



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1566 – Review of immunoglobulin use for Myasthenia Gravis

Applicant: National Blood Authority

Date of MSAC consideration: MSAC 78th Meeting, 3 April 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

This Post-market Review requests MSAC advice on the Government funded supply of human gamma immunoglobulin (IgG) therapy under the National Blood Arrangements for the treatment of myasthenia gravis (MG). The application (referral) was received by the Department of Health from the National Blood Authority (NBA).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC advised that funding should continue for all three indications of myasthenia gravis. MSAC noted there is likely clinical benefit and cost-effectiveness to support continued funding of immunoglobulin for patients at risk of, or in, myasthenic crisis (indication 1). For patients with advanced MG with planned surgery (indication 2) and patients on maintenance therapy for moderate to severe MG (indication 3), MSAC advised that the evidence suggests that immunoglobulin is an effective therapy. MSAC recommended maintaining access to immunoglobulin therapy for these two indications on the basis of low Ig use and high clinical need for indication 2, and equity of access issues to an alternative treatment (plasma exchange) for indication 3. However, MSAC advised that more data should be collected on the long-term benefits and patterns of use of immunoglobulin therapy, particularly for maintenance treatment of MG, which represents the majority of use in this condition and with uncertain cost-effectiveness.

MSAC noted the estimated net costs to government of approximately \$40.7 million in 2020, increasing to \$53.7 million by 2024, and totalling approximately \$236 million over the 5 year projected period to 2024. However, MSAC noted that these are overestimates, as they do not include cost-offsets associated with reductions in comparator therapies (including plasma exchange, surgery or pharmaceuticals).

Consumer summary

The National Blood Authority (NBA) sought advice from MSAC on the government-funded supply of human antibodies (immunoglobulin, or Ig) used to treat myasthenia gravis (MG).

MG is an autoimmune condition: a condition where the body's immune or disease fighting system attacks healthy cells. MG affects the transmission of signals from the nerves to the muscles, causing muscle weakness and fatigue. People affected by MG often have difficulty swallowing, double vision and roping eyelids. We don't know exactly how immunoglobulin works – we just know it reduces the way the body attacks healthy cells.

People with MG may have access to Ig therapy for short-term treatment, for example prior to surgery or for a myasthenic crisis i.e. where muscle weakness affects breathing to the extent that a person needs assistance to breathe, or for long-term maintenance therapy.

MSAC considered that in general, Ig use is likely to be safe and effective for the treatment of people with MG, but that more data should be collected on the long-term health benefits and how Ig is being used, especially with people receiving maintenance treatment for moderate to severe MG. MSAC noted that there is poor evidence on which to make decisions about the effectiveness and cost-effectiveness of Ig for the long-term maintenance treatment of MG compared with other treatments.

MSAC noted that the main alternative treatment for MG (plasma exchange) is usually performed in major hospitals and that restricting access to Ig may mean that an effective treatment is not accessible to all people who need it. Overall, MSAC advised that funding of Ig for the treatment of MG should continue.

In 2017/18, approximately 1,174 people accessed Ig therapy for MG and this number is expected to increase to around 1,718 people by 2024. MSAC noted that Ig is a high cost therapy – the review estimated that Ig will cost the government approximately \$40.7 million to treat patients with MG in 2020. In 2018/19, a total of 6.57 million grams of Ig was supplied nationally for all medical conditions, representing a total cost of \$613.0 million (including the cost of plasma for fractionation i.e. separating the components of blood). This cost is increasing because more people are being prescribed Ig every year to treat a range of conditions.

MSAC's advice to the National Blood Authority

MSAC advised that no changes to the eligibility criteria are required and that patients should continue to have access to Ig therapy under the current MG treatment criteria. MSAC advised that more clinical data should be collected on the long-term health benefits and patterns of use of Ig therapy, particularly for maintenance treatment, which represents the majority of use for MG and has uncertain cost-effectiveness.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that patients with MG may be eligible for Ig treatment under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria) under any of the three indications:

- Indication 1: Myasthenic crisis as an alternative treatment to plasma exchange (PE);
- Indication 2: MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange; or
- Indication 3: As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

MSAC noted that the number of patients receiving intravenous Ig (IVIg) for MG in Australia (1,174 in 2017-18) is within the expected population based on the prevalence estimates from epidemiological studies. However, the prevalence of MG reported in international epidemiological studies does appear to be increasing over time.

MSAC noted that the comparator to IVIg in indications 1 and 2 was plasma exchange (PE), while comparators in indication 3 included PE as well as oral steroids, cholinesterase inhibitors, immunosuppressant/immunomodulatory drugs, and thymectomy. However, due to the lack of studies meeting the inclusion criteria there was insufficient evidence to make conclusions about the safety or effectiveness of IVIg compared to alternative therapies other than PE.

Regarding safety, MSAC noted that in the assessment report IVIg was considered to be safer than PE for MG patients in crisis (indication 1), while the body of evidence was determined too small to draw conclusions about the safety of IVIg compared to PE in patients preparing for surgery (indication 2). MSAC noted that the assessment concluded that relative to PE, IVIg has non-inferior safety for maintenance therapy (indication 3). The type of adverse events varied according to treatment with either IVIg or PE; for example, IVIg treatment was associated with more headaches and nausea, while patients with PE experienced more hypotension and venous access problems (e.g. citrate reaction, restricted venous access). No differences in safety outcomes between IVIg and PE were identified for indication 3, however it was noted in the assessment that this may be due to inadequate statistical power. There was limited safety data available on the long-term use of IVIg for MG, but MSAC noted clinical input from the Immunoglobulin Review Reference Group that suggested that PE would be less safe than IVIg due to septicaemia associated with central line access for PE.

Regarding clinical effectiveness, MSAC noted that IVIg relative to PE was considered to have non-inferior effectiveness for MG patients in crisis and maintenance therapy (indications 1 and 3). MSAC noted that further results from a trial currently underway comparing Ig to standard therapies may provide further evidence on the clinical benefits of Ig in terms of change in the Quantitative Myasthenia Gravis Score (QMGS) (Griffin 2017a and 2017b). The effectiveness of IVIg compared to PE appears similar in patients pre surgery (indication 2), however this conclusion was considered very uncertain due to the limited data in this population (two small comparative studies).

MSAC noted that the assessment had chosen the most appropriate economic analysis for each of the three indications based on the conclusions of safety and clinical effectiveness.

For indication 1, a cost utility analysis (CUA) was performed on the basis of superior safety and non-inferior clinical effectiveness. MSAC noted this CUA produced an incremental cost-

effectiveness ratio (ICER) of \$7 million per quality-adjusted life year (QALY) when based only on direct trial evidence for a single MG crisis episode. The ICER was reduced to \$45,776/QALY when modelled over 15 years, taking into account PE-associated sepsis and resulting long-term mortality and morbidity outcomes. MSAC noted that the data on safety differences was based on limited patient numbers with little clinical information and no long-term follow-up or quality of life data.

For indication 2, a cost analysis was performed based on uncertain safety and uncertain clinical effectiveness, which found that using PE (\$46,751) may be marginally less expensive than IVIg (\$47,257) in this population, although the difference is small in the context of the surgery cost (included in these estimates). On the basis of low Ig use and high clinical need in indications 1 and 2, MSAC recommended maintaining access to Ig therapy for these patients.

For indication 3, the Department Contracted Assessment Report (DCAR) presents a cost comparison for IVIg versus PE over varying doses and time horizons (one to 10 years) and includes no adverse event costs. MSAC noted that where IVIg is costed at the estimated average maintenance dose (492g/patient/year based on NBA data), it is more expensive than low intensity PE (4-weekly), but less expensive than high intensity PE (weekly). MSAC noted that an exploratory CUA was performed at the request of the Ig Review Reference Group on the assumption of superior safety of IVIg over PE. The model assumed a 0.2% rate of sepsis in patients accessing PE via a central venous catheter. The resulting ICERs ranged from dominant (when low dose IVIg was compared to low intensity PE, and in all doses of IVIg compared to high intensity PE) to \$18 million/QALY (when average NBA doses are compared to low dose PE over 10 years). MSAC noted that these estimates are based on non-comparative data and are highly uncertain.

Regarding financial implications, MSAC noted the estimated net cost to government of Ig for the treatment of MG was approximately \$40.7 million in 2020, increasing to \$53.7 million by 2024, and totalling approximately \$236 million over the 5 year projected period to 2024. MSAC noted that these estimates include the combined financial impact across the three indications and considered that it could be informative to present these results by indication. MSAC noted the pre-MSAC response from a sponsor company which raised that the financial estimates were overestimated, as they do not include cost-offsets associated with reductions in comparator therapies (including PE, surgery or pharmaceuticals). MSAC agreed with this, but noted that this was acknowledged in the assessment report.

MSAC noted the pre ESC and MSAC responses from the NBA and stakeholders. One sponsor argued that the conclusion of superior safety and non-inferior effectiveness of Ig compared to PE established in indication 1 should extend to all three indications for MG. Another stakeholder suggested the capacity for PE treatments in public hospitals could be increased significantly to ease growing demand for Ig, and consumers also supported increased access to alternative treatments such as PE and rituximab (currently not PBS subsidised for MG).

MSAC considered that access to Ig treatment for indications 1 and 2 should continue, noting the small proportion of Ig use in these populations and high clinical need. For indication 3, MSAC also recommended continued access to Ig therapy due to equity of access issues with the main comparator, PE, which is limited to tertiary metropolitan centres. MSAC noted, as raised in the assessment report and by stakeholders, that restricting access to Ig for patients with MG may cause relative harm to patients who do not have timely access to PE.

MSAC noted the high degree of uncertainty regarding comparative safety, effectiveness and costs/cost-effectiveness across all three indications, but particularly in indication 3, which

represents the largest proportion of IVIg use in patients with MG. MSAC advised that additional collection of data on IVIg use for maintenance treatment, as well as additional research on the long-term benefits of IVIg, should be explored. MSAC also suggested that the NBA consider introducing a financial cap based on the utilisation of Ig for MG, noting that the prevalence of this condition does seem to be increasing over time.

4. Background

All Australian Governments, through the Jurisdictional Blood Committee (JBC), have agreed to conduct robust Health Technology Assessments (HTAs) of immunoglobulin use (Ig Reviews) funded under the National Blood Agreement to ensure government-funded immunoglobulin use is based on strong evidence of clinical and cost-effectiveness. The National Blood Agreement provides for MSAC to undertake evidence-based evaluation of blood products funded under the national blood supply arrangements at the request of the JBC.

The Review of Immunoglobulin use in Australia is supported by a bespoke reference group, which oversees and provides advice on evaluation of all immunoglobulin HTA review applications. The PICO Confirmations for the Ig Reviews have been considered by the Review Reference Group instead of the PICO Advisory Sub-committee (PASC). Otherwise the MSAC evaluation process remains the same as for applications for funding of items on the Medical Benefits Schedule (MBS).

Application 1565 – Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT) was the first report from the Immunoglobulin Review Pilot to be progressed to MSAC in November 2019. Applications 1564 – Immunoglobulin for chronic inflammatory demyelinating polyneuropathy, and 1566 – Myasthenia gravis were considered by MSAC in April 2020, to complete the first tranche of Immunoglobulin Reviews.

Other applications relevant to the Immunoglobulin Reviews include:

- Application 1590 – Review of Immunoglobulin for multifocal motor neuropathy;
- Application 1591 – Review of Immunoglobulin for secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplant
- Application 1592 – Review of Immunoglobulin for primary immunodeficiency diseases with antibody deficiency

5. Prerequisites to implementation of any funding advice

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). There are two Ig products registered for MG on the ARTG:

- a. Intragam 10 – can only be administered intravenously (IV). It is a domestic product. The price excludes the cost of plasma collection. It is available under the National Blood Arrangements for MG.
- b. Privigen 10%. – can only be administered IV. It is an imported product. It is available in four different doses (5g, 10g, 20g, 40g) and is funded under the National Blood Arrangements for MG.

In addition to the two Ig products registered for MG on the ARTG, at the time of referral the NBA provides Ig by intravenous infusion (IVIg) for a further three products for MG. These

are: Flebogamma 5%, Flebogamma 10% and Intragam P. The latter will be removed from the Product List once current stocks expire (replaced by Intragam 10).

A further 12 Ig products are listed on the ARTG, either for IV or SC infusion, but are not indicated for MG.

Table 1 Ig products listed on the ARTG

| ARTG no. | TGA registered indications including MG | Route of Administration | TGA indication for MG? | NBA Funded for MG*? |
|---|---|-------------------------|------------------------|---------------------|
| 199979-199981, 162486-162489 | Intragam 10 – CSL Behring Australia P/L | IV | Yes | Yes ^a |
| 146273, 143337, 143368, 219160, 265147, 269689-269691, 306801, | Privigen 10% – CSL Behring Australia P/L | IV | Yes | Yes ^a |
| 285345, 285344, 207386, 207385, 207384, 207383 | Hizentra – CSL Behring Australia P/L | SC | No | No ^b |
| 116689, 117237-117240 | Gamunex 10% – Grifols Australia P/L | IV and SC | No | No |
| 182358, 182359, 184353 | Flebogamma 10% – Grifols Australia P/L | IV | No | Yes ^a |
| 140602, 143800-143803 | Flebogamma 5% – Grifols Australia P/L | IV | No | Yes ^a |
| 219007, 171139, 171140, 158712, 154210, 66295, 66300, 68632-68635, 74356, 74540 | Intragam P – CSL Behring Australia P/L | IV | No | Yes ^b |
| 291644-291648, 291740 | Panzyga – Octapharma Australia P/L | IV | No | No |
| 235178 | Hyqvia – Shire Australia P/L | SC | No | No |
| 232077, 232078, 232084, 232085 | Intratect – Pfizer Australia P/L | IV | No | No |
| 164548-164551 | Intratect 5% – Pfizer Australia P/L | IV | No | No |
| 173315, 173323, 173324, 204954-204956 | Evogam 16% – CSL Behring Australia P/L | SC | No | No |
| 113925-113928, 155601-155604 | Octagam – Octapharma P/L | IV | No | No |
| 128703, 128705 | Gammanorm – Octapharma P/L | SC and IM | No | No |
| 131953, 131966, 131968, 131969, 131973, 198488 | Kiovig – Shire Australia P/L | IV and SC | No | No |
| 282579 | Cuvitru – Shire Australia P/L | SC | No | No |
| 61215, 61216 | CSL Normal Immunoglobulin VF- CSL Behring Australia P/L | IM | No | No ^c |

Source: Contracted Assessment, Table 7 (Therapeutic Goods Administration, accessed 20 May 2019)

ARTG = Australian Register of Therapeutic Goods; IV = intravenous; SC = subcutaneous; IM = intramuscular; MG = myasthenia gravis; NBA = national Blood Authority; TGA = Therapeutic Goods Administration

^a Indicates that Ig is *currently* funded for MG. Note that tendering arrangements may change products funded in the future.

^b Intragam P will be removed from funded access under the National Blood Arrangements once current inventory reserves have expired

^c IMIg is not in scope for this review.

6. Proposal for public funding

Ig therapy for MG is presently funded under the national blood supply arrangements, but the cost-effectiveness of this use has not been established. NBA procurement of Ig is via competitive tendering and negotiation with suppliers.

Table 2 indicates prices for NBA funded Ig products for MG (at 14 February 2019).

Table 2: Ig products registered on the ARTG for use in Australia

| Product name and company | Route of Administration | TGA indication for MG? | NBA Funded for MG*? | NBA price |
|---|-------------------------|------------------------|---------------------|---------------------|
| Intragam 10 – CSL Behring Australia P/L (2.5g/25mL to 20g/200mL) | IV | Yes | Yes | \$146.23-\$1,169.86 |
| Privigen 10% – CSL Behring Australia P/L (5g/50mL to 40g/400mL) | IV | Yes | Yes | \$225 - \$1,800 |
| Flebogamma 10% – Grifols Australia P/L (5g/50mL up to 40g/400mL) | IV | No | Yes | \$225-\$900 |
| Flebogamma 5% – Grifols Australia P/L (0.5g/10mL up to 20g/400mL) | IV | No | Yes | \$22.50-\$900 |
| Intragam P – CSL Behring Australia P/L | IV | No | Yes** | \$175.48 |
| Hizentra – CSL Behring Australia P/L (1g/5mL to 10g/50mL) | SC | No | No*** | \$57.43 to \$574.30 |
| Evogam 16% – CSL Behring Australia P/L (0.8g/5mL or 3.2g/20mL) | SC | No | No*** | \$46.79 or \$187.18 |

* Indicates that Ig is *currently* funded for MG. Note that tendering arrangements may change products funded in the future.

**Intragam P will be removed from funded access under the National Blood Arrangements once current inventory reserves have expired

*** While Hizentra and Evogam are NBA funded for some conditions, they are not currently funded for MG but this may change in the future.

IV – intravenous

SC – subcutaneous

Source: Referral 1566, Table 2

Access to IVIg in this population requires an Australian Health Practitioner Regulation Agency (AHPRA) registered neurologist to diagnose MG in the patient initially, and to carry out patient reviews.

Clinical criteria for eligible patients to access subsidised Ig are specified in Version 3 of the Criteria. MG patients must be approved by meeting criteria for Indication 1, 2 or 3 in order to access the products. The Criteria, including eligibility criteria are periodically updated and may be refined according to recommendations of the relevant NBA working group and subsequent approval by the JBC.

7. Summary of public consultation feedback/consumer Issues

Public consultation was undertaken on the Referral and draft Contracted Assessment, and sponsor companies had an additional opportunity to comment on the PICO and provide input to the Contracted Assessment.

Feedback from consumers was supportive of IVIg use, and considered that IVIg allows MG sufferers to experience a better quality of life with no disadvantages associated with its treatment. Consumers acknowledged that studies used in the report often reported small patient numbers, which make it difficult to justify confirmed results. However overall, they

agreed with the benefits and safety/side effects associated with Ig as described in the assessment report.

Consumers agreed there are accessibility and delivery issues associated with PE treatment, and expressed that all treatment options (including PE and rituximab) should be available to patients with MG due to the variable nature of the condition. Feedback indicated that out-of-pocket costs for receiving Ig and access to treatments can vary dependent on patient location and available resources (e.g. private patients, or patients living in remote locations).

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

This application is for Immunoglobulin (Ig) used as immunomodulation therapy.

Immunoglobulin is a plasma-derived product manufactured to treat a range of medical conditions. Access to government-funded Ig is through the national blood arrangements and is determined by the NBA's *Criteria for Clinical Use of Immunoglobulin in Australia* (the Criteria). Although the exact mechanism of action that IVIg has on MG patients is not known, it acts as an immune modulator, reducing the abnormal immune response and neuromuscular symptoms. Due to its high cost, IVIg is usually given as a short-term therapy, although some patients remain on IVIg maintenance therapy longer term.

Description of Medical Condition(s)

MG is an autoimmune condition associated with the presence of antibodies to acetylcholine receptors (AChR) or to muscle-specific tyrosine kinase (MuSK) at the neuromuscular junction. Some patients with myasthenia gravis are antibody negative. The condition affects transmission of signals from the nerves to the muscles, causing muscle weakness. Clinical features are characterised by fluctuating weakness and fatigability of voluntary muscles, and patients usually present with drooping of the eyelids, double vision and difficulty swallowing.

This application includes patients with MG who are currently eligible for Ig treatment in Australia according to Version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*¹ (the Criteria). There are three indications for which these patients may be eligible for IVIg therapy:

- a. Indication 1: Myasthenic crisis as an alternative treatment to plasma exchange
- b. Indication 2: MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange
- c. Indication 3: As a maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

According to the applicant, 1,174 patients received IVIg for MG in Australia from July 2017-June 2018, and the reported prevalence in the PICO for MG in Western countries is 2-7/10,000 population. Based on this prevalence estimate, around 5,000-17,500 patients are affected by MG based on an Australian population² of approximately 25 million at June 2018. The applicant calculated the spread across Indications 1, 2, and 3 to be 17.1% (201), 2.8% (33) and 80.1% (940) respectively in terms of patient numbers. However, the Applicant advised that usage in terms of grams of IVIg, is estimated to be distributed across the three indications in the proportions of 9%: 1%:90% respectively.

¹ National Blood Authority, 2018, [Criteria for the clinical use of immunoglobulin in Australia](#) (version 3).

² <https://www.abs.gov.au/>

Place in clinical management

Diagnosis by a neurologist must be made for patients to receive Ig for any of the MG indications covered by NBA *Criteria V3*.

For Indication 1, a patient must have respiratory insufficiency requiring intubation and assisted ventilation, or have symptoms to show they are at risk of life-threatening myasthenic crisis to meet the eligibility criteria. Patients are often already receiving immunosuppressants (IS) or corticosteroid (CS) therapy or a combination of therapies. In these circumstances, the neurologist may consider IVIg or PE treatment.

Thymectomy may be considered in MG patients to reduce the autoimmune response. For Indication 2, patients at an advanced stage in MG disease may require stabilization prior to surgery, through treatment with IVIg if patients meet the eligibility criteria. The patient should be monitored for stabilization post-surgery.

To qualify for IVIg for Indication 3, a patient with non-life-threatening moderate to severe MG symptoms must have already tried and failed at least two alternative therapies. Alternatively, patients may be contraindicated for alternative therapies (including by development of side effects or comorbidities) or have alternative therapies unavailable to them.

The clinical management pathways for Indications 1, 2, and 3 are shown in Figure 1, Figure 2 and Figure 3, respectively.

Indication 1

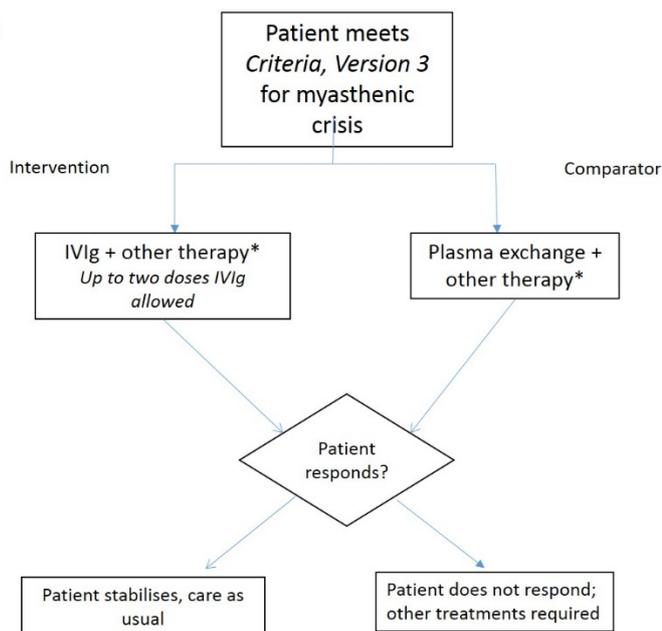


Figure 1 Clinical management pathway for patients with, or at risk of, myasthenic crisis

IVIg = intravenous immunoglobulin therapy

*Other therapies include corticosteroids, anticholinesterases, and immunotherapy; patients would not receive IVIg and plasma exchange concurrently.

Source: Contracted Assessment, Figure 1

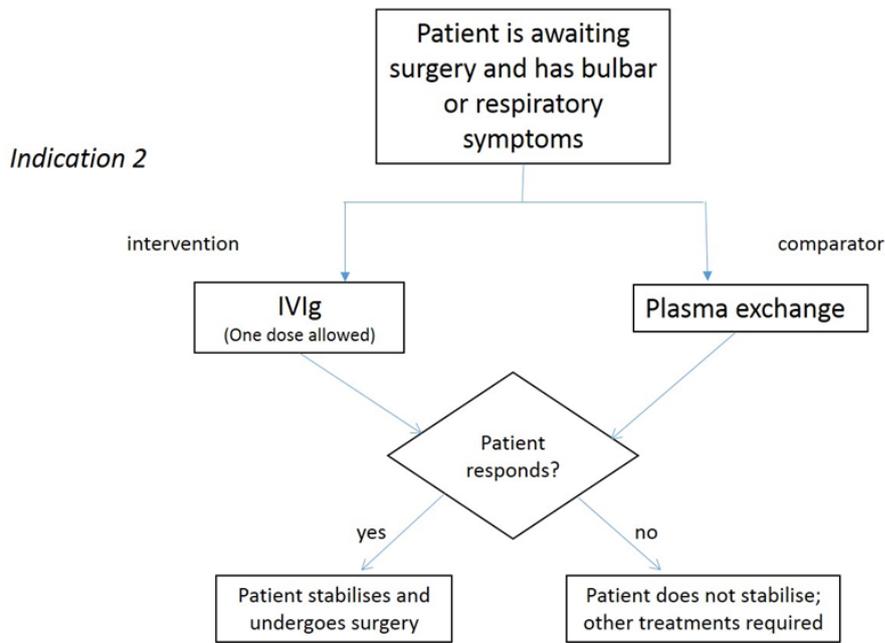


Figure 2 Clinical management pathway for patients with MG awaiting surgery and/or thymectomy

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis

Source: Contracted Assessment, Figure 2

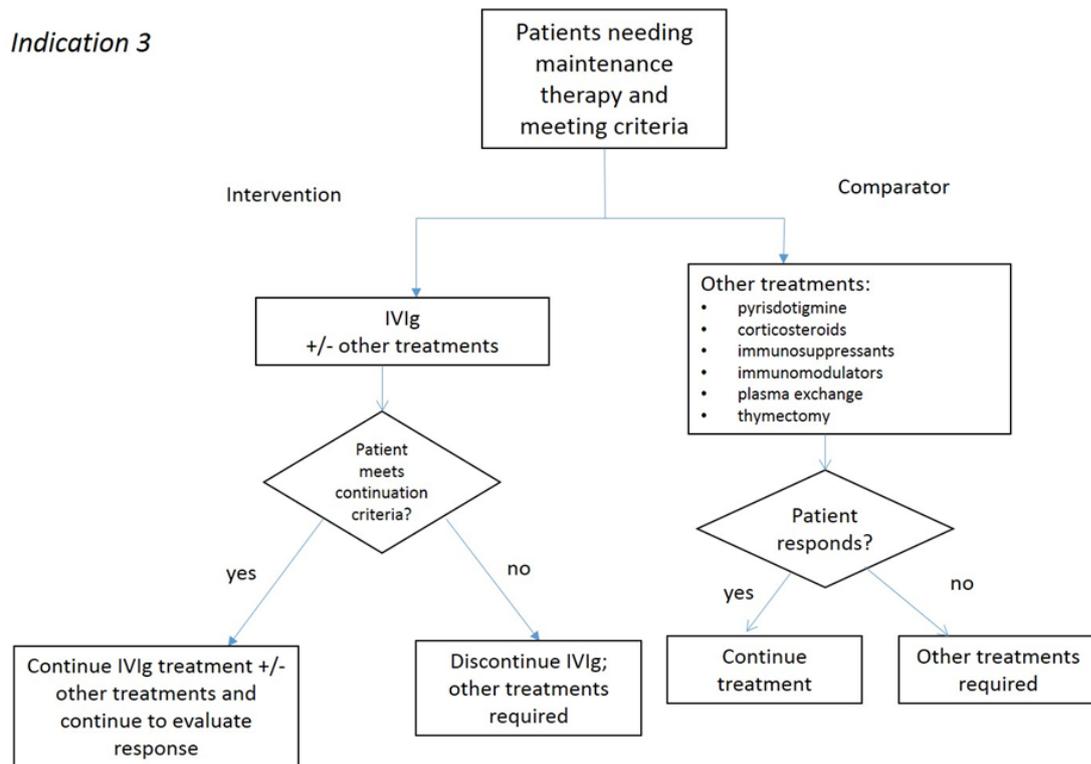


Figure 3 Clinical management pathway for patients with moderate to severe MG on maintenance therapy

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis

Source: Contracted Assessment, Figure 3

9. Comparator

The proposed comparator for Indications 1 and 2 is plasma exchange. Both Ig and plasma exchange are seen as short-term therapies to be used to stabilise a patient whilst waiting for other therapies to become effective. Other than the choice of stabilising therapy, other treatment is expected to be the same for both intervention and comparator.

The proposed comparators for Indication 3 were oral steroids, cholinesterase inhibitors, immunosuppressant/immunomodulatory drugs, and thymectomy. It is likely that most patients with moderate to severe MG would be on two other therapies. To be eligible for Ig maintenance therapy, at least two other treatments must have been ineffective, contraindicated, unavailable or have caused intolerable side effects.

The Applicant noted that PE is not usually provided on an outpatient basis and cannot be used long term in most places; however, the Criteria V3 for ongoing use of Ig in the maintenance population lists PE as an alternative therapy. Expert advice from the Ig Review Reference Group indicated that PE should also be a comparator in this indication.

10. Comparative safety

A summary of the comparative safety of Ig is discussed for each Indication below.

Indication 1: Myasthenic crisis

Six comparative studies (one RCT, and five retrospective cohort studies) reporting adverse events (AEs) found there were more AEs associated with PE than IVIg treatment and a greater proportion of patients experienced AEs in the PE group compared to IVIg. This difference reached significance in one RCT³ and a large cohort study⁴ but not in the lower level studies.

Gajdos et al. 1997 found that 19.5% of patients in the PE group experienced AEs compared with 2.2% in the IVIg group. Of the eight patients in the PE group who experienced AEs, two were serious enough to require discontinuation of treatment (one experiencing femoral thrombosis and one experiencing retroperitoneal haematoma). Findings from the large cohort study supported these results, with a significantly greater number of AEs in the PE group.

Overall, the studies found that some events were more common in either the PE or IVIg group. Hypotension was a common AE in the PE group, while headaches and nausea were more common the IVIg group, but these were all considered minor symptoms. There appeared to be a large number of systemic infections associated with PE treatment reported by Mandawat et al. 2010. However, selection bias could not be ruled out, as the reported baseline data reflected a significantly higher number of patients who underwent PE experienced acute respiratory failure and were intubated compared to those given IVIg ($p < 0.0001$). This indicates that treatment selection in more seriously ill patients may have been influenced with PE being the favoured treatment for myasthenic crisis due to its suspected faster onset of action. There is evidence in the literature that PE is given in preference to IVIg in life-threatening crises because it is thought to be faster acting, and some treatment guidelines for MG also indicate the longer action time of IVIg compared to PE in crisis

³ Gajdos, P, Chevret, S, Clair, B, Tranchant, C & Chastang, C 1997, 'Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis', *Annals of Neurology*, vol. 41, no. 6, pp. 789-796.

⁴ Mandawat, A, Kaminski, HJ, Cutter, G, Katirji, B & Alsheklee, A 2010, 'Comparative analysis of therapeutic options used for myasthenia gravis', *Annals of Neurology*, vol. 68, no. 6, pp. 797-805.

patients. It is possible that this preference extends to the other cohort studies, although overall the assessment concluded that IVIg was safer than PE for MG patients in crisis.

Indication 2: Patients preparing for surgery

One RCT⁵ and one retrospective matched cohort study⁶ compared AEs between patients given IVIg or PE in preparation for thymectomy; however, patient numbers were very small (24 patients in the RCT and 18 in the cohort study) and the studies were not well powered.

Results from Alipour-Faz et al found that intubation was required significantly more frequently in the PE group (2/12 versus 7/12; $p = 0.01$), and found that the two patients who went into crisis were in the PE group. The retrospective comparison reported data on AEs for the IVIg group only however, the authors commented that in the PE group there was difficulty with line insertion, transient hypotension, and asymptomatic coagulation abnormalities.

As for Indication 1, results may be confounded by the preference for PE treatment for patients in crisis or at higher risk of crisis. Overall the assessment concluded that the body of evidence was too small to draw conclusions about the safety of IVIg compared to PE for this indication.

Indication 3: Maintenance therapy

There was no evidence comparing IVIg with oral steroids, anticholinesterases, or immunosuppressants that met the inclusion criteria and therefore, there was insufficient evidence to make conclusions about the safety of IVIg compared to standard therapies other than PE. The majority of evidence identified compared IVIg with PE for maintenance therapy of MG.

Adverse events for IVIg and PE were compared in three RCTs, and one comparative retrospective cohort study. Results for these are displayed in Table 3. One moderate quality RCT (Barth et al. 2011) in adults found significantly more headaches and vomiting in the IVIg population, and more venous access problems (citrate reaction, restricted venous access, and vasospasm) in the PE group. Serious events (cardiac failure, vasoreaction) were infrequent but all occurred in the PE group.

Two other studies reporting AEs for IVIg and PE in adults found no difference between treatment groups. Over all, there were too few serious AEs to conclude either treatment as safer than the other.

Overall the assessment concluded that relative to PE, IVIg has non-inferior safety.

⁵ Alipour-Faz, A, Shojaei, M, Peyvandi, H, Ramzi, D, Oroei, M, Ghadiri, F & Peyvandi, M 2017, 'A comparison between IVIG and plasma exchange as preparations before thymectomy in myasthenia gravis patients', *Acta neurologica belgica*, vol. 117, no. 1, pp. 245-249.

⁶ Jensen, P & Bril, V 2008, 'A comparison of the effectiveness of intravenous immunoglobulin and plasma exchange as preoperative therapy of myasthenia gravis', *Journal of Clinical Neuromuscular Disease*, vol. 9, no. 3, pp. 352-355.

Table 3 Adverse events for IVIg compared with PE for MG maintenance

| Study ID, country Level of evidence Quality | Event | IVIg n with event/N (%) | PE n with event/N (%) | Difference p-value (95% CI) |
|---|--|-------------------------------|-----------------------------|---------------------------------------|
| (Barth et al. 2011), Canada Level II Low risk of bias | Allergic reaction | 2/41 (4.9%) | 0/43 | P = 0.14 (-4.03%, 16.1%) ^a |
| | Nausea, vomiting | 7/41 (17.0%) | 0/43 | P = 0.005 (5.17%, 31.2%) |
| | Headache | 8/41 (19.5%) | 0/43 | P = 0.0025 (7.12%, 34.0%) |
| | Chills | 2/41 (4.9%) | 0/43 | P = 0.14 (-4.03%, 16.1%) |
| | Fever | 3/41 (7.3%) | 0/43 | P = 0.073 (-2.20%, 19.4%) |
| | Haemolytic anaemia | 1/41 (2.45%) | 0/43 | P = 0.30 (-5.99%, 12.6%) |
| | Hypertension | 1/41 (2.4%) | 0/43 | P = 0.30 (-5.99%, 12.6%) |
| | Citrate reaction | 0/41 | 6/43 (14.0%) | P = 0.013 (2.67%, 27.3%) |
| | Poor venous access delaying treatment | 0/41 | 4/43 (9.3%) | P = 0.047 (-.948%, 21.6%) |
| | Vasospasm | 0/41 | 8/43 (18.6%) | P = 0.0039 (6.27%, 32.6%) |
| | Vasovagal reaction | 0/41 | 2/43 (4.7%) | P = 0.16 (-4.51%, 15.5%) |
| | Myocardial infarction | 0/41 | 1/43 (2.3%) | P = 0.30 (-5.99%, 12.6%) |
| (Liu et al. 2010), China Level II Moderate risk of bias | Hypotension | 0/15 | 2/15 (13.3%) | P = 0.15 (-9.23%, 37.8%) ^a |
| | Haematoma | 0/15 | 1/15 (6.7%) | P = 0.32 (-14.4%, 29.9%) |
| | Vomiting | 1/15 (6.7%) | 0/15 | P = 0.32 (-14.4%, 29.9%) |
| | Anaphylaxis | 0/15 | 0/15 | - |
| (Mandawat et al. 2010), USA Level III-2 Moderate risk of bias | Patient number | 171 | 737 | - |
| | Mortality | (0.58%) | (0.41%) | P = 0.56 ^b |
| | Any complication | (10.53%) | (11.40%) | P = 0.89 |
| | Cardiac | (7.60%) | (9.50%) | P = 0.55 |
| | Acute renal failure | (1.17%) | (0.27%) | P = 0.16 |
| | Systemic infection | (1.7%) | (1.63%) | P = 1.00 |
| | Thrombotic complications | (0.58%) | (0.27%) | P = 0.46 |
| (Rønager et al. 2001), Denmark Level II High risk of bias | Number of AEs | 14 | 7 | |
| | Hypotension | 0 | 4 | |
| | Nausea, vomiting | 3 | 1 | |
| | Septicaemia | 0 | 1 | |
| | Deep vein thrombosis | 0 | 1 | |
| | High temperature | 5 | 0 | |
| | Headache | 7 | 0 | |
| | Patients with no AE | 4/12 (33.3%) | 8/12 (66.7%) | P = 0.11 (-5.64%, 61.0%) ^a |

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy

^a Chi-squared test, MedCalc online calculator

^b Fisher's exact test (Mandawat et al. 2010)

Source: Contracted Assessment, Table 21

11. Comparative effectiveness

The clinical effectiveness outcomes of interest reported by the included studies were:

- mortality
- change in symptoms (change in disability and muscle strength by various scales, described below)
- change in quality of life (by various scales described below)
- rate of remission
- disease stability
- time to relapse

- need for ventilation or other life support systems
- adverse events (AEs) associated with administration of the therapy or side effects of therapy (such as IV line insertion risks, line sepsis, haemodynamic effects, inflammatory and thrombotic effects).

A summary of the comparative effectiveness of Ig is discussed for each Indication below. See Tables 5-8 for the balance of clinical benefits and harms of IVIg relative to its comparators.

Indication 1: Myasthenic crisis

Three retrospective cohort studies compared the rate of mortality between patients treated with IVIg and PE. Mandawat et al. 2010 found that of the patients who underwent either IVIg or PE in MG crisis, unadjusted mortality rates were significantly higher in the PE group compared to the IVIg group (5.67% v 0.59%; $p = 0.002$). However the difference in mortality rates may not be as large as indicated by the data, given the baseline population characteristics indicate patients given PE are more likely to have systemic infection ($p < 0.0001$). This indicates that patients at a more critical stage may be more likely to be treated with PE as it is thought to act more quickly.

Two smaller studies did not find any difference in mortality between the patients treated with IVIg or PE. In the IVIg group, one death resulted from sepsis, one due to withdrawal of care and one patient could not be stabilised or revived in crisis. In the PE group, one death was due to ventilator related infection and the other was due to cardiac arrest.

None of the included studies used the MGC to measure change in symptoms for the MG crisis population. For other symptom measures (myasthenia muscle score MMS and myasthenia severity scale MSS) from baseline at 15 days, patients receiving either IVIg or PE both improved, but there was either no significant difference between the groups, or the significance of results was not determined.

Mean improvement in MMS was also assessed comparing lower dose (1 g/kg) and higher dose (2 g/kg over two days) IVIg. Patients receiving the higher IVIg dose achieved a higher mean improvement in MMS but the difference was not significant and the author concluded that the lower dose may be the best dose in clinical practise when cost benefits are considered in using the smaller dose.

Table 4 Change in MMS after 15 days for MG patients treated with IVIg (dose comparison) (Gajdos, Chevret & Toyka 2012)

| Measure | IVIg (2 g/kg) N = 87 Mean (SD) | IVIg (1g/kg) N = 81 Mean (SD) | Mean difference (95% CI) | Overall effect |
|---------------|--------------------------------------|-------------------------------------|-----------------------------|-----------------------|
| Change in MMS | 19.33 (16.48) | 15.49 (15.4) | 3.84 (-0.98, 8.66) | P = 0.12 ^a |

IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS myasthenia muscle score; SD = standard deviation

^a Result reported in Gajdos, Chevret and Toyka, 2012

Source: Contracted Assessment, Table 29

Quality of life, rate of remission, time to relapse and need for ventilation were not reported in any of the studies assessing IVIg and PE for patients in this indication. Overall it was considered that IVIg has non-inferior effectiveness relative to PE.

Indication 2: Patients preparing for surgery

One RCT and one retrospective matched cohort study were included in the assessment of IVIg and PE in this group. The cohort study reported there was no sepsis observed in either

group, and the RCT stated that two cases of myasthenic crisis in the PE group were related to pneumonia infections while no such cases were reported in the IVIg group.

With respect to change in symptoms, Jensen & Bril et al. 2008 found that there was no statistical difference in the degree of improvement between either group. Symptoms improved (change in Osserman grade) following surgery and treatment in both the IVIg and PE groups with two out of nine patients in each group improving by two Osserman grades. However, it is likely that the thymectomy contributed to the improved status.

In Alipour-Faz et al. 2017, patients had a shorter intubation period on average and fewer required intubation when randomised to IVIg compared to PE, however the number of patients was very small (12 in each group).

Neither studies reported on mortality rates, rate of remission or time to relapse. Overall there was no strong evidence favouring IVIg or PE in patients preparing for surgery.

Indication 3: Maintenance therapy

There was insufficient data comparing IVIg with standard maintenance therapies other than PE. Further data on the changes in symptoms (QMGS) from ongoing trials (NCT02473952) comparing IVIg and placebo may be of interest. These outcomes were not yet published during the preparation of the DCAR. .

One RCT and one retrospective cohort study compared the number of infections between patients receiving IVIg or PE for MG maintenance therapy. Rønager et al. 2001 used a crossover design where all 12 patients received IVIg and PE separated by an observation period. One case of septicaemia was reported in a patient undergoing PE. There was no difference in proportions of systemic infection between groups in the retrospective cohort study.

No studies used the MGC tool for assessing symptom improvement for patients, but three RCTs used the QMGS tool. Patients on IVIg and PE had similar improvement in symptoms at 4 weeks⁷ and 16 weeks⁸ from start of treatment. Only a small degree of improvement appeared to be sustained for up to 16 weeks for either IVIg or PE. Longer term comparative studies may be more informative on the degree of sustained symptom improvement. The degree of improvement may be influenced by the severity of symptoms at baseline.

Quality of life (QoL) was reported in an RCT (Barnett et al. 2013) and there was no statistically significant difference found in change of QoL between IVIg and PE treatment groups at 14, 21, or 28 days from start of treatment. QoL increased from baseline at all time-points but appeared to plateau in the PE group.

None of the included studies reported on disease stability or time to relapse.

Clinical claim

Compared to PE, IVIg was found to have non-inferior effectiveness for MG patients given these maintenance therapies.

⁷ Barth, D, Nabavi Nouri, M, Ng, E, Nwe, P & Bril, V 2011, 'Comparison of IVIg and PLEX in patients with myasthenia gravis', *Neurology*, vol. 76, no. 23, pp. 2017-2023.

⁸ Rønager, J, Ravnborg, M, Hermansen, I & Vorstrup, S 2001, 'Immunoglobulin treatment versus plasma exchange in patients with chronic moderate to severe myasthenia gravis', *Artificial organs*, vol. 25, no. 12, pp. 967-973.

Table 5 Balance of clinical benefits and harms of IVIg relative to PE in MG patients in or at risk of MG crisis (Criteria V3 Indication 1), as measured by the critical patient relevant outcomes in the key studies

| Outcome | Participants Studies | Effect | GRADE | Comments |
|--|-----------------------------|---|--------------------------|---|
| Safety | | | | |
| Adverse events (% patients with an event) | n=897 k=1 RCT, 5 Ret CoH | There were fewer adverse events associated with IVIg compared to PE | ⊕⊕⊕⊖ Moderate quality | There were fewer AEs overall occurring in patients who received IVIg compared to PE. This result was consistent across studies. Selection bias could not be ruled out in the cohort studies, and this may reduce the effect, but benefit is still likely. |
| Effectiveness | | | | |
| Mortality (% patients) | n=773 k=3 Ret CoH | There was no difference between IVIg and PE | ⊕⊕⊖⊖ Low quality | There were fewer deaths occurring in patients who received IVIg compared to PE, but suspicion of selection bias in one large cohort study prevents this result from being reliable. |
| Infection rate (% patients with an event) | n=778 k=3 Ret CoH | There was no difference between IVIg and PE | ⊕⊕⊖⊖ Low quality | There were fewer infections overall occurring in patients who received IVIg compared to PE. Suspicion of selection bias in one large cohort study, and inconsistent reporting of infections prevents this result from being reliable. |
| Change in MMS (change in score at 15 days from baseline) | n=87 k=1 RCT | There was no difference between IVIg and PE | ⊕⊕⊕⊖ Moderate quality | There was no benefit for patients receiving IVIg over those who received PE found by change in MMS at 15 days. |

GRADE Working Group grades of evidence

⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MMS = myasthenia muscle score; NA = not applicable; PE = plasma exchange therapy; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

Source: Contracted Assessment, Table 48

Table 6 Balance of clinical benefits and harms of IVIg relative to PE in MG patients preparing for surgery (Criteria V3 Indication 2) as measured by the critical patient relevant outcomes in the key studies

| Outcome | Participants Studies | Effect | GRADE | Comments |
|---------------------------------------|----------------------|-----------------------------|---------------------|--|
| Safety | | | | |
| Adverse events (% patients intubated) | n=24 k=1 RCT | No conclusion could be made | ⊕⊕⊖⊖ Low quality | Overall there were fewer AEs occurring in patients who received IVIg compared to PE, however the participant numbers in the RCT were so small that the study did not have power to make a strong conclusion. |
| Effectiveness | | | | |
| Effectiveness | - | No conclusion could be made | - | The evidence for effectiveness was of too poor quality to make any conclusions about the effectiveness of IVIg compared to PE |

GRADE Working Group grades of evidence

⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse event; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; PE = plasma exchange therapy; RCT = randomised controlled trial;

Source: Contracted Assessment, Table 49

Table 7 Balance of clinical benefits and harms of IVIg relative to comparators (therapeutics other than PE) in MG patients changing maintenance therapy (Criteria V3 Indication 3) as measured by the critical patient relevant outcomes in the key studies

| Outcome | Participants Studies | Effect | GRADE | Comments |
|--|----------------------|------------------------------|---------------------|--|
| Safety | | | | |
| Adverse events (% patients with any event) IVIg v placebo | n=62 k=1 RCT | No conclusions could be made | ⊕⊕⊖⊖ Low quality | There was no difference in frequency of AEs detected between groups. Patients in both arms were on other maintenance therapies, the impact of which was not determined. |
| Effectiveness | | | | |
| Mortality (% patients with event) IVIg v placebo | n=62 k=1 RCT | No conclusions could be made | ⊕⊕⊖⊖ Low quality | There was no difference in frequency between groups. . Patients in both arms were on other maintenance therapies, the impact of which was not determined. |
| Change in QMGS (change in score from baseline to day 28) IVIg v placebo | n=51 k=1 RCT | No conclusions could be made | ⊕⊕⊖⊖ Low quality | The symptom improvement in the IVIg group at 28 days was not statistically significant. At 14 days the difference was stronger (p = 0.03). Some patients in both arms were taking one or more standard therapies. This outcome may show an incremental benefit of IVIg over standard therapies |
| Change in absolute score in children (mean change from baseline) IVIg + MPN v MPN alone | n=70 k=1 Ret CoH | No conclusions could be made | ⊕⊕⊖⊖ Low quality | Symptom improvement favoured IVIg but may be unreliable due to poor study quality. Patients were also given other standard therapies over the course of the study. This outcome may show incremental benefit of IVIg over high dose IV MPN. |
| <p>GRADE Working Group grades of evidence</p> <p>⊕⊕⊕⊕ High quality: Further research is very unlikely to change our confidence in the estimate of effect.</p> <p>⊕⊕⊕⊖ Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</p> <p>⊕⊕⊖⊖ Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</p> <p>⊕⊖⊖⊖ Very low quality: We are very uncertain about the estimate.</p> | | | | |

AE = adverse events; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MPN = methylprednisolone therapy; PE = plasma exchange therapy; QMGS = quantitative myasthenia gravis score; Ret CoH = retrospective cohort study; RCT = randomised controlled trial;

Source: Contracted Assessment, Table 50

Table 8 Balance of clinical benefits and harms of IVIg relative to PE in MG patients changing maintenance therapy (Criteria V3 Indication 3) as measured by the critical patient relevant outcomes in the key studies

| Outcome | Participants Studies | Effect | GRADE | Comments |
|---|--------------------------------|---|--------------------------|--|
| Safety | | | | |
| Adverse events (% patients with any event) | n=1,034 k=3 RCTs, 1 Ret CoH | There was no difference between IVIg and PE | ⊕⊕⊕⊖ Moderate quality | There was no difference in frequency of AEs detected between groups. This outcome may be impacted by selection bias in the cohort studies, however the results are consistent across all studies. |
| Adverse events (% children with pyrexia and rigors or central line sepsis) | n=17 k=1 Ret CoH | No conclusions could be made | ⊕⊖⊖⊖ Very low quality | The frequency of AEs was lower in children given PE but the difference was not statistically significant. This result may be unreliable due to small participant numbers. |
| Effectiveness | | | | |
| Infection rate (% patients with event) | n=920 k=1 RCT, 1 Ret CoH | There was no difference between IVIg and PE | ⊕⊕⊖⊖ Low quality | There was no difference in frequency of infections between groups. This outcome may be impacted by selection bias in the cohort study, and the RCT was underpowered for a strong conclusion. |
| Change in QMGS (mean change in score from baseline to 14 days or % change from baseline) | n=124 k=2 RCTs | There was no difference between IVIg and PE | ⊕⊕⊖⊖ Low quality | The RCTs both favoured PE with one trial finding clinically important improvements in both IVIg and PE groups without a statistically significant difference between groups, and the other finding a statistically significantly greater improvement in the PE group compared to the IVIg group, but it is not possible to tell if this is clinically significant. These results are based on small participant numbers. |
| Change in QMGS (mean change in score from baseline to 21 days) | n=84 k=1 RCT | There was no difference between IVIg and PE | ⊕⊕⊕⊖ Moderate quality | Symptom improvement favoured PE at 21 days but was not statistically significant. Results were from a single small RCT with low risk of bias. |
| Change in QMGS (mean change in score from baseline to 28 days) | n=84 k=1 RCT | There was no difference between IVIg and PE | ⊕⊕⊕⊖ Moderate quality | Symptom improvement favoured PE at 28 days but was not statistically significant. Results were from a single small RCT with low risk of bias. |
| Change in QoL (change in MG-QoL-60 from baseline to day 28) | n=62 k=1 RCT | There was no difference between IVIg and PE | ⊕⊕⊕⊖ Moderate quality | Improvement in QoL favoured IVIg but there was no statistical difference between groups. Results were from a single RCT with low risk of bias. |
| Response to treatment in children (% children who responded measured with non-standardised tools) | n=17 k=1 Ret CoH | No conclusions could be made | ⊕⊖⊖⊖ Very low quality | Response in children was better for those given PE. This result may be unreliable due to non-standardised tools and small participant numbers. |

GRADE Working Group grades of evidence

⊕⊕⊕⊕ **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕⊖⊖ **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕⊖⊖⊖ **Very low quality:** We are very uncertain about the estimate.

AE = adverse events; IVIg = intravenous immunoglobulin therapy; MG = myasthenia gravis; MG-QoL-60 = myasthenia gravis quality of life 60 questions; PE = plasma exchange therapy; QMGS = quantitative myasthenia gravis score; QoL = quality of life; Ret CoH = retrospective cohort study; RCT = randomised controlled trial

Source: Contracted Assessment, Table 51

12. Economic evaluation

A decision algorithm (Table 9) was used to determine what type of economic analysis to undertake for each Indication.

For Indication 1, a full cost-utility analysis was undertaken; however, the data on safety differences is based on limited patient numbers with little clinical information and no long-term follow-up or quality of life information.

For Indication 2, based on the decision algorithm, a cost analysis was undertaken.

For Indication 3, based on the decision algorithm, a cost-minimisation analysis (IVIg v PE) was considered appropriate. However at the request of the Ig Review Reference Group and their advice that PE is less safe than Ig due to septicaemia associated with central line access, an exploratory cost-utility analysis was conducted based on a reduced infection rate using IVIg compared to PE. However, the results of this analysis are highly uncertain, and caution should be taken interpreting them.

Table 9 Decision algorithm for undertaking an economic evaluation in the setting of the Ig Review.

| Comparative safety of Ig | Comparative effectiveness of Ig | | | | |
|--------------------------|---------------------------------|-------------------|-----------|----------------|----------------|
| | Inferior | | Uncertain | Non-inferior | Superior |
| | No active comparator | Active comparator | | | |
| Inferior | x | F | ? | F ^b | F ^a |
| Uncertain | x | F ^a | ? | ? | F ^a |
| Non-inferior | x ^c | F | ? | \$ | F |
| Superior | x ^c | F ^a | ? | F ^b | F |

x = health forgone (at cost). An economic evaluation is not warranted and continued use of Ig should not occur in this circumstance unless there are other supportive factors.

F = undertake a full economic evaluation. These may take the form of cost-utility analyses (preferred if adequate data are available) or cost effectiveness analyses in terms of clinically relevant outcome(s).

? = high levels of uncertainty will occur in an economic evaluation (if it is feasible to construct one). A cost analysis (partial economic evaluation) could be performed.

\$ = cost minimisation analysis (partial economic evaluation that explicitly assumes no significant differences in health outcomes, associated with either effectiveness or safety, and analyses cost-differences only).

a where the conclusions with respect to effectiveness and safety are not congruent, then analyses identifying all relevant health consequences (i.e. effectiveness and safety outcomes in opposing directions of benefit) need to be presented. If a CUA is presented, this should capture effectiveness and safety collectively. If a CUA is not possible, then a single CEA may not capture all health consequences adequately and so a CCA is likely to be required. Where possible, the CCA should be quantitative, but in the absence of adequate data, a minimum qualitative identification of consequences should be presented.

b where effectiveness is assessed as non-inferior but safety differences exist, and in the absence of a CUA being possible, the outcomes component of the analysis should include a clinically relevant outcome which reflects the safety differences between Ig and the comparator.

c The small but unavoidable potential risks associated with administering a blood product means that a conclusion of non-inferior or superior Ig safety relative to no active comparator, should never arise.

Source: Contracted Assessment, Table 59

Indication 1 conclusion shaded blue, Indication 2 conclusion shaded orange, Indication 3 conclusion vs PE shaded green; vs surgery/pharmaceuticals shaded orange.

Source: Contracted Assessment, Table 59

A summary of the key characteristics of the economic analysis is presented in Table 10.

Table 10 Summary of the economic evaluations

| | Indication 1 MG crisis | Indication 2 MG patients pre-surgery | Indication 3 Maintenance in refractory MG disease |
|---|--|--|---|
| Perspective | Healthcare system | Healthcare system | Healthcare system |
| Comparator | PE | PE | Various pharmacological treatments (anticholinesterases, immunomodulation), surgery or PE |
| Type of economic evaluation | Cost-utility analysis. Cost-consequences analysis | Cost-analysis | Individual non-comparative cost-analyses. Exploratory cost-utility analysis IVIg vs PE. |
| Sources of evidence | Gajdos 1997 is the basis of the clinical outcomes (single RCT detailed in <i>Section B</i>). Additional references for utility values and to inform resource requirements (see C.4, D.4) | Alipour-Faz et al. 2017 is the basis of the clinical outcomes (single RCT identified in Systematic Review in <i>Section B</i>). | Various sources (no RCTs for most comparators in Systematic Review, <i>Section B</i>). Sources detailed in D.4 |
| Time horizon | Base case: 3 months (Exploratory analysis including QALY loss due to fatal AE: 10 years) | 4 weeks | 1 year to 10 years |
| Outcomes | \$ per QALY, \$ per adverse event avoided | Cost difference | Costs (including discounted costs) |
| Methods used to generate results | Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data: cohort expected value analysis. | Trial-based analysis, with stepped analysis incorporating NBA IVIg usage data | Expected value analysis |
| Discount rate | NA (5% pa to costs and outcomes in exploratory analysis) | NA | 5% pa to costs and outcomes |
| Software packages used | Excel | Excel | Excel |

IVIg = intravenous immunoglobulin; MG = myasthenia gravis; NA = not applicable; NBA = National Blood Authority; PE = plasma exchange; QALY = quality adjusted life year; RCT = randomised controlled trial
Source: Contracted Assessment, Table 1

The overall costs and incremental costs for IVIg and PE are presented below.

The analysis for Indication 1 found that the cost per additional adverse event avoided was \$53,324. Where the adverse event outcomes are transformed into utility decrements; the total difference in utility is small; thus, where only the direct trial evidence is used to inform the economic analysis, the ICER is high, at approximately \$7 million/QALY.

The report presents modelling incorporating estimates of mortality and morbidity associated with sepsis based on external data, but the accuracy and applicability of this data is uncertain. The ICER and cost-effectiveness of IVIg is heavily dependent on the assumption that PE is associated with sepsis, and this in turn has mortality and/or long-term morbidity implications. Accepting the estimates of long-term morbidity and mortality associated with rare but serious PE adverse events drastically reduces the ICER to approximately \$46 thousand/QALY.

Table 11 Indication 1: Selected results from a stepped cost consequences and cost utility analysis

| | IVIg | PE | Increment |
|--|----------|-----------|--------------------|
| Step 4: RCT evidence base adapted to Australian resource use patterns | | | |
| Total Costs | \$58,895 | \$50,998 | \$7,898 |
| Health outcome (safety) consequences | | | |
| Patients with adverse events | 2.2% | 19.5% | -17.3% |
| Patients with clinically significant adverse events | 0% | 4.9% | -4.9% |
| QALY decrement due to AEs | | -0.001100 | 0.001100 |
| ICER (\$/QALY) | | | \$7,177,933 |
| Step 7: Modelling sepsis morbidity/mortality over 15 years | | | |
| Total Costs | \$58,895 | \$52,388 | \$6,558 |
| QALY decrement due to AEs | | -0.143261 | 0.143261 |
| ICER (\$/QALY) | | | \$45,776 |

AE = adverse event; IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange; QALY = quality adjusted life years; RCT = randomised controlled trial.

Source: Contracted Assessment, Table 2

The overall costs and incremental costs for IVIg and PE in the Indication 2 analysis, using the base case assumptions, are shown below. The cost analysis suggests PE may be marginally less expensive than IVIg for this group of patients; however, the difference is small in the context of the surgery cost.

Table 12 Indication 2: Cost-minimisation analysis

| Resources (disaggregated) | IVIg | PE | Incremental cost |
|--|-----------------|-----------------|------------------|
| | Total Cost | Total Cost | |
| IVIg product (156g) | \$9,424 | \$0 | \$9,424 |
| PE replacement fluid (Albumin 4%) | \$0 | \$685 | -\$685 |
| All outpatient Tx administration costs (pre-admission) | \$922 | \$7,231 | -\$6,309 |
| Thymectomy Operating Theatre | \$9,393 | \$11,317 | -\$1,924 |
| Other hospitalisation (for surgery) costs | \$27,518 | \$27,518 | \$0 |
| Total | \$47,257 | \$46,751 | \$506 |

IVIg = intravenous immunoglobulin; FFP = fresh frozen plasma; PE = plasma exchange

Source: Contracted Assessment, Table 3

The cost analysis for IVIg and PE in Indication 3, using the base case assumptions, are shown below.

Table 13 Indication 3: Cost analysis over varying time horizons, discounted at 5% pa

| | Total discounted costs over varying time horizons | | |
|--------------------------------------|---|------------|------------|
| | 1 year | 5 years | 10 years |
| IVIg | | | |
| NBA data derived average annual dose | \$34,516 | \$156,164 | \$277,001 |
| PE | | | |
| low intensity (every 4 weeks) | \$33,362 | \$120,554 | \$207,165 |
| high intensity (every 1 week) | \$100,219 | \$442,675 | \$782,848 |
| Cost Difference IVIg vs PE | | | |
| IVIg base case – low intensity PE | \$1,154 | \$35,610 | \$69,836 |
| IVIg base case – high intensity PE | -\$65,703 | -\$286,511 | -\$505,847 |

IVIg = intravenous immunoglobulin; PE = plasma exchange; NBA = National Blood Authority Source: Contracted Assessment, Table 4

Exploratory analysis of ICERs allowing for a sepsis cost and QALY decrement yielded ICERs ranging between ‘dominant’ (in all cases where the comparison is vs high intensity PE or low dose IVIg is compared to low dose PE), through to \$18 million per QALY. This demonstrates the high sensitivity to relative treatment costs given outcome differences are minimal, and the overall uncertainty in the comparison.

13. Financial/budgetary impacts

A market-based approach was used to estimate the financial implications of Ig in MG, based on current utilisation of Ig products in Australian patients with MG. The base case financial estimates assume a constant cost per gram of Ig of \$60.41 over the projected period (2020-2024).

The financial implications associated with funding Ig for MG are summarised in Table 14.

Table 14 Net financial implications to government associated with Ig for MG

| | 2019-20 | 2020-21 | 2021-22 | 2022-23 | 2023-24 |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|
| Total cost of Ig | \$36,181,120 | \$39,060,321 | \$41,939,401 | \$44,818,602 | \$47,697,742 |
| Cost of Ig to the Commonwealth | \$22,794,105 | \$24,608,002 | \$26,421,823 | \$28,235,719 | \$30,049,578 |
| Cost of Ig to the States | \$13,387,014 | \$14,452,319 | \$15,517,578 | \$16,582,883 | \$17,648,165 |
| Additional cost to states (administration) | \$5,338,380 | \$5,756,046 | \$6,179,705 | \$6,598,293 | \$7,021,952 |
| Total cost offsets due to a reduction in PE | \$781,695 | \$836,982 | \$897,993 | \$961,196 | \$1,024,399 |
| Offsets to the Commonwealth | \$323,921 | \$349,642 | \$374,413 | \$400,565 | \$426,717 |
| Offsets to the States | \$457,774 | \$487,341 | \$523,581 | \$560,632 | \$597,683 |
| Net cost | \$40,737,805 | \$43,979,384 | \$47,221,113 | \$50,455,699 | \$53,695,295 |
| Net cost to the Commonwealth | \$22,470,184 | \$24,258,360 | \$26,047,410 | \$27,835,154 | \$29,622,861 |
| Net cost to States | \$18,267,621 | \$19,721,024 | \$21,173,703 | \$22,620,544 | \$24,072,434 |

Ig = immunoglobulin; PE = plasma exchange
Source: Contracted Assessment. Table 97

These estimates do not include likely cost offsets associated with reduced comparator therapy use in Indication 3 patients, therefore these costs are likely to overestimate net costs.

14. Key issues from ESC for MSAC

Table 15 Summary of key issues from ESC to MSAC

| ESC key issue | ESC advice to MSAC |
|---|---|
| <p>More information is needed on the type of data collected by BloodSTAR to determine whether patients qualify for Ig therapy under the indications for Myasthenia Gravis (MG).</p> | <p>To note that indication 3 represents the largest proportion of Ig use in the MG population (estimated 90% of grams used) and this population is much more heterogeneous than the other two indications.</p> <p>ESC considered that although the V3 Criteria is quite specific for this indication, assessment of eligibility relies heavily on clinical judgement. More information is needed on the type of data collected to determine whether patients qualify for Ig treatment. In particular:</p> <ul style="list-style-type: none"> • information collected when patients are reviewed leading to a decision to commence, continue or repeat Ig administration • other therapies failed/contraindicated, and the order or administration • the type/frequency of adverse events in this population. <p>ESC advised that utilisation data could be useful to inform compliance with the Criteria (what evidence is collected/provided).</p> <p>ESC advised consideration of optimal methods to collect data on QoL changes associated with ongoing Ig use.</p> |
| <p>More information is needed on the actual use of Ig in this population. This is most important for Indication 3, as there is little understanding of how many patients remain on treatment without a break.</p> | <p>ESC noted that the DCAR estimated incremental cost-effectiveness ratio (ICER) is indicative only. If intravenous Ig (IVIg) is considered effective, the costs are variable and depend on number of patients receiving Ig, duration of Ig use, and remission rates/treatment breaks.</p> <p>ESC considered that current collection of data through BloodSTAR should continue, and include information on the amount of Ig used per patient, and on patterns of use, which would be important.</p> <p>In particular, more information is required to inform if:</p> <ul style="list-style-type: none"> • clinical governance and provisions are sufficient • current guidelines are appropriate (e.g. dosing based on actual or ideal body weight). |
| <p>Access to plasma exchange (PE) (the main comparator) is inequitable and not widely available outside major centres.</p> | <p>ESC noted that equity of access to PE is an issue due to the delivery of this service in tertiary metropolitan centres. Limited access to PE means that restricting access to IVIg for patients with MG may cause relative harm to patients who do not have access to PE.</p> |

| ESC key issue | ESC advice to MSAC |
|--|--|
| | Data provided by a medical device company suggest that an additional 15,000 patients per year could be treated within the current PE capacity of Australian hospitals. However, there are competing needs of hospital bed capacity and staffing which impact the ability to increase PE delivery further. |
| Given the lack of available evidence on the comparative safety and effectiveness of IVIg to other treatments, estimates on cost-effectiveness of IVIg were uncertain across the three indications. | <p>ESC considered that access to Ig should be maintained for Indications 1 and 2, given the small populations and high clinical need.</p> <p>ESC advised for Indication 3 there was insufficient evidence to construct a reliable CUA, despite Indication 3 being responsible for the majority of Ig used to treat MG. ICERs were highly sensitive to the adverse event rates associated with PE and the frequency/dose of Ig and PE treatments.</p> |

ESC discussion

Application 1566 requests MSAC advice on the supply of immunoglobulin (Ig) therapy under the national blood arrangements for the treatment of Myasthenia Gravis (MG). In line with the PICO confirmation, the DCAR reviews the evidence on safety and effectiveness of intravenous Ig (IVIg) for MG to ensure Ig use under the national blood arrangements is based on strong evidence of clinical and cost-effectiveness.

MG is an autoimmune disease characterised in the majority of patients (85%) by antibodies to acetylcholine receptors of the neuromuscular junction. Patients experience muscle weakness, which can include ptosis, double vision, proximal and respiratory muscle weakness, and difficulty swallowing. The natural history of MG is characterised by exacerbations and remissions; usually the remissions are temporary with an average duration of five years, although occasionally permanent remission can occur. IVIg is used as an immunomodulation therapy in patients with MG, although the exact mechanism of action is unknown.

The clinical criteria for subsidised access to IVIg for MG is set out under version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*⁹ (the Criteria). The three current indications under which patients with MG may be eligible for IVIg therapy according to Version 3 of the Criteria are:

- Indication 1 – MG crisis as an alternative to plasma exchange (PE).
- Indication 2 – MG prior to surgery and/or thymectomy in patients with advanced disease, bulbar symptoms or respiratory involvement, as an alternative treatment to plasma exchange (PE).
- Indication 3 – As a maintenance therapy for moderate to severe MG where other treatments have been ineffective or caused intolerable side effects.

ESC considered that the two clinical algorithms for Indications 1 (crisis) and 2 (pre-surgery) are clearly defined; these patients are usually very unwell and IVIg is used as a short term therapy and alternative to PE in order to stabilise patients. On the other hand, patients in Indication 3 (maintenance) are a much more heterogeneous group. In order to qualify for initial treatment with IVIg, patients must have moderate to severe MG, and at least two other treatments must have been ineffective, contraindicated, unavailable, or caused intolerable

⁹ National Blood Authority, 2018, [Criteria for the clinical use of immunoglobulin in Australia](#) (version 3).

side effects. Under this indication, IVIg is used as a stop-gap when switching therapies, or when patients are unable to use other therapies. Review by a neurologist is required within the first four months, and then annually thereafter, and documentation of clinical effectiveness is necessary for continuation of IVIg therapy. For patients to be eligible for continuation treatment under Indication 3, a trial of weaning/cessation must be planned for patients who are clinically stable to identify those who are in remission, or a reason provided as to why a trial is not planned.

The DCAR reported that the proportion of patients across the three indications were approximately 17%, 2.8% and 80.1%, respectively, based on percentages extracted from NBA BloodSTAR for the period 2017-18. The proportion based on amount of IVIg used in each indication was estimated to be 9%, 1% and 90%, respectively as advised by the Applicant. ESC noted that the absolute patient numbers in this population are small, NBA data for 2017-18 indicates there were a total of 1,174 patients across all three MG indications.

ESC noted that Indication 3, which represents 90% of IVIg used amongst patients with MG, has the most patient variability and that additional data are most important to inform cost-effectiveness in this indication. ESC acknowledged that the requirements in the Criteria to qualify for treatment with IVIg, both initial and continuing, are very detailed; however, assessment of patient eligibility relies heavily on clinical judgement. ESC queried what data are collected by BloodSTAR in determining whether patients qualify for initial and continuing therapy, as gauging prescriber compliance to the V3 Criteria is an important component of clinical governance for high cost therapies and relevant to a review of cost-effectiveness.

Overall, ESC agreed with the DCAR results for the comparative safety and effectiveness of IVIg across the three indications. For Indication 1, ESC agreed with the conclusion of superior safety and non-inferior effectiveness of IVIg compared to PE. Patients treated with PE were found to experience more AEs compared to patients treated with IVIg. However, the quality of evidence was open to selection bias as in one large cohort study the PE group was likely more seriously ill than the IVIg group and this influenced their treatment selection.

ESC noted that the economic model used in Indication 1, a cost utility analysis, produces a high incremental cost-effectiveness ratio (ICER) of \$7 million/QALY when only direct evidence of AEs is used to inform the model. When estimates of mortality and morbidity associated with sepsis are incorporated, this reduces the ICER to \$45,778/QALY, although the accuracy and applicability of this data is uncertain. The ICERs for Indication 1 in the DCAR assume an estimated dose of 230g per patient, which was based on an estimated amount of Ig used per indication from NBA summary level data collected under Criteria V2. When calculated using a dose of 139g per patient, (estimated in Addendum 1 based on NBA data collected for patients initiating Ig therapy under the V3 Criteria) the ICER is lower, at \$9,276/QALY. ESC considered that the uncertainty associated with sepsis related AEs in patients treated with PE, together with the model's sensitivity to this, makes the estimated ICER very uncertain. ESC noted that more reliable data were required to better estimate the ICER for indication 1.

ESC noted that estimated ICER for Indication 1 are indicative only, and that costs are variable and dependent on future projections for MG cases, duration of use, and remission rates. ESC considered that collecting EQ-5D data would be more reliable than basing the economic model on AE rates and extrapolating utilities from the literature (especially from other conditions).

ESC noted the lack of available evidence for Indication 2, and that no firm conclusions could be made regarding the safety and effectiveness of IVIg versus PE. Studies had small patient numbers, were possibly confounded by selection bias, and did not have adequate power to make any reliable conclusions.

For Indication 2, a cost-minimisation analysis was performed which found PE to be marginally less expensive than IVIg for this group of patients. The cost difference for IVIg versus PE was \$506 based on an assumed dose of 156g in the DCAR, and considered small in the context of surgery cost. The cost difference increased to \$1,956 when a dose of 180g (from Addendum 1 to the DCAR) was used.

Comparators according to the PICO confirmation for Indication 3 included corticosteroids, anticholinesterases, immunosuppressants, immunomodulators, PE and thymectomy. No conclusions could be made regarding the comparative safety and effectiveness of IVIg versus any of these treatments, except PE. Three randomised controlled trials (RCTs) used the quantitative myasthenia gravis score (QMGS) as an outcome measure and showed similar improvements between PE and IVIg, and no difference in quality of life (QoL) scores. ESC considered the conclusion of non-inferior safety and effectiveness of IVIg compared to PE in this population to be reasonable based on the available evidence.

Studies comparing the comparative safety and effectiveness of IVIg to placebo were of low quality and found either no difference, or non-significant differences between the two groups.

For Indication 3, non-comparative cost analyses were presented over varying time horizons (one, five, and 10 years). ESC noted that the age of patients at the start of the time horizon is 66 years, which is based on NBA data on the average patient age. This is much older than the reported age of MG onset as described in the DCAR for women and men, being 28 and 42 years, respectively. ESC considered it is possible that younger patients would try other therapies first, before initiating treatment with IVIg.

ESC noted some translation issues, such as the applicability of data from other studies, and issues with extrapolation including the appropriate time horizon for Indication 3.

An exploratory cost-utility analysis comparing low and high dose IVIg with low and high dose PE yielded ICERs ranging between 'dominant', through to \$18 million/QALY, however ESC considered these to be based on very uncertain evidence and not conclusive. Overall, ESC considered that the evidence for comparative effectiveness was low and the costs were uncertain and dependent on the AEs included.

In addition, further data on patterns of IVIg use in chronic MG treatment, such as treatment discontinuation, trials off therapy, tapering of Ig dose and average Ig doses used for maintenance treatment could be used to inform the model.

Using a market-based approach, the DCAR estimated a total cost to government for Ig treatment of MG of approximately \$236 million over the 5 year projected period to 2024. ESC considered the net costs to be substantial, assuming the inputs are correct. ESC noted that these projections include all three MG indications, and considered that looking at the budget impact for each indication may allow prioritisation. However, new data would be needed to inform this.

ESC considered comments from stakeholders including revisions to the algorithm for Indication 3 that was submitted by one sponsor, and sponsor comments on the appropriate price to be used in the model. However, ESC did not consider these suggestions would make

a meaningful difference to the overall economic and financial estimates, and noted that a range of prices for Ig were modelled in sensitivity analyses.

Overall, ESC considered the available clinical evidence to be limited and that more data on Ig use and disease remission would be needed to inform any further economic evaluation. A future model to examine cost-effectiveness of SCIG would need to consider costs associated with patient/carer training and education programs, but reduced hospital care costs.

Current collection of BloodSTAR data should continue, but there could be a greater focus on Indication 3, which represents the highest proportion of Ig use. ESC considered that more data was required on utilisation (including use of ideal or actual body weight to determine Ig dose), frequency of AEs, and how reviews for treatment continuation are performed. ESC queried the level of data that is collected on eligibility for access to initial and continuing treatment for MG under Indication 3 and noted that the text fields in BloodSTAR were non-compulsory. ESC considered that it was important to ensure an appropriate balance between the administrative burden associated with data collection and ensuring appropriate clinical governance.

ESC considered that for patients in Indications 1 and 2, any treatment shown to be non-inferior should be made available. ESC noted that limited access to PE is a concern, and therefore restricting access to IVIg for MG patients may cause harm to patients and raise issues of inequity.

ESC also noted the DCAR's consideration of the use of rituximab for patients with MG and considered that it may ease the use of IVIg, although there are currently no comparative studies and Ig is not PBS subsidised for MG. ESC noted that the V3 Criteria did not require clinicians to have considered thymectomy, but assumed that this would be part of standard practice.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The National Blood Authority appreciates MSAC's recommendations and agrees that data should continue to be collected on the patterns of use of Ig therapy, particularly for maintenance therapy. The ability of BloodSTAR, and/or other sources, to capture long-term health benefits in this group will be considered and prescriber compliance to the V3 Criteria will continue to be monitored through the Ig Governance Program. This review has occurred immediately following the transition from Version 2 to Version 3 of the Criteria for Clinical Use of Immunoglobulin in Australia. An important addition to Version 3 of the Criteria was to provide greater guidance for prescribers as to when a patient may be ready to trial off Ig therapy. The effect of changes to the Criteria are only now being seen in the data, with a material and encouraging reduction in the overall rate of growth of Ig use now becoming apparently visible. The Criteria will continue to be reviewed on both a reactive and proactive basis, based on available evidence and clinical expert advice, to ensure the supply of Ig continues for those patients who benefit from it the most. Furthermore, the NBA plans to continue to undertake and support research into the effectiveness and utilisation of Ig, of which these recommendations will assist to prioritise. The NBA negotiates prices of Ig through tendering processes and will continue to strive to achieve the best prices for governments within existing limitations.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)