

Myasthenia Gravis Stakeholder Meeting Outcome Statement

Friday 3 May 2024

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC) and the Economic Sub-Committee, clinicians with expertise in the management of generalised myasthenia gravis (gMG), representatives from health consumer organisations, Alexion Pharmaceuticals Australasia Pty Ltd (the sponsor of ravulizumab), UCB Australia Pty Ltd (the sponsor of zilucoplan) and the Department of Health and Aged Care were in attendance.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

Following the February 2024 ESC consideration of ravulizumab for the treatment of generalised myasthenia gravis (gMG), the Chair of the PBAC considered that it would be appropriate for a stakeholder meeting to be convened to better understand the appropriate place in therapy for new agents for gMG and how these agents will likely be used in clinical practice.

The following points were identified as areas of discussion:

- From a patient perspective, what are the key limitations of existing therapies (corticosteroids, immunosuppressants, IVIg/PLEX, rituximab)?
- What do patients want from the newer myasthenia gravis treatments (ravulizumab, zilucoplan, efgartigimod, rozanolixizumab)?
- What is likely to be the primary role (i.e. place in therapy) of the newer agents in Australian clinical practice?
- Should the newer agents be used as chronic or time-limited therapies?
- Should patients who discontinue therapy be allowed to re-initiate therapy with the same or different agent?
- What are appropriate initiation criteria for the newer agents, particularly regarding functional impairment and prior therapy criteria?
- What are appropriate continuation criteria for the newer agents, particularly regarding treatment response?

Meeting discussion

Patient perspective

- The consumer representatives discussed generalised myasthenia gravis (gMG) from the patient perspective, including the lived experience, unmet needs, current and new treatments.
- The consumer representatives outlined that gMG places a substantial burden on people living with MG particularly when symptoms are not well-controlled including during disease fluctuations (e.g.

in a recent survey by Myasthenia Alliance Australia, 47% of the respondents did not feel their MG symptoms were well controlled by current treatments). Current treatment regimens can be intrusive, time-consuming, and can have a range of undesirable adverse events. Further, quality of life and participation in the workforce and society can be significantly impacted and this impact can extend to a patient's family.

- Patients would like access to safe and manageable treatments that provide more comprehensive relief of symptoms, induce remission and provide options for those with refractory disease.
- The consumer representatives highlighted that ideally clinicians would be able to offer access to newer medications based on individual patient needs and benefits, for all disease severities (i.e. from mild to severe disease) and for all disease settings (i.e. at diagnosis, for exacerbations or myasthenia crisis, remission induction and in those patients who are refractory to current treatments). Further, the assessment processes should not be complex or burdensome to either the patient or the clinician and should provide meaningful and wholistic evaluation to allow equitable access.
- The collaborative approach between gMG patients, clinicians and the patient support groups was highlighted.

The current situation

- It was noted that this discussion related only to the acetylcholine receptor-antibody (AChR+) form of the disease.
- The clinicians described that before diagnosis the typical gMG patient would experience a period of symptom worsening. It was noted that the majority of disability is experienced in the first few years post-diagnosis while attempts are made to induce remission. Patients experience large impacts on their quality of life, as noted above, during this period.
- It was noted that gMG is unlike other conditions such as multiple sclerosis or rheumatoid arthritis where disability accrues over time, as in gMG the neuromuscular junction can repair.
- Although there are ongoing complexities for patients, it was noted that at present approximately 70% of patients experience on-treatment remission, and that 30% are treatment refractory.
- It was noted that the majority of patients will respond/achieve remission with the classic treatment options (i.e. pyridostigmine and/or corticosteroids and/or non-steroid immunosuppressants). Although, some patients require high doses of steroids to achieve remission.
- Some patients require combination therapy of the classic treatment options from early on and, often, bridging therapies to provide relief from symptoms whilst remission induction occurs. It was stated that it can take up to two years for the non-steroid immunosuppressants to induce remission.
- It was noted that at present, the only bridging therapies available are intravenous immunoglobulin (IVIg) and plasma exchange (PLEX). The evidence for rituximab in this setting is poor. Clinicians advised that the availability of PLEX was not equitable as it is available mostly in metropolitan hospitals across Australia. In addition, PLEX treatment is very intensive. For IVIg, there is only limited long-term evidence of its benefit, the dosing schedule is demanding, it is expensive, and it is associated with safety issues and side effects.
- The clinicians stated that the adverse events associated with the long-term use of high dose corticosteroids are well known. In addition, some patients cannot tolerate or are contraindicated to corticosteroids.

New treatments

- It was noted that there are currently two new therapies (ravulizumab and zilucoplan, also known as complement inhibitors) that are being considered by the PBAC. Two additional therapies (efgartigimod and rosanolixizumb) are currently being considered by Australian and/or international regulators – see Attachment 1.
- These new agents have not yet been incorporated into key treatment guidelines, and the manner in which they would likely be used in the Australian setting was discussed.
- The new therapies appear to have a relatively rapid onset of action, and the clinicians present at the meeting considered complement inhibitors should be available to be used early in combination with standard therapy i.e. as a bridging therapy, with specific patient criteria to be determined (e.g. a hypothetical case study of a typical patient who could benefit from the new therapies was discussed which took into account the patient's response to standard therapy). The clinicians noted that there is also a role for complement inhibitors later in the disease course in refractory patients and in patients requiring rescue therapy for myasthenic crisis.
- The clinicians considered there should be robust stopping rules to prevent ongoing use. It was noted that it would be harder to cease treatment in refractory patients.
- The clinicians outlined the following potential stopping rules when used early in disease:
 - Given that it appears that these agents work quickly, it was stated that it would be possible to determine whether they were having an effect within 12 weeks.
 - If it was established that an agent was effective in improving symptoms, patients could remain on treatment for 12 months, as it usually takes at least 12 to 24 months for the standard disease modifying agents to have an effect.
 - At 12 months, treatment with the complement inhibitors should be ceased. If the patient deteriorated, the complement inhibitor would be restarted, with 6-monthly rechallenges up to 2 years of total treatment. At that point treatment with the complement inhibitor would cease.
- The clinicians proposed that patients may access re-treatment with a complement inhibitor if the disease is refractory, or if the patient experiences an exacerbation or is at risk of a myasthenia crisis.
- The clinicians stated that in the event of an exacerbation or in a patient who is at risk of a myasthenia crisis, the complement inhibitors could be used as a rescue therapy in place of IVIg and PLEX.
 - At this stage the complement inhibitors and FcRNs have not been trialled or widely used in the context of an actual crisis (e.g. in patients admitted to ICU, who would often be intubated in this context).
- The clinicians stated that it is hoped that these new treatment options will enable a greater proportion of moderate to severe disease patients to achieve remission. In addition, it is hoped that the use of the newer agents would reduce the need for high dose and/or long-term corticosteroid use. The treatments are expected to reduce the need for IVIg and PLEX which are complex and burdensome to administer.
- In all disease settings, the clinicians and consumer representatives stated that patients would have to be assessed for treatment response via measures that provided a robust, yet wholistic reflection, of the disease state. It was suggested that this would likely consist of the Myasthenia Gravis-Activities of Daily Living (MG-ADL) and/or Myasthenia Gravis Composite (MGC) score tools.

Conclusion

The PBAC Chair thanked stakeholders for their time in attending the meeting and the advice provided.

Attachment 1 – New MG therapies that have been considered by Australian and/or international regulators

Drug	Class	Administration (maintenance dosing)	Regulatory status
Efgartigimod	FcRn-targeted immunosuppression	Cyclical administration, IV infusion once weekly for 4 weeks, variable duration between cycles based on response.	FDA approved for the treatment of gMG in adult patients who are anti-AChR antibody positive in December 2021 (intravenous infusion) and in June 2023 (subcutaneous injection). EMA approved in August 2022 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody positive.
Ravulizumab	C5-targeted immunosuppression	IV infusion every 8 weeks (requires supplemental dosing with rescue IVIg/PLEX).	TGA approved in May 2023 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody positive. FDA approved in April 2022 for the treatment of adult patients with gMG who are anti-AChR antibody positive. EMA approved in September 2022 as an add-on to standard therapy for the treatment of adult patients with gMG who are anti-AChR antibody positive.
Rozanolixizumab	FcRn-targeted immunosuppression	Cyclical administration, IV infusion once weekly for 6 weeks, variable duration between cycles based on response.	Submitted to TGA in November 2023 for the treatment of gMG. FDA approved in March 2024 for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive. EMA approved in January 2024 as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR or anti-MuSK antibody positive.
Zilucoplan	C5-targeted immunosuppression	Subcutaneous injection daily (does not require supplemental dosing with rescue IVIg/PLEX).	Submitted to TGA in July 2023 for the treatment of adult patients with gMG. FDA approved in October 2023 for the treatment of gMG in adult patients who are anti-AChR antibody positive. EMA approved in December 2023 as an add-on to standard therapy for the treatment of gMG in adult patients who are anti-AChR antibody positive.

Source: EMA, FDA and TGA drug databases

Abbreviations: AChR, acetylcholine receptor; C5, complement component 5; EMA, European Medicines Agency; FcRN, Neonatal fragment crystallisable receptor; FDA, US Food and Drug Administration; gMG, generalised myasthenia gravis; IV, intravenous; IVIg, intravenous immunoglobulin; MuSK, muscle-specific kinase; PLEX, plasma exchange; TGA, Therapeutic Goods Administration