the July 2024 zilucoplan submission.</p> <p>Mean body weight was based on the baseline weight in the MycarinG trial (loading dose 2 g/kg x 80.2 kg x 60% = 96.2 g; maintenance dose 1 g/kg x 80.2 kg x 60% = 48.1 g).</p> <p>The annual number of treatment cycles per year (2.14) was estimated based on intermittent IVIg users in the first 12 months of treatment using data from a retrospective review of US claims data (Qi 2022).</p>	<p>This was not appropriate. The dosing regimen used in the Brill 2024 trial is unlikely to reflect Australian clinical practice as it is inconsistent with the approved product information, exceeds the maximum subsidised dose under the NBA and is substantially higher than supported by the available Australian IVIg utilisation data.</p> <p>The estimated 40% reduction used in the submission was based on an incorrect interpretation of a sensitivity analysis reported in the zilucoplan July 2024 PBAC commentary which noted that a 60% reduction (i.e. 40% of base case units) was needed to reduce the estimated dose of 1,247 g (based on 89.1 kg patients with 2 g/kg loading dose and 1 g/kg maintenance dose every 4 weeks) to a dose consistent with the average dose reported in the MSAC review of IVIg use for myasthenia gravis (492 g per patient).</p> <p>The Qi (2022) study defined a treatment cycle as all IVIg doses received within 5 days of each other (e.g. average duration of a treatment cycle was 1.81 days) and has no relevance to the dose per cycle estimated in the Brill 2024 trial.</p>
Rozanolixizumab cost	\$ [redacted] per vial based on the proposed effective AEMP	The proposed cost-minimised price of rozanolixizumab compared to IVIg was highly uncertain and included a [redacted] % price premium for rozanolixizumab.
IVIg cost	\$ [redacted] per gram. Based on the price of Intragam 10 (2.5 g/25 mL: \$154.65; NBA National Product Price List October 2024).	Estimates were based on domestic IVIg products which may underestimate the cost per gram for IVIg as it does not account for plasma fractionation or imported product costs.

Source: Table 4.1-1, pp178-179 of the submission

Abbreviations: DUSC, Drug Utilisation Sub-Committee; IVIg, intravenous immunoglobulin; MBS, Medical Benefits Schedule; NBA, National Blood Authority; PLEX, plasma exchange; RCT, randomised controlled trial

6.93 Table 18 summarises the estimated eligible population, scripts dispensed and net cost to government of listing rozanolixizumab presented in the submission.

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Table 18: Estimated use and financial implications of listing rozanolixizumab (as estimated in the submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Prevalent MG patients	1	1	1	1	1	1
Eligible population	2	2	2	2	2	2
Treated population	2	2	2	2	2	2
Total rozanolixizumab scripts	2	2	2	2	2	2
Cost to PBS/RPBS^a less copay	\$ 3	\$ 4	\$ 3	\$ 3	\$ 5	\$ 5
Reduced NBA costs for IVIg	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
Reduced NBA cost for PLEX	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
Increased MBS costs for rozanolixizumab administration ^b	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7	\$ 7
Reduced MBS costs for IVIg administration	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
Reduced MBS costs for PLEX administration	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6	-\$ 6
Net cost to PBS/RPBS/NBA/MBS	\$ 8	\$ 8	\$ 8	\$ 9	\$ 9	\$ 9

Source: Table 4.2-1, p196; Table 4.2-2, p196; Table 4.2-3, p167; Table 4.2-5, p198; Table 4.2-6, p198; Table 4.2-8, p199; Table 4.5-2, p201; Table 4.5-3, p202; Table 4.5-4, p202 of the submission 'Rystiglo (Rozanolixizumab) - gMG – UCM' Excel workbook

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

^a Based on an average of 11.04 vials per script

^b The sponsor proposed to fund a home administration program for the first [redacted] month of use for each patient.

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 500 to < 5,000

³ \$50 million to < \$60 million

⁴ \$40 million to < \$50 million

⁵ \$60 million to < \$70 million

⁶ net cost saving

⁷ \$0 to < \$10 million

⁸ \$20 million to < \$30 million

⁹ \$30 million to < \$40 million

6.94 The submission estimated the net cost to the PBS/RPBS of listing rozanolixizumab as a bridging therapy for generalised myasthenia gravis would be \$50 million to < \$60 million in Year 1, increasing to \$60 million to < \$70 million in Year 6, a total cost of \$300 million to < \$400 million over the first six years of listing.

6.95 The submission estimated the net cost to the PBS/RPBS/NBA/MBS would be \$20 million to < \$30 million in Year 1, increasing to \$30 million to < \$40 million in Year 6, a total cost of \$100 million to < \$200 million over the first six years of listing.

6.96 The main drivers of the increased cost to government were the requested [redacted]% price premium for rozanolixizumab and the application of treatment response criteria to chronic IVIg/PLEX but not rozanolixizumab (consistent with the proposed restriction).

6.97 DUSC considered the submission’s estimated cost to government was underestimated. DUSC commented that:

- the estimates were highly sensitive to assumptions for market share and prevalence.

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- prevalence is highly uncertain, DUSC considered the submission's estimate was low (22.4 per 100,000 persons) given the prevalence estimate is higher when based on studies published in the last five years (27.9 per 100,000 persons).
 - the use of all Australian Bureau of Statistics (ABS) populations, rather than restricting the population group to 18+ years inflated the estimates.
 - the percentage of patients requiring rozanolixizumab as bridging therapy is likely to be lower than the 100% estimated.
 - the proportion of AChR-positive gMG patients with MGC score ≥ 4 estimate is low as it is based on a broader gMG population. DUSC considered that more reliable estimates may be available from the MGBase registry.
 - Changes to the restrictions could reduce therapy utilisation.
- 6.98 The evaluation considered that it was unclear whether the treatment patterns (number of cycles, number of infusions per cycles) reported for rozanolixizumab over a median duration of one year in the clinical studies would be representative of treatment patterns in clinical practice over the longer-term.
- 6.99 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.
- 6.100 The PBAC agreed with the ESC and advised the parameters outlined in Table 19 may be reasonable for determining the estimated use and financial implications of the new therapies for gMG.

Table 19: 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 20)
Market growth	3.96% per year based on the last five years of IVIg data (i.e. 1,431 patients in Year 1 and 1,738 patients in Year 6)
% with AChR+	85.57% based on the totality of the evidence presented across all the submissions, and similar to the estimate of 88% provided in Hendricks et al. 2019 (i.e. 1,224 patients in Year 1 and 1,487 patients in Year 6)
Uptake across all new gMG therapies that are listed	Uptake from new patients and existing IVIg users with ongoing functional impairment: The PBAC, in its expert opinion, considered this could be up to █%, and this could represent around one-third of current IVIg users based on: █% of IVIg pts commenced within the most recent year, plus of the remaining █% around █% may be using IVIg but experiencing ongoing functional impairment (i.e. █% + (█% * █%) = █% of the market). Total uptake of █% in █% of the market. Uptake from prevalent patients already established on IVIg: The PBAC, in its expert opinion, considered this could be up to █%, and this could represent around two-thirds of current IVIg users based on: of the █% of IVIg users who commenced more than a year ago, around █% are responding (i.e. █% * █% = █/█%). Total uptake of █% in █% of the market. Total market uptake of █% in Year 1 (i.e. █ ¹ patients in Year 1).
Increase in uptake over time	█ percentage points each year for the first six years of listing (i.e. █ ¹ patients in Year 6)

Source: Compiled during preparation of the PBAC Minutes

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

6.101 The PBAC considered that uptake rates would be the largest source of uncertainty in the financial estimates, particularly given the range of patients currently taking IVIg (with new patients and existing IVIg users with ongoing functional impairment expected to have substantially higher uptake than those prevalent patients already established on IVIg) and also given that the uptake rates would need to account for: any additional eligible patients (e.g. patients who are not responding to, or who are unable to be treated with IVIg); the PBS restriction being narrower than the current IVIg criteria; and the stopping rules (as these would generally mirror how IVIg is used in practice).

Financial Management – Risk Sharing Arrangements

6.102 The sponsor proposed a risk sharing arrangement (RSA) based on the financial estimates presented in the submission. No further details were provided.

6.103 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 rozanolizumab 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)³ 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 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

³ 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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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.^{4,5} The ESC considered that any PBS restriction for bridging therapy should require the patient to cease the new therapy after around six months of treatment (acknowledging that variations in treatment duration between therapies may be required to align with treatment courses). After three months of therapy cessation (i.e. a total of at least 12 months since NS-IST initiation), patients whose condition remains uncontrolled may recommence under the refractory listing. Overall, the maximum treatment duration in the bridging setting would be around six months.
- 7.7 The ESC considered that another key issue in the bridging setting was the lower level of certainty in the incremental benefit versus optimisation of existing therapies given the availability of therapies that are effective for many patients, and that this would impact on the cost-effectiveness of the new therapies. The ESC considered that it was unclear whether these concerns would be adequately addressed by limiting use in this setting to a maximum duration of six months, along with a combined RSA for any recommended drugs across both setting.

Refractory setting

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

Both settings

- 7.9 The ESC considered that restrictions should be consistent across any new gMG therapies recommended for listing.
- 7.10 Across both settings, the following aspects of the restrictions would need to be determined:
- functional impairment criteria
 - response criteria
 - requirements around prior and concomitant treatments

⁴ 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/>

⁵ 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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- restriction structure around: balance of supply; grandfather arrangements (where applicable); six-month ion 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 IVIg⁶ specifies that the patient has a Myasthenic Gravis Composite (MGC) of at least 4 points; and at least 2 other treatments are ineffective, contraindicated, unavailable or caused intolerable side effects. The ESC considered this was broad as the other treatments could comprise two of: an anti-cholinesterase; a corticosteroid; or thymectomy (i.e. there is no requirement for the patient to have trialled a 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 trialled prior IVIg (or PLEX)
 - amendments to the prescribing criteria for IVIg may be required, along with systems to ensure that the anticipated reductions in IVIg use are realised.

ESC’s view on the comparator

- 7.14 At its July 2024 meeting, the PBAC considered “for the non-refractory group, the comparator should be optimisation of existing therapies. For refractory patients and those who are unable to use or not responding to existing therapies, the PBAC acknowledged that there are variations in access to IVIg/PLEX and that any clinical comparisons may be limited by the lack of evidence for IVIg/PLEX. As such, the PBAC considered that placebo may be a reasonable comparator in this group. However, the PBAC considered that chronic IVIg/PLEX remained a relevant comparator for providing a frame of reference for interpreting the cost per patient of ravulizumab

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

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in the refractory setting” (paragraph 7.10, ravulizumab PSD, July 2024 PBAC meeting).

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

ESC’s view on the comparative effectiveness and safety

- 7.17 The ESC noted the PBAC’s previous advice that “for the non-refractory group, the comparator should be optimisation of existing therapies”, but that none of the trials for the new therapies required baseline therapies to have been optimised.
- 7.18 The ESC considered that there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab). The ESC considered that the published NMAs had substantial limitations, notably the poor transitivity between the included trials and lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 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 20 summarises data received from the NBA on the utilisation of IVIg as maintenance therapy for myasthenia gravis in 2023-24.

Table 20: Data received from the NBA on the use of IVIg for maintenance treatment of gMG

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

Overall notes:

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

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

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

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

^d Result is similar (3.4%) using the most recent two years of data

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

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

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considered that there was insufficient evidence to suggest superior efficacy or safety of rozanolixizumab versus chronic IVIg or PLEX. Further, the PBAC considered that there was no reliable evidence to suggest that rozanolixizumab was superior in terms of efficacy or safety compared with the other three therapies considered at the March 2025 meeting for the treatment of gMG (zilucoplan, efgartigimod and ravulizumab). 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 patient's families. The comments also described the limitations of currently available treatment options including adverse events and lengthy administration times. Consumers outlined that the new therapies represent a substantial improvement in administration time compared with IVIg, and also shorter travel distances for patients outside metropolitan areas. The comments described a hope that the new therapies will reduce gMG symptoms quickly, reduce the need for other medications and associated side-effects, and reduce hospital visits, contributing to an overall improved quality of life. The PBAC noted the strong support for access to both complement inhibitors (ravulizumab and zilucoplan) and FcRn blockers (efgartigimod and rozanolixizumab) across both the bridging and refractory settings.
- 8.4 The PBAC advised that the restrictions were complex and further work would be required to finalise the restrictions including further consultation with expert neurologists and immunologists before listing can proceed.
- 8.5 The PBAC noted that the submission requested listing of rozanolixizumab in the bridging setting and as a replacement for IVIg. The PBAC considered that IVIg is being used in both the bridging and refractory settings in clinical practice (supported by the NBA data on IVIg utilisation). Overall, the PBAC advised that 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:

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- Immediate access for patients whose condition is acute and severe, and who are at high risk of rapid deterioration. The PBAC advised that the restriction in this setting should require patients to be treated with concomitant corticosteroid and NS-IST therapy with the flexibility that NS-IST can be commenced within two weeks of initiation of the new therapy. A maximum time on treatment of 3-months would apply for this setting.
 - Bridging: early in the treatment algorithm, in combination with standard therapy to provide bridging immunosuppression whilst immunosuppression with NS-IST/thymectomy takes effect. A maximum time on treatment of 6-months would apply for this setting.
 - Refractory: later in the disease course where other treatments have failed.
- 8.7 The PBAC considered the restriction in the bridging setting should provide access for patients whose condition is moderate-to-severe, and who have trialled at least three months of therapy with remission-inducing intent. The PBAC advised this should be defined as two of the following three: NS-IST; a corticosteroid; thymectomy. The NS-IST and/or corticosteroid should have been administered at optimised dosing (definition of optimised doses not specified and will be up to the treating physician to determine). The PBAC advised the initiation criteria in this setting should require patients to meet a disease severity threshold similar to most of the key trials, e.g. around MG-ADL ≥ 6 (consistent with two of the four trials of the new therapies for gMG). The PBAC agreed with the clinician correspondence which expressed a preference for also including a clinician-reported component i.e. using the MGC instrument (with a threshold to be determined based on consultation with expert neurologists and immunologists) in addition to the MG-ADL (paragraph 6.6b).
- 8.8 The PBAC considered the restrictions in the refractory setting should require patients to have trialled at least 12 months of two of the following three treatments: a NS-IST; a corticosteroid; thymectomy. This would allow patients to transition from the bridging setting (with a 3-month treatment break) as the NS-IST and/or corticosteroid should have been co-administered in the previous bridging setting. The PBAC advised the disease severity thresholds for initiation in the refractory setting should be the same as those for the bridging setting.
- 8.9 The PBAC considered that, in the acute and bridging settings, there should be a maximum time on treatment of 3 months and 6 months respectively, to prevent ongoing use given the potential for the condition to respond to NS-IST therapy or improve over time. The PBAC considered that the initial restriction for the treatment refractory setting should require the patient to have trialled cessation of the new therapy for three months to be eligible for further treatment with new therapy for this setting (consistent with the ESC advice in paragraph 7.6).
- 8.10 In terms of response criteria in the refractory setting, the PBAC considered that response should be based on an MG-ADL ≥ 2 (plus a corresponding MGC level to be

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- determined based on consultation with expert neurologists and immunologists), achieved at 2 to 16 weeks, per the clinician correspondence (paragraph 6.6e).
- 8.11 The PBAC considered it would be appropriate to list the required number of doses with repeats to enable the approximate full treatment time of 3-months for the acute severe setting, and 6-months for bridging therapy. The PBAC also advised it would be appropriate to list the number of doses with repeats for each 6-months of treatment in the refractory setting. The PBAC acknowledged there will be some variability in the number of doses and treatment when taking into account the specific dosing regimens of each drug. 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
 - the prescribing criteria for IVIg should be revised to ensure use remains appropriate in the context of the availability of the new therapies.
- 8.15 The PBAC considered that chronic IVIg was a relevant comparator for providing a frame of reference for interpreting the cost-per-patient of the newer gMG therapies across both the refractory and bridging settings. The PBAC acknowledged the ESC's concerns that, in the bridging setting, there is a lower level of certainty in the incremental benefit versus optimisation of existing therapies but considered these concerns would be adequately addressed by having a maximum duration of use in this setting, along with a combined RSA across both settings.

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- 8.16 The PBAC also considered that the four new gMG therapies (efgartigimod, rozanolixizumab, ravulizumab and zilucoplan) were all near-market comparators to each other.
- 8.17 The PBAC considered there was no evidence to suggest superior efficacy or safety between any of the four new gMG therapies (zilucoplan, ravulizumab, efgartigimod and rozanolixizumab). The PBAC further considered that the published network meta-analyses had substantial limitations, in particular the lack of accounting for the treatment effects of FcRn blockers waning over time during the off-treatment period.
- 8.18 The PBAC noted the submission's indirect comparison between the MycarinG rozanolixizumab trial and the Bril 2024 IVIg trial, which found no statistically significant differences in functional outcomes or serious adverse events between rozanolixizumab and IVIg. The PBAC acknowledged the limitations of the available evidence for chronic IVIg and based on the totality of the evidence presented across the four submissions, the PBAC agreed with the submission's claim of non-inferior efficacy and safety versus chronic IVIg and PLEX.
- 8.19 Overall, the PBAC considered that rozanolixizumab has non-inferior comparative effectiveness and safety versus chronic IVIg and also against zilucoplan, efgartigimod and ravulizumab.
- 8.20 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: 1-2 g/kg and maintenance dose: 0.4-1 g/kg every 4 to 6 weeks) given the wide dose range specified which could result in annual doses from 352 g to 1,172 g per patient (using an average patient weight of 83.7 kg per Bril 2024). Further, in Bril 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).
- 8.21 The PBAC acknowledged the NBA data was based on the average dose across all severity levels and thus included patients with less severe disease than the threshold for initiation of the new therapies. Further, use of the 2023-24 NBA data would not account for the varying cost per gram of IVIg (which depends on the proportion of imported IVIg, with the cost in 2023-24 being higher than previous years). Notwithstanding this, the PBAC considered the IVIg utilisation data from the NBA was the most appropriate data available for determining the average annual dose of IVIg being used in Australian patients.
- 8.22 The PBAC noted that a key uncertainty in the estimation of the average annual dose of rozanolixizumab was the treatment-free interval between cycles (refer to paragraphs 6.73 to 6.74). The PBAC noted the base case estimate in the submission (derived from a *post hoc* analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension) equated to a treatment-free interval of 9.3 weeks between cycles (3.4 cycles per year). The PBAC considered this may have

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underestimated the number of infusions in clinical practice given longer-term data from the extension studies indicated decreasing treatment-free intervals over time (Table 8), and also given the strict retreatment criteria applied in the trial. The evaluation noted that updated data from the MG0007 extension study equated to an 8.5-week interval between cycles (3.59 cycles per year), which the PBAC considered may also have underestimated the number of infusions in clinical practice. 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.

- 8.23 The PBAC considered that a cost-comparison versus IVIg would need to be based on the drug cost per patient per year accounting for:
- the total average annual dose of IVIg per patient observed in the NBA data (for maintenance gMG) of 541.1 grams per year (shown in Table 20).
 - the rozanolixizumab dose recommended in the product information assuming the same weight distribution as patients in the MycarinG trial (i.e. 2.11 vials per infusion and 6 infusions per cycle), with the number of cycles per patient per year based on the updated data from the MG0007 extension study of 3.59 cycles per year. Based on these assumptions the average annual dose of rozanolixizumab would be: 12,711 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.
- 8.24 The PBAC noted the results of a cost-per-responder analysis versus placebo which assumed the same drug cost per patient as IVIg (based on the NBA data), along with the average incremental response rate across the four gMG trials (refer to paragraph 6.29). The PBAC considered cost-per-responder analysis supported that the new therapies would be cost effective if priced based on the IVIg cost as outlined above.
- 8.25 The PBAC advised that the financial estimates should take the total number of patients accessing IVIg as gMG maintenance therapy as a starting point, which was 1,324 in 2023-24 (refer to Table 20). The PBAC considered the following should then be applied: market growth (of around 1% per year, based on the last five years of IVIg data); and the proportion of patients whose gMG is AChR+ (of around 86%, based on the pooled estimates provided in one of the submissions, noting this is similar to the estimate of 88% provided in Hendricks et al. 2019, which was the only estimate included in the ravulizumab submission that was based on a gMG population).
- 8.26 The PBAC advised that uptake should be based on the new therapies as a group, and should be from two key groups within existing IVIg users:

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- uptake from new patients and existing IVIg users with ongoing functional impairment (i.e. $\frac{1}{2}$ % of the AChR+ patient cohort, Table 19). This group would likely have relatively high uptake of the new therapies (potentially up to $\frac{1}{2}$ %).
 - uptake from prevalent patients (i.e. the remaining $\frac{1}{2}$ % of the AChR+ patient cohort) already established on IVIg (uptake of around $\frac{1}{2}$ %).
- 8.27 The PBAC advised that the aforementioned uptake rates were intended to account for: any additional eligible patients (e.g. patients who are not responding to, or who are unable to be treated with IVIg); the PBS restriction being narrower than the current IVIg criteria; and the stopping rules (as these would generally mirror how IVIg is used in practice). The aforementioned rates would equate to an overall uptake rate of around $\frac{1}{2}$ % in Year 1 (i.e. $\frac{1}{2}$ % of all patients on IVIg for AChR+ gMG would commence a new gMG therapy in Year 1 of listing, refer to Table 20). The PBAC considered this was at the higher end of plausibility given the proportion of patients on IVIg who would be eligible for the new therapies could potentially be quite low.
- 8.28 The PBAC advised that uptake was likely to increase over time, and that this may be gradual given the large prevalent pool with a long history of IVIg use. As such, the PBAC advised that it would be reasonable for the estimated uptake rates to increase by $\frac{1}{2}$ percentage points each year for the first six years of listing.
- 8.29 The PBAC advised that the dose assumptions (e.g. number of doses per patient per year) in the financial estimates should be the same as those applied in the cost-comparison (refer to paragraph 8.23).
- 8.30 The PBAC considered that any listing of the new gMG therapies would be associated with a substantial reduction in the utilisation of IVIg for gMG maintenance, given the lack of other treatment options but also acknowledging that a small proportion of patients cannot tolerate or access IVIg, or have ceased IVIg due to lack of response.
- 8.31 The PBAC noted that more complex approaches to estimating the financial impacts could be used (e.g. calculating utilisation in the bridging and refractory settings separately, taking stopping rules into account) but considered the simplified approach outlined above was likely to provide more accurate forecasts given the: lack of robust data to inform a more complex approach; and the intent of the restrictions to mimic the current use of IVIg in clinical practice (in terms of use across both the bridging and refractory settings, with clinicians regularly assessing the on-going need for continuing IVIg therapy including through treatment breaks).
- 8.32 The PBAC advised that a single RSA that includes all of the new therapies (in all settings) would be required to mitigate the risk of use outside the intended restriction. For the FcRn blockers, the RSA would also need to mitigate the risk of an increase in the frequency of cycles received over time. The PBAC advised that the risk of higher dosing frequency is less relevant for the complement inhibitors and thus these sponsors should not be adversely affected by more frequent FcRn blocker dosing. The PBAC advised that the Department and each sponsor should work to

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ensure the cost per patient does not exceed the estimates in the cost-comparison and the financials.

- 8.33 The PBAC acknowledged the financial estimates as outlined in paragraphs 8.25 to 8.29 were associated with some uncertainty and considered that it may be reasonable for the risk of use outside the intended restriction to be managed through a $\frac{1}{2}$ RSA – with the $\frac{1}{2}$ based on the financial estimates outlined by the PBAC (e.g. with the AChR+ proportion and uptake rates applied as outlined in paragraphs 8.25 to 8.29 and Table 19) with a rebate of less than $\frac{1}{2}$ %, then a $\frac{1}{2}$ based on the total number of patients using IVIg for maintenance gMG with a rebate of $\frac{1}{2}$ %.
- 8.34 The PBAC advised that a utilisation review by DUSC should be conducted two years after listing of any new therapies, which should also assess whether the newer therapies have resulted in a reduction in IVIg use (noting this would require data from the NBA).
- 8.35 The PBAC advised that rozanolixizumab is not suitable for prescribing by nurse practitioners.
- 8.36 Rozanolixizumab should be exempt from the Early Supply Rule as it does not be apply to Section 100 Highly Specialised Drug listings.
- 8.37 The PBAC advised that rozanolixizumab should not be treated as interchangeable with any other drugs.
- 8.38 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 rozanolixizumab:
- 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.
- 8.39 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

9 Recommended listing

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

10 Context for Decision

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

11 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2025 PBAC Minutes:**3.01 ROZANOLIXIZUMAB,
Solution for subcutaneous infusion,
280 mg in 2 mL (140 mg per mL),
Rystiggo[®],
UCB Australia Pty Ltd.****12 Purpose of submission**

- 12.1 Rozanolixizumab was recommended for the treatment of generalised myasthenia gravis (gMG) at the March 2025 PBAC meeting. Following the recommendation, the sponsor provided a submission requesting that the PBAC modify the average annual dose of rozanolixizumab that was estimated by the Committee in March 2025. This average annual dose was used for the purposes of the cost-comparison versus IVIg and the financial estimates.

13 Background***Previous PBAC consideration***

- 13.1 At the March 2025 PBAC meeting, the PBAC recommended rozanolixizumab on the basis of a cost-comparison versus intravenous immunoglobulin (IVIg). As part of its consideration, the PBAC:
- “noted that a key uncertainty in the estimation of the average annual dose of rozanolixizumab was the treatment-free interval between cycles (refer to paragraphs 6.73 to 6.74). The PBAC noted the base case estimate in the submission (derived from a post hoc analysis of data from the MycarinG trial and an interim analysis of the MG0007 extension) equated to a treatment-free interval of 9.3 weeks between cycles (3.4 cycles per year). The PBAC considered this may have underestimated the number of infusions in clinical practice given longer-term data from the extension studies indicated decreasing treatment-free intervals over time (Table 8), and also given the strict retreatment criteria applied in the trial. The evaluation noted that updated data from the MG0007 extension study equated to an 8.5-week interval between cycles (3.59 cycles per year), which the PBAC considered may also have underestimated the number of infusions in clinical practice. 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” (paragraph 8.22, rozanolixizumab Public Summary Document, March 2025 PBAC Meeting).
- 13.2 Thus, the PBAC estimated the average annual dose of rozanolixizumab based on:

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“the dose recommended in the product information assuming the same weight distribution as patients in the MycarinG trial (i.e. 2.11 vials per infusion and 6 infusions per cycle), with the number of cycles per patient per year based on the updated data from the MG0007 extension study of 3.59 cycles per year. Based on these assumptions the average annual dose of rozanolixizumab would be: 12,711 mg per year” (paragraph 8.23, rozanolixizumab Public Summary Document, March 2025 PBAC Meeting).

13.3 These doses are summarised in Table 21.

Average annual dose of rozanolixizumab

- 13.4 The submission stated that the average annual dose of rozanolixizumab estimated by the PBAC in March 2025 was not representative of likely clinical practice as it was based on the full safety set of the MG0007 open label extension, which included data from patients who had received continuous weekly dosing or fixed cycles not aligned with symptom-driven treatment. This was because MG0007 was a roll-over extension study which enrolled patients from MG0004 (who received continuous weekly dosing of rozanolixizumab) and patients directly from MG0003 (who received a fixed cycle without symptom worsening).
- 13.5 The submission argued that the Product Information for rozanolixizumab states: “each subsequent treatment cycle may be administered based on clinical evaluation of symptom recurrence.”
- 13.6 The submission proposed that the rozanolixizumab dose estimates should be based on the “Safety Pool S2” data which only included patients treated according to symptom recurrence. Safety Pool S2 excluded:
- patients from MG0004 who received continuous weekly dosing
 - patients from MG0003 who received a fixed cycle without symptom worsening.
- 13.7 The submission further argued that use in the acute and bridging settings may also result in a lower annual rozanolixizumab dose per year than the March 2025 PBAC recommendation, given the maximum time on treatment specified in the PBS restrictions in these settings is 3 months (acute) and 6 months (bridging).
- 13.8 Table 21 summarises the average annual dose of rozanolixizumab estimated by the PBAC in March 2025 compared with the submission considered in November 2025.

Table 21: Calculation of the number of the average annual dose of rozanolixizumab

		PBAC March 2025 PSD		Submission considered in November 2025	
	Per patient	Assumption	Source/Rationale	Assumption	Source/Rationale
A	Average vials per infusion	2.11	Distribution of patients across weight categories in MG0003	2.11	Unchanged
B	Average infusions per cycle	6	Assumed full compliance	5.24	Safety Pool S2 (8 July 2022 data cut) – only includes the symptom driven cycles i.e. excludes:
C	Average cycles per year (based on annualised cycles)	3.59 8.5 weeks between cycles	Final MG0007 (OLE) study report, safety set. This includes patients who were previously enrolled in the MG0004 (chronic weekly treatment) study.	3.4 9.3 weeks between cycles	<ul style="list-style-type: none"> participants from MG0004 (who underwent continuous weekly dosing of rozanolixizumab) and; patients directly from MG0003 who received a fixed cycle without symptom worsening ^a
D	mg per vial	280 mg	Each 2mL vial contains 140 mg/mL	280 mg	Unchanged
E	Average total mg per year	19.9 infusions = 12,711 mg ^b	A x B x C x D	17.8 infusions = 10,508 mg ^b	A x B x C x D

Source: Table 1 of the submission; blue shading indicates PBAC's previous consideration.

OLE = open label extension

^a The sponsor's proposal and the PSCR for the March 2025 submission further highlighted that the final analysis of the Safety Pool S2 found an average of 2.9 cycles (mean infusions of 16.0 per year or 9,445 mg per year).

^b Minor discrepancies due to rounding

For more detail on PBAC's view, see section 12 PBAC outcome.

14 PBAC Outcome

- 14.1 The PBAC provided further advice in regard to its March 2025 recommendation for rozanolixizumab for the treatment of generalised myasthenia gravis (gMG). The PBAC considered that the average annual dose of rozanolixizumab outlined in the submission (i.e. 10,508 mg) would be reasonable for the purposes of the cost-comparison calculations and financial estimates, and reaffirmed its advice that an RSA would be required to mitigate the risk of an increase in the frequency of cycles received over time (as well as use outside the restriction). As such, the PBAC advised that the cost-effectiveness of rozanolixizumab would be acceptable based on a cost-comparison versus IVIg using the revised rozanolixizumab dose.
- 14.2 The PBAC reaffirmed its March 2025 advice that rozanolixizumab has non-inferior comparative effectiveness and safety versus chronic IVIg and also against zilucoplan, efgartigimod and ravulizumab (paragraph 8.19, rozanolixizumab PSD, March 2025 PBAC Meeting).
- 14.3 The PBAC noted the submission proposed that the average annual dose of rozanolixizumab should be 10,508 mg, based on the average number of infusions

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reported in the Safety Pool S2 (8 July 2022 data cut) which excluded patients who received chronic dosing. On the other hand, the average dose advised by the PBAC in March 2025 (12,711 mg) was based on the safety set of the final MG0007 (open label extension study) which included some data from patients who had received continuous dosing or a fixed cycle. The submission argued that the Product Information for rozanolixizumab states “each subsequent treatment cycle may be administered based on clinical evaluation of symptom recurrence”, which supported the use of the Safety Pool S2 dataset. The PBAC accepted the annual dose of rozanolixizumab outlined in the submission i.e., an average annual rozanolixizumab dose of 10,508 mg.

- 14.4 However, the PBAC considered there was a risk that the average annual dose in clinical practice may be higher than 10,508 mg per year given: strict re-treatment criteria were applied in MG0003 and MG0007 which would be difficult to implement in practice (refer to paragraphs 6.74 and 8.11); the data are based on the mean number of infusions across both the 7mg/kg and 10mg/kg dosing groups (i.e., it includes doses that are higher than recommended in the PI, as only the 7mg/kg dose is in the PI); the potential for decreasing treatment-free intervals over time; and real world data for efgartigimod (another FcRN blocker) indicated a higher number of cycles per patient per year in clinical practice (in the United States) compared with the clinical trial for that drug (paragraph 6.103, efgartigimod Public Summary Document, March 2025 PBAC Meeting). Thus, the PBAC re-iterated that the RSA would need to mitigate the risk of an increase in the frequency of cycles received over time (paragraph 8.32).
- 14.5 The PBAC reiterated its previous advice regarding the financial estimates and the RSA, including: 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 (paragraph 8.29); and 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 (paragraph 8.32).

Outcome:

Advice provided

15 Recommended listing

The finalised restrictions for listing are presented as follows. Add new listing:

Acute severe patients

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ROZANOLIXIZUMAB					
rozanolixizumab 280 mg/2mL injection, 2 mL vial	NEW (HSD Public) NEW (HSD Private)	18	18	1	Rystiggo

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<p>Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)</p>
<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
<p>Restriction type: <input checked="" type="checkbox"/> Authority Required (Written/Online – immediate assessment)</p>
<p>Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)</p>
<p>Administrative Advice: Definitions for the purposes of administering this restriction.</p> <p>Where the term ‘gMG biological agent’ is referenced in this restriction, it refers to efgartigimod alfa, ravulizumab, rozanolizumab, and zilucoplan.</p> <p>The following are settings and time limits where a gMG biological agent are PBS subsidised:</p> <ol style="list-style-type: none"> (1) 3 months of acute treatment - ‘acute severe gMG’ (2) 6 months of bridging therapy - ‘bridging therapy for gMG’ (3) Continuous therapy - ‘treatment refractory gMG’ <p>A patient may transition sequentially from one setting to another where all criteria are met e.g. (1) to (2) to (3), but cannot return to an earlier treatment setting.</p> <p>Definitions: A non-steroidal immunosuppressant (NS-IST) is one of the following:</p> <ol style="list-style-type: none"> (i) azathioprine, (ii) ciclosporin, (iii) cyclophosphamide, (iv) methotrexate, (v) mycophenolate (vi) tacrolimus <p>The Myasthenia Gravis Foundation of America (MGFA) Disease Classification can be accessed at https://myasthenia.org/</p> <p>The Myasthenia Gravis Composite (MGC) scoring profile can be accessed at https://www.criteria.blood.gov.au/NeurologicalScales#MGC</p> <p>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) scoring profile can be accessed at https://myasthenia.org/</p>
<p>Administrative Advice: Treatment switching: Switching between gMG biological agents is permitted. Treatment switching should be limited to when a patient moves between different treatment settings, i.e. moving from ‘acute severe gMG’ to ‘bridging therapy for gMG’ [(1) to (2)]; or moving from ‘bridging therapy for gMG’ to ‘treatment refractory gMG’ [(2) to (3)].</p> <p>In the acute severe (1) or bridging therapy (2) settings a patient may switch to an alternate gMG biological agent if they are experiencing an intolerance or toxicity necessitating treatment withdrawal. Patients can switch by requalifying through the relevant restrictions. Only a balance of the time limits specified within the relevant treatment phase will be approved i.e. the remaining of the 3 months (acute severe gMG); or 6 months (bridging therapy for gMG) after accounting for the treatment of the previous gMG biologic.</p> <p>In the treatment refractory setting (3), a patient may switch to an alternate gMG biological agent via either:</p> <ol style="list-style-type: none"> a) the initial restriction if they have trialed a different gMG biologic, but did not respond to treatment; or b) the continuing restriction if they have trialed a different gMG biological agent and have responded to treatment. <p>Mark any remaining unused repeat prescriptions as “cancelled”.</p>
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>

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<p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Special Pricing Arrangements apply.</p>
<p>Restriction Summary / Treatment of Concept:</p>
<p>Indication: Acute severe generalised myasthenia gravis (gMG)</p>
<p>Treatment Phase: [Blank]</p>
<p>Clinical criteria:</p>
<p>Patient must have a diagnosis of MGFA Disease Class II to IV</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not be experiencing a myasthenic crisis</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must be considered by the treating clinician to have rapidly deteriorating gMG disease in the absence of immediate treatment with a gMG biological agent</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not be receiving concomitant treatment with any of the following: (i) another gMG biological agent, (ii) intravenous immunoglobulin (IVIg), (iii) plasma exchange (PLEX), (iv) rituximab for this condition.</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must be receiving concomitant treatment with a non-steroidal immunosuppressant (NS-IST); or</p>
<p>Patient must be commencing treatment with an NS-IST within 2 weeks; or</p>
<p>Patient must have had a thymectomy</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must be receiving concomitant treatment with an oral corticosteroid</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not receive more than 3 months of total treatment with gMG biological agents under this PBS indication (e.g. for 'acute severe gMG')</p>
<p>AND</p>

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Clinical criteria:
Patient must not have accessed a prior PBS-subsidised gMG biological agent; or
Patient must have developed an intolerance/toxicity to a PBS-subsidised gMG biological agent necessitating a change in treatment
Treatment criteria:
Must be treated by a prescriber who is either: (i) a neurologist; (ii) a clinical immunologist with expertise in the treatment of myasthenia gravis; or
Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with an agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion
Prescribing Instructions:
The authority application must be via the Online PBS Authorities System or in writing via HPOS form upload or mail.
If the application is submitted through HPOS form upload or mail, it must include the following: (1) details of the proposed prescription (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)

Bridging therapy

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
ROZANOLIXIZUMAB					
rozanolixizumab 280 mg/2mL injection, 2 mL vial	NEW (HSD Public) NEW (HSD Private)	18	18	2	Rystiggo
Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Written/Online – immediate assessment)					
Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)					
Administrative Advice:					
Definitions for the purposes of administering this restriction.					
Where the term ‘gMG biological agent’ is referenced in this restriction, it refers to efgartigimod alfa, ravulizumab, rozanolixizumab, and zilucoplan.					
The following are settings where a gMG biological agent are PBS subsidised:					
(1) 3 months of acute treatment - ‘acute severe gMG’					
(2) 6 months of bridging therapy - ‘bridging therapy for gMG’					
(3) Continuous therapy - ‘treatment refractory gMG’					
A patient may transition sequentially from one setting to another where all criteria are met e.g. (1) to (2) to (3), but cannot return to an earlier treatment setting.					
Definitions:					
A non-steroidal immunosuppressant (NS-IST) is one of the following:					
(i) azathioprine,					
(ii) ciclosporin,					
(iii) cyclophosphamide,					
(iv) methotrexate,					
(v) mycophenolate					
(vi) tacrolimus					

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<p>The Myasthenia Gravis Foundation of America (MGFA) Disease Classification can be accessed at https://myasthenia.org/</p> <p>The Myasthenia Gravis Composite (MGC) scoring profile can be accessed at https://www.criteria.blood.gov.au/NeurologicalScales#MGC</p> <p>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) scoring profile can be accessed at https://myasthenia.org/</p>
<p>Administrative Advice: Treatment switching: Switching between gMG biological agents is permitted. Treatment switching should be limited to when a patient moves between different treatment settings, i.e. moving from ‘acute severe gMG’ to ‘bridging therapy for gMG’ [(1) to (2)]; or moving from ‘bridging therapy for gMG’ to ‘treatment refractory gMG’ [(2) to (3)].</p> <p>In the acute severe (1) or bridging therapy (2) settings a patient may switch to an alternate gMG biological agent if they are experiencing an intolerance or toxicity necessitating treatment withdrawal. Patients can switch by requalifying through the relevant restrictions. Only a balance of the time limits specified within the relevant treatment phase will be approved i.e. the remaining of the 3 months (acute severe gMG); or 6 months (bridging therapy for gMG) after accounting for the treatment of the previous gMG biologic.</p> <p>In the treatment refractory setting (3), a patient may switch to an alternate gMG biological agent via either: a) the initial restriction if they have trialled a different gMG biologic, but did not respond to treatment; or b) the continuing restriction if they have trialled a different gMG biological agent and have responded to treatment. Mark any remaining unused repeat prescriptions as “cancelled”.</p>
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Special Pricing Arrangements apply.</p>
<p>Restriction Summary / Treatment of Concept:</p>
<p>Indication: Bridging therapy for generalised myasthenia gravis (gMG)</p>
<p>Treatment Phase: [Blank]</p>
<p>Clinical criteria: Patient must have a diagnosis of MGFA Disease Class II to IV</p>
<p>AND</p>
<p>Clinical criteria: Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies</p>
<p>AND</p>
<p>Clinical criteria: Patient must not be experiencing a myasthenic crisis</p>

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AND
Clinical criteria:
Patient must be receiving concomitant treatment with a non-steroidal immunosuppressant (NS-IST); or
Patient must have had a thymectomy
AND
Clinical criteria:
Patient must be receiving concomitant treatment with an oral corticosteroid
AND
Clinical criteria:
Patient must have a MG-ADL score of ≥ 6 and a MGC score of ≥ 10 , despite having undergone 2 of the following 3 remission inducing treatments: (i) NS-IST for 3 months; (ii) oral corticosteroids for 3 months; (iii) a thymectomy
AND
Clinical criteria:
Patient must not be receiving concomitant treatment with any of the following: (i) another gMG biological agent, (ii) intravenous immunoglobulin (IVIg), (iii) plasma exchange (PLEX), (iv) rituximab for this condition
AND
Clinical criteria:
Patient must not receive more than 6 months of bridging treatment with any gMG biological agent under this PBS indication
Treatment criteria:
Must be treated by a prescriber who is either: (i) a neurologist; (ii) a clinical immunologist with expertise in the treatment of myasthenia gravis; or
Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with an agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion
Prescribing Instructions:
The authority application must be via the Online PBS Authorities System or in writing and must include: (a) the MG-ADL and MGC score after 3-months of remission-inducing treatments (include the date the assessment was conducted) (b) details of remission-inducing treatments [date commencement and duration of drug therapy including drug names and dosages, and/or date of the thymectomy]
If the application is submitted through HPOS form upload or mail, it must include the following: (1) details of the proposed prescription (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice)
Prescribing Instruction:
A retrospective assessment for one of the MGC score or MG-ADL score can be accepted in cases where it was not conducted after completing 3 months of remission inducing treatments.

Treatment Refractory patients

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ROZANOLIXIZUMAB					
rozanolixizumab 280 mg/2mL injection, 2 mL vial	NEW (HSD Public) NEW (HSD Private)	18	18	2	Rystiggo
Category / Program: <input checked="" type="checkbox"/> Section 100 – Highly Specialised Drugs Program – Public (Code HB) / Private (Code HS)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (Written/Online – immediate assessment)					
Authority type: <input checked="" type="checkbox"/> Complex Authority Required (CAR)					
<p>Administrative Advice: Definitions for the purposes of administering this restriction.</p> <p>Where the term ‘gMG biological agent’ is referenced in this restriction, it refers to efgartigimod alfa, ravulizumab, rozanolixizumab, and zilucoplan.</p> <p>The following are settings where a gMG biological agent are PBS subsidised:</p> <ol style="list-style-type: none"> (1) 3 months of acute treatment - ‘acute severe gMG’ (2) 6 months of bridging therapy - ‘bridging therapy for gMG’ (3) Continuous therapy - ‘treatment refractory gMG’ <p>A patient may transition sequentially from one setting to another where all criteria are met e.g. (1) to (2) to (3), but cannot return to an earlier treatment setting.</p> <p>Definitions: A non-steroidal immunosuppressant (NS-IST) is one of the following:</p> <ol style="list-style-type: none"> (i) azathioprine, (ii) ciclosporin, (iii) cyclophosphamide, (iv) methotrexate, (v) mycophenolate (vi) tacrolimus <p>The Myasthenia Gravis Foundation of America (MGFA) Disease Classification can be accessed at https://myasthenia.org/</p> <p>The Myasthenia Gravis Composite (MGC) scoring profile can be accessed at https://www.criteria.blood.gov.au/NeurologicalScales#MGC</p> <p>The Myasthenia Gravis-Activities of Daily Living (MG-ADL) scoring profile can be accessed at https://myasthenia.org/</p>					
<p>Administrative Advice: Treatment switching: Switching between gMG biological agents is permitted. Treatment switching should be limited to when a patient moves between different treatment settings, i.e. moving from ‘acute severe gMG’ to ‘bridging therapy for gMG’ [(1) to (2)]; or moving from ‘bridging therapy for gMG’ to ‘treatment refractory gMG’ [(2) to (3)].</p> <p>In the acute severe (1) or bridging therapy (2) settings a patient may switch to an alternate gMG biological agent if they are experiencing an intolerance or toxicity necessitating treatment withdrawal. Patients can switch by requalifying through the relevant restrictions. Only a balance of the time limits specified within the relevant treatment phase will be approved i.e. the remaining of the 3 months (acute severe gMG); or 6 months (bridging therapy for gMG) after accounting for the treatment of the previous gMG biologic.</p>					

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<p>In the treatment refractory setting (3), a patient may switch to an alternate gMG biological agent via either:</p> <ul style="list-style-type: none"> a) the initial restriction if they have trialled a different gMG biologic, but did not respond due to an intolerance to treatment; or b) the continuing restriction if they have trialled a different gMG biological agent and have responded to treatment. <p>Mark any remaining unused repeat prescriptions as “cancelled”.</p>
<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
<p>Administrative Advice: Special Pricing Arrangements apply.</p>
<p>Restriction Summary] / Treatment of Concept:</p>
<p>Indication: Treatment refractory generalised myasthenia gravis (gMG)</p>
<p>Treatment Phase: Initial treatment – Treatment refractory gMG patients</p>
<p>Clinical criteria:</p>
<p>Patient must have a diagnosis of MGFA Disease Class II to IV</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not be experiencing a myasthenic crisis</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not have received treatment with a gMG biologic within 3 months prior to the first authority application for this indication (i.e. in treatment refractory setting); or</p>
<p>Patient must be considered by the treating clinician to have deteriorating gMG disease during a treatment break with a gMG biological agent;</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not be receiving concomitant treatment with any of the following: (i) another gMG biological agent, (ii) intravenous immunoglobulin (IVIg), (iii) plasma exchange (PLEX), (iv) rituximab for this condition.</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must be receiving concomitant treatment with a non-steroidal immunosuppressant (NS-IST); or</p>
<p>Patient must have had a thymectomy</p>

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AND
Clinical criteria:
Patient must have a MG-ADL score of ≥ 6 and a MGC score of ≥ 10 , despite having undergone 2 of the following 3 remission inducing treatments: (i) NS-IST for a minimum of 12 months, (ii) oral corticosteroids for a minimum of 12 months; (iii) a thymectomy.
AND
Clinical criteria:
The treatment must provide no more than 6 months of therapy per initial authority application
Treatment criteria:
Must be treated by a prescriber who is either: (i) a neurologist; (ii) a clinical immunologist with expertise in the treatment of myasthenia gravis, or
Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with an agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion
Prescribing Instruction:
Patients who are considered to have deteriorating gMG disease while on a treatment break with a gMG biologic may qualify with 9 months of remission inducing treatments (rather than 12 months)
Prescribing Instructions:
The authority application must be via the Online PBS Authorities System, or in writing and must include:
<ul style="list-style-type: none"> (a) details of remission-inducing treatments [date commencement and duration of drug therapy including drug names and dosages, and/or date of the thymectomy] (b) the baseline MG-ADL and MGC scores assessed after completing the 12 months of remission-inducing treatments (include the date the assessments were conducted)
If the application is submitted through HPOS form upload or mail, it must include:
<ul style="list-style-type: none"> (1) details of the proposed prescription; (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice);
Restriction Summary / Treatment of Concept:
Indication: Treatment refractory generalised myasthenia gravis (gMG)
Treatment Phase: Continuing treatment – Treatment refractory gMG patients
Clinical criteria:
Patient must have previously received PBS subsidised treatment with a gMG biological agent for this PBS indication.
AND
Clinical criteria:
Patient must have demonstrated a clinical improvement based on a decrease in MG-ADL score of at least 2 points from baseline
AND
Clinical criteria:
Patient must have demonstrated a clinical improvement based on a decrease in MGC score of at least 3 points from baseline
AND
Clinical criteria:
Patient must not be receiving concomitant treatment with any of the following:
<ul style="list-style-type: none"> (i) another gMG biological agent, (ii) intravenous immunoglobulin (IVIg), (iii) plasma exchange (PLEX), (iv) rituximab for this condition.
AND
Clinical criteria:

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Patient must be receiving concomitant treatment with a non-steroidal immunosuppressant (NS-IST); or
Patient must have had a thymectomy
AND
Clinical criteria:
The treatment must provide no more than 6 months of therapy per continuing authority application
AND
Treatment criteria:
Must be treated by a prescriber who is either: (i) a neurologist; (ii) a clinical immunologist with expertise in the treatment of myasthenia gravis; or
Must be treated by a medical practitioner who has consulted at least one of the above-mentioned specialist types, with an agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion.
Prescribing Instructions:
The authority application must be via the Online PBS Authorities System, or in writing and must include the MG-ADL and MGC scores assessed from the most recent course of treatment.
If the application is submitted through HPOS form upload or mail, it must include:
(1) details of the proposed prescription;
(2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice);
Restriction Summary / Treatment of Concept:
Indication: Treatment refractory generalised myasthenia gravis (gMG)
Treatment Phase: Transitioning from non-PBS to PBS-subsidised treatment - Grandfathering treatment
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug for this PBS indication prior to [PBS listing date].
AND
Clinical criteria:
Patient must have a diagnosis of MGFA Disease Class II to IV
AND
Clinical criteria:
Patient must have a positive serology for acetylcholine receptor (AChR) binding autoantibodies
AND
Clinical criteria:
Patient must not be experiencing a myasthenic crisis
AND
Clinical criteria:
Patient must not be receiving concomitant treatment with any of the following:
(i) another gMG biological agent,
(ii) intravenous immunoglobulin (IVIg),
(iii) plasma exchange (PLEX),
(iv) rituximab for this condition.
AND
Clinical criteria:
Patient must be receiving concomitant treatment with a non-steroidal immunosuppressant (NS-IST); or
Patient must have had a thymectomy
AND
Clinical criteria:

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Patient must have had a MG-ADL score of ≥ 6 and a MGC score of ≥ 10 , despite having undergone 2 of the following 3 remission inducing treatments: (i) NS-IST for a minimum of 12 months, (ii) oral corticosteroids for a minimum of 12 months; (iii) a thymectomy.
AND
Clinical criteria:
Patient must have demonstrated a clinical improvement based on a decrease in MG-ADL score of at least 2 points from baseline
AND
Clinical criteria:
Patient must have demonstrated a clinical improvement based on a decrease in MGC score of at least 3 points from baseline
AND
Clinical criteria:
The treatment must provide no more than 6 months of therapy under this restriction
Treatment criteria:
Must be treated by a prescriber who is either: (i) a neurologist; (ii) a clinical immunologist with expertise in the treatment of myasthenia gravis, or
Must be treated by a medical practitioner who has consulted at least one of the above mentioned specialist types, with an agreement reached that the patient should be treated with this pharmaceutical benefit on this occasion
Prescribing Instructions:
The authority application must be via the Online PBS Authorities System, or in writing and must include: <ul style="list-style-type: none"> (a) details of remission-inducing treatments [date commencement and duration of drug therapy including drug names and dosages, and/or date of the thymectomy] (b) the baseline MG-ADL and MGC scores assessed after completing the 12 months of remission-inducing treatments (include the date the assessment was conducted) (c) the MG-ADL and MGC scores assessed from the most recent course of treatment demonstrating clinical improvement to treatment (include the date the assessment was conducted)
If the application is submitted through HPOS form upload or mail, it must include: <ul style="list-style-type: none"> (1) details of the proposed prescription; (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice);
Prescribing Instruction:
A retrospective assessment for one of the MGC score or MG-ADL score after completing the 12 months remission inducing treatments can be accepted for grandfathered patients in cases where it was not conducted prior to commencing non-PBS subsidised treatment for this indication.
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

16 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.

17 Sponsor's Comment

UCB Australia acknowledges the PBAC for its updated advice, which appropriately aligns the average utilisation estimate, based on the best available evidence from the rozanolixizumab clinical trial program, with expected clinical use in Australia as recommended in the Rystiggo Product Information and with the recommended PBS restriction criteria. We remain committed to working collaboratively with the Department of Health, Disability and Ageing to facilitate timely and equitable access for Australian patients.