



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application 1564 – Review of Immunoglobulin (Ig) for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Applicant: National Blood Authority (NBA)

Date of MSAC consideration: MSAC 82nd Meeting, 29-30 July 2021

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 replacement human gamma immunoglobulin (IgG) therapy under the National Blood Arrangements for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). The application (referral) was received by the Department of Health from the National Blood Authority (NBA).

Previous consideration of this application

The first Application 1564 for CIDP was considered by ESC in February 2020, and by MSAC in April 2020. MSAC deferred providing advice and requested:

- an update of the systematic literature review on the safety and effectiveness of Ig for CIDP (including IVIg and SCIG), especially with relation to the safety of comparators
- revised economic modelling and evaluation of Ig for the management of patients with CIDP, including the development of three distinct models using three different comparators, and addressing specific issues raised by MSAC.

This reconsideration of the Application 1564 examines recent evidence on the safety and effectiveness of Ig therapy and comparator treatments for the management of CIDP. It also provides new economic modelling for the management of CIDP.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the comparative safety, clinical effectiveness, and cost-effectiveness, MSAC advised that funding of Ig therapy for the treatment of CIDP should continue on the basis that it appears safe and is already an accepted first-line treatment in Australia. However, MSAC was concerned about the size of the

population receiving Ig therapy for CIDP compared to published estimates of disease incidence and prevalence, and advised that Ig therapy did not appear acceptably cost-effective.

The total Ig costs, (including delivery) were estimated to be \$128.2 million in 2021-22, increasing to \$152.6 million in 2025-26 and were sensitive to the price of Ig and amount of Ig used. MSAC noted that the cost and demand of Ig is likely to increase and was concerned about the projected increase in Ig use in the face of constrained supply. MSAC recommended that the diagnostic requirements and current thresholds to access Ig therapy for CIDP under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria) be reviewed to ensure that treatment is directed to patients with CIDP who are most likely to derive benefit. MSAC also considered data collection and reporting could be optimised through BloodSTAR to help inform an optimum dose regimen in CIDP, and a separate review of the cost-effectiveness of subcutaneous Ig compared with intravenous Ig should also be explored.

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 chronic inflammatory demyelinating polyneuropathy (CIDP). The NBA is the statutory agency within the Australian Government Health portfolio that manages and coordinates arrangements for the supply of blood and blood products and services on behalf of the Australian Government and state and territory governments. This referral to review the use of Ig in CIDP is included as part of the Ig Reviews, which aim to ensure that government-funded Ig use within Australia is based on evidence of clinical safety, clinical effectiveness, and cost-effectiveness.

CIDP is caused by the body's immune system inappropriately reacting against and damaging myelin that covers the nerves. Symptoms include tingling, numbness or altered feeling which often begins in the feet and hands; weakness of the arms and legs; fatigue; and aching pain in the muscles.

MSAC noted that there is limited high quality evidence comparing Ig to other therapies for CIDP such as corticosteroids, plasma exchange and other immunosuppressants, but noted that Ig appears to be safe and is an accepted first-line treatment for CIDP in Australia. Therefore, MSAC advised that Ig should continue to be available to treat people with CIDP, but further work is needed to manage demand for Ig.

MSAC acknowledged that Ig is a very expensive therapy and the review predicted that over the next five years, the cost to government of supplying Ig was estimated to increase from approximately \$128.2 million in 2021-22, to \$152.6 million in 2025-26. MSAC was concerned that nearly four times more patients in Australia (according to NBA data) received Ig for CIDP than expected, and that the diagnostic and eligibility requirements to access Ig therapy may not be sufficient to ensure that only those people with a confirmed CIDP diagnosis receive Ig. MSAC advised that given the increasing cost and demand for Ig product, it is critical that these eligibility requirements are reviewed to ensure that Ig is being used to treat only those patients who benefit clinically.

Consumer summary

MSAC also recommended areas for future research and for data collection and reporting through BloodSTAR* to be improved, which may inform any future evaluations of the cost effectiveness of treating CIDP with Ig.

* BloodSTAR (<https://www.blood.gov.au/bloodstar>) is the online system used in Australia to manage access to the supply of government funded immunoglobulin products. The system manages the authorisation request and review process for the treatment of conditions identified in the Criteria for the clinical use of immunoglobulin in Australia (<https://www.criteria.blood.gov.au/>).

MSAC's advice to the National Blood Authority

MSAC supported the continued funding of immunoglobulin (Ig) for CIDP but advised that further work is needed to manage demand for Ig. MSAC remained concerned about the size of the population receiving Ig therapy for CIDP compared to published estimates, and the projected increase in usage in the face of constrained supply. MSAC also advised that, from the revised cost-effectiveness analysis presented, Ig in this indication does not appear acceptably cost-effective.

MSAC advised that the diagnosis requirements for CIDP in the eligibility criteria be reviewed to ensure that access to Ig is appropriately maintained for only those patients with a CIDP diagnosis. MSAC also recommended that the BloodSTAR data system be enhanced to help inform research to establish an optimum dose regimen in CIDP, and a separate review of the cost-effectiveness of subcutaneous Ig compared with intravenous Ig should also be explored.

MSAC considered that there is an urgent need and ethical responsibility to ensure this limited resource is appropriately managed and prioritised to patients who will derive the most benefit and for whom it is most cost-effective.

MSAC requested a stakeholder meeting be held to discuss criteria relating to CIDP diagnosis, thresholds for initial or continued access to Ig therapy and optimal dose regimens. The outcomes of the stakeholder meeting are intended to clarify and enhance MSAC's advice on these issues. The stakeholder meeting outcome statement will be considered by MSAC and further advice provided to the Jurisdictional Blood Committee (JBC) through the National Blood Authority (NBA) as applicant.

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

In Australia, Ig for the treatment of CIDP is funded for patients who are eligible under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria).

MSAC recalled that it had previously considered and deferred this referral at its February 2020 meeting. At this meeting, MSAC requested the Department Contracted Assessment Report (DCAR) be revised before providing its advice on the clinical effectiveness and cost effectiveness of Ig for the treatment of CIDP. MSAC specifically requested that the revised economic evaluation include comparisons of Ig versus corticosteroids; Ig versus plasma exchange (PE); and Ig versus placebo (in a corticosteroid resistant population). MSAC also

requested an update of the systematic literature review on the safety and effectiveness of Ig for CIDP (including IVIg and SCIG), especially in relation to the safety of its comparators.

MSAC considered the revised DCAR largely addressed the specific requests made at its deferral in April 2020, although the updated systemic literature review of comparative safety and clinical effectiveness of Ig for treatment of CIDP found no additional RCT evidence comparing Ig with corticosteroids, PE, immunosuppressants, or combination therapies for CIDP. MSAC considered the evidence presented and noted that the clinical claim in the revised DCAR was unchanged from the conclusions at its previous consideration:

- Ig has non-inferior effectiveness and superior safety compared to corticosteroids.
- There was insufficient evidence to comment on the relative safety and effectiveness of Ig compared to PE, immunosuppressant or combination therapy.
- Ig has superior effectiveness and inferior safety to no treatment, noting that the treatment is generally safe and well-tolerated.

MSAC noted that consistent with its previous request, the economic evaluation structure presented in the revised DCAR now includes three distinct models using 3 different comparators and:

- Included health states where patients cease/stop Ig or the comparator due to remission or treatment failure;
- A base-case starting with trial-based inputs for efficacy, safety, cessation rates and doses over trial time horizon; and
- Additional inputs on dose and time on treatment reflective of clinical practice in Australia.

MSAC noted that for the comparison of Ig versus corticosteroids, the base-case incremental cost-effectiveness ratio (ICER) was \$116,088, driven mainly by the cost of Ig. MSAC agreed with ESC that the estimated ICER is high and uncertain, although lower than that estimated in the original DCAR (\$197,472) due to the incorporation of severe/long term adverse events (AEs) associated with corticosteroids. MSAC noted comments from ESC and stakeholders that the severe AE assumptions associated with long-term corticosteroid use was based on a study of patients with giant cell arteritis rather than CIDP patients, but MSAC considered that AEs arising from long-term corticosteroid use are not likely to vary by underlying disease and so the use of these studies was reasonable.

MSAC noted that for the secondary comparison of Ig versus PE, the base-case ICER was \$128,614. MSAC considered this ICER high and highly uncertain, noting there was insufficient clinical evidence regarding the relative effectiveness of these treatments.

MSAC also noted the base-case ICER of \$92,983 estimated for second-line use Ig in the corticosteroid resistant population versus placebo.

MSAC advised that while the revised economic model addresses some uncertainties and estimated lower ICERs than that presented in the original DCAR, the estimated base-case ICERs in all comparisons remain higher than what MSAC would consider cost-effective when recommending a new service or treatment for government funding.

Regarding financial and budgetary impacts, MSAC noted that total Ig costs (including delivery) were estimated to be \$128.2 million in 2021-22, increasing to \$152.6 million in 2025-26. These

estimates are sensitive to the cost of Ig and amount of Ig used. MSAC considered these estimated costs to Government to be substantial but were cognisant that Ig is already an accepted first-line treatment for CIDP in Australia. The economic model and financial estimates used a base case cost of Ig of \$60.41/g for consistency across all of the Reviews of Immunoglobulin (the Reviews). MSAC considered it appropriate to use the same base case cost per gram of Ig for consistency and comparability across each of the Reviews, but noted that the cost of imported Ig has risen since the commencement of these Reviews, and that cost and demand of Ig is likely to increase in the future due to current global shortages of Ig product. Further, MSAC considered that there is an urgent need and ethical responsibility to ensure this limited resource is appropriately managed and prioritised to patients who will derive the most benefit and for whom it is most cost-effective.

Therefore, MSAC recommended that access to Ig for the treatment of CIDP should continue, but with additional measures to manage the demand and appropriate use of Ig.

MSAC recalled concerns from its first consideration of this submission regarding the overdiagnosis of CIDP, that even with the inclusion of probable and possible cases of CIDP in the estimated prevalence rate of 3 per 100,000 (range: 1/100,000 to 7/100,000) (Broers 2019)¹, nearly four times more patients in Australia (NBA data) received Ig for CIDP than expected. MSAC acknowledged that there is recent literature to suggest that misdiagnosis of CIDP is common. A recent Dutch study² noted that amongst other reasons, common diagnostic pitfalls included misinterpretation of nerve conduction studies, poor adherence to electrodiagnostic criteria, and failure to exclude other causes of polyneuropathy.

The eligibility criteria allowing access to Ig for treatment of CIDP are described in *version 3 of the Criteria for the clinical use of immunoglobulin in Australia* (Criteria V3). MSAC considered current thresholds to access Ig therapy under the Criteria for the clinical use of immunoglobulin in Australia (version 3) (the Criteria) for this indication are insufficiently defined. MSAC considered issues relating to the Criteria V3 regarding initiation, continuation and cessation criteria may be a contributing factor in the high number of patients currently treated with Ig for CIDP in Australia.

For patients with CIDP, initial access to Ig is permitted in patients for whom walking is compromised or there is significant disability, and is defined in the Criteria V3 as:

- in adults or children over 10 years, based on the Overall Neuropathy Limitations Scale (ONLS) of at least two points and the Medical Research Council (MRC) sum score,
- in children aged less than 10 years measured by the six-minute walk test (6MWT) and/or Modified Rankin Score (MRS) of at least two points.

¹ Broers, MC, Bunschoten, C, Nieboer, D, Lingsma, HF & Jacobs, BC 2019, 'Incidence and Prevalence of Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Systematic Review and Meta-Analysis', *Neuroepidemiology*, vol.52, pp. 161-72.

² Broers MC, Bunschoten C, Drenthen J, et al. Misdiagnosis and diagnostic pitfalls of chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol*. 2021;28:2065–2073. <https://doi.org/10.1111/ene.14796>

MSAC recalled its previous advice that the Criteria V3 do not include a threshold (for initiation or continued access) for the MRC sum score, or the 6MWT, in the respective populations, and that this imprecision may compound poor sensitivity and specificity of diagnostic criteria, and contribute to the higher than expected use of Ig in this condition. With respect to diagnostic tests, MSAC considered it is unclear what tests or results are collected/recorded in BloodSTAR to justify a diagnosis of CIDP. MSAC considered the accountability and transparency of the BloodSTAR system should be clarified and improved to be more consistent with requirements for access to other government funded treatments with high costs per patient and high total opportunity cost to the health system, to ensure initial and continued treatment is limited to specific patient groups and the use of higher than usual doses are managed appropriately to optimise cost-effective use.

Therefore, MSAC recommended that a stakeholder meeting be held to discuss issues relating to CIDP diagnosis, thresholds for initial or continued access to Ig therapy and dose regimen to clarify and enhance its advice to the Jurisdictional Blood Committee (JBC) through the National Blood Authority (NBA) as applicant.

In addition to its recommendation to hold a stakeholder meeting, MSAC identified areas of potential research or enhancements to the BloodSTAR system which could be used to inform future HTA analyses of Ig:

SCIg versus IVIg comparison

MSAC advised that an economic analysis considering dose ratios for IVIg to SCIg and resource costs in Australia is an important area for potential further research. MSAC noted that while SCIg may be less expensive than IVIg as maintenance therapy given the relative infusion costs, the mean dose equivalence of SCIg to IVIg is not well defined and varies from a ratio of 1.024 to 1.37 based on US and European studies. The DCAR noted that based on BloodSTAR data, the impact of dosing route (IV or SC) on total Ig use is uncertain but it appears more likely that SC administration would be associated with increased Ig use rather than decreased use.

Preference study

MSAC noted that Ig use is highly dependent on patient and/or clinician preference and an improved understanding of these preferences and behavioural responses may inform possible criteria changes that would better respond to what is required. MSAC advised that a preference study (patients and clinicians) could be conducted with assistance from the Behavioural Insights and Evaluation area of the Department.

Enhancement of the BloodSTAR data system

MSAC advised that optimisation of data collection and reporting through BloodSTAR could be used to collect patient characteristics in order to allow analysis to assist identification of subgroups where Ig may be more cost effective, capture outcome measures and explore dosing regimens. Data linkage of BloodSTAR to a relevant registry or other health datasets (MBS and PBS) would also increase research options in line with Government initiatives to

maximise the use of integrated datasets and access the value inherent in public data³. MSAC considered that further analysis (if data are available) or enhancement of the BloodSTAR data system to enable future analysis of the association between the magnitude of the clinical scores specified in the Criteria for initial and continuing access (i.e. ONLS/MRC, 6MWT/MRS) and subsequent patient response to Ig. This would be useful and lead to the development of an optimum dose regimen for patients with CIDP (i.e. dose amount and frequency, interval between reviews, use of supplementary doses).

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 best evidence of clinical effectiveness 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 Ig Reviews are supported by a bespoke Reference Group, which oversees and provides advice on evaluation of all Ig HTA review applications. The PICO Confirmations for the Ig Reviews have been considered by the Reference Group instead of the PICO Advisory Subcommittee (PASC).

MSAC have considered and provided advice on five of the six Ig Reviews so far:

- [Application 1565](#) – Review of Ig for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
- [Application 1566](#) – Review of Ig for myasthenia gravis
- [Application 1590](#) – Review of Ig for multifocal motor neuropathy
- [Application 1591](#) – Review of Ig for secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplant
- [Application 1592](#) – Review of Ig for primary immunodeficiency diseases with antibody deficiency

[Application 1564](#) – Review of Ig for CIDP was considered and deferred by MSAC in April 2020, pending this resubmission. The resubmitted/revised Application 1564 is the final report from the pilot Ig Reviews to proceed to ESC.

At its April 2020 meeting MSAC requested that the revised DCAR specifically address the following:

Comparator(s) for new economic analysis

- Main comparison - Ig versus corticosteroids
- Secondary comparison - Ig versus PE

³ <https://www.pmc.gov.au/public-data/data-integration-partnership-australia>

- Tertiary comparison Ig versus Placebo in corticosteroid resistant population (possibly a scenario analysis of the main comparison)

Safety

- Review evidence for safety of corticosteroid use over the modelled lifetime of the disease and the appropriate utility decrements.
- The DCAR reported insufficient evidence to make an assessment of the comparative safety between Ig and PE and this could be problematic for an economic comparison. Also review safety concerns resulting from vascular access for PE.

Efficacy

- For Ig versus corticosteroids, the claim is non-inferiority based on Nobile-Orazio et al (2012b) and Hughes (2002) to be used in the base case but include a sensitivity analysis to model superior efficacy as per Reference Group clinical opinion.
- For Ig versus PE a claim on non-inferiority based on Dyck (1994)
- For Ig versus corticosteroid resistant - a claim of superiority over placebo – based on trial evidence in corticosteroid resistant trial populations.

Structure of the economic model

- Consider health states where patients cease/stop Ig or the comparator due to remission in addition to treatment failure.
- Base case should start with trial-based inputs for efficacy, safety, cessation rates and doses over trial time horizon.
- Add inputs on dose and time on treatment reflective of clinical practice in Australia. This may come from BloodSTAR data and/ or clinician input.

5. Prerequisites to implementation of any funding advice

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). Ig for this indication is already funded by the NBA. The purpose of this application is to consider the clinical effectiveness and cost-effectiveness of these products as currently funded under the Criteria V3.

6. Proposal for public funding

Ig therapy for CIDP is currently funded by the NBA under the national blood supply arrangements, but the cost-effectiveness of this use has not been evaluated in Australia. NBA procurement of Ig is via competitive tendering and negotiation with suppliers.

Version 3 of the Criteria categorises Ig use in this population as a “Condition for which Ig has an established therapeutic role”, with a ‘Level of evidence’ Category 1 (clear evidence of benefit).

Clinical criteria for eligible patients to access subsidised Ig are specified in Version 3 of the Criteria. Applications for Ig are made through the BloodSTAR online portal and assessed

against the Criteria⁴. The Criteria outlines qualifying criteria for Ig therapy for CIDP with the requirement for the diagnosis and the initial review at four months by a neurologist to determine whether the patient has responded. Ongoing annual review to assess the clinical benefit or effectiveness (by a neurologist or general physician). A trial of weaning towards cessation of Ig therapy should be considered each 12 months in patients in remission or on maintenance therapy. 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

At its first consideration of Application 1564 in February 2020, ESC considered all the consultation feedback received relating to the Referral, PICO and original Contracted Assessment. In April-May 2021, public consultation was also undertaken on the updated Contracted Assessment.

All consumer feedback was broadly supportive of Ig use for CIDP. Noted advantages associated with Ig use were high response rates to treatment and generally high tolerability to treatment. Noted disadvantages of Ig use included adverse events associated with treatment, requirement for in-hospital treatment, and access-to-treatment issues arising from increasing demand for Ig. It was noted that access to SCIg may negate the disadvantage of hospital attendance.

8. Proposed intervention's place in clinical management

Description of proposed intervention

This application is for Ig therapy versus the comparators of: corticosteroids (oral or intravenous); plasma exchange; immunosuppressant and/or immunomodulatory drugs and therapies not including Ig or corticosteroids; combination therapy; and no active treatment (no Ig).

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 \(the Criteria\)](#). Immunoglobulin is used as immunomodulation therapy in CIDP. Ig can be administered intravenously (IVIg) or injected subcutaneously into the tissue under the skin (SCIg).

Description of medical conditions(s)

The application includes patients with CIDP who are eligible for Ig treatment in Australia according to the Version 3 Criteria. This includes patients with an established diagnosis of CIDP with significant disability and/or compromised walking.

CIDP is an acquired sensorimotor polyneuropathy characterised by a progressive or relapsing/remitting course developing over at least two months with evidence of demyelination

⁴ National Blood Authority, 2018, [Criteria for the clinical use of immunoglobulin in Australia](#) (version 3).

on electrophysiological or pathological studies and response to immunomodulating therapies. CIDP is caused by the body's immune system inappropriately reacting against and damaging myelin. Symptoms include tingling, numbness or altered feeling which often begins in the feet and hands; weakness of the arms and legs; fatigue; and aching pain in the muscles.

The use of Ig for the management of CIDP is currently funded in Australia by the NBA and it is available as a first-line treatment for patients in whom walking is compromised or there is significant disability. Other current active interventions that are available as first-line treatments include corticosteroids (oral and intravenous), plasma exchange, and immunomodulatory or immunosuppressant drugs (other than corticosteroids).

Figure 1 describes the current management of patients with CIDP, funded by the NBA (for initial access to Ig and continued access to Ig, respectively)⁵.

Figure 2 describes the current management of patients with CIDP where IVIg is not a treatment option⁶ (e.g. due to contraindications or ineligibility according to the Criteria Version 3).

⁵ Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT.

⁶ Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT.

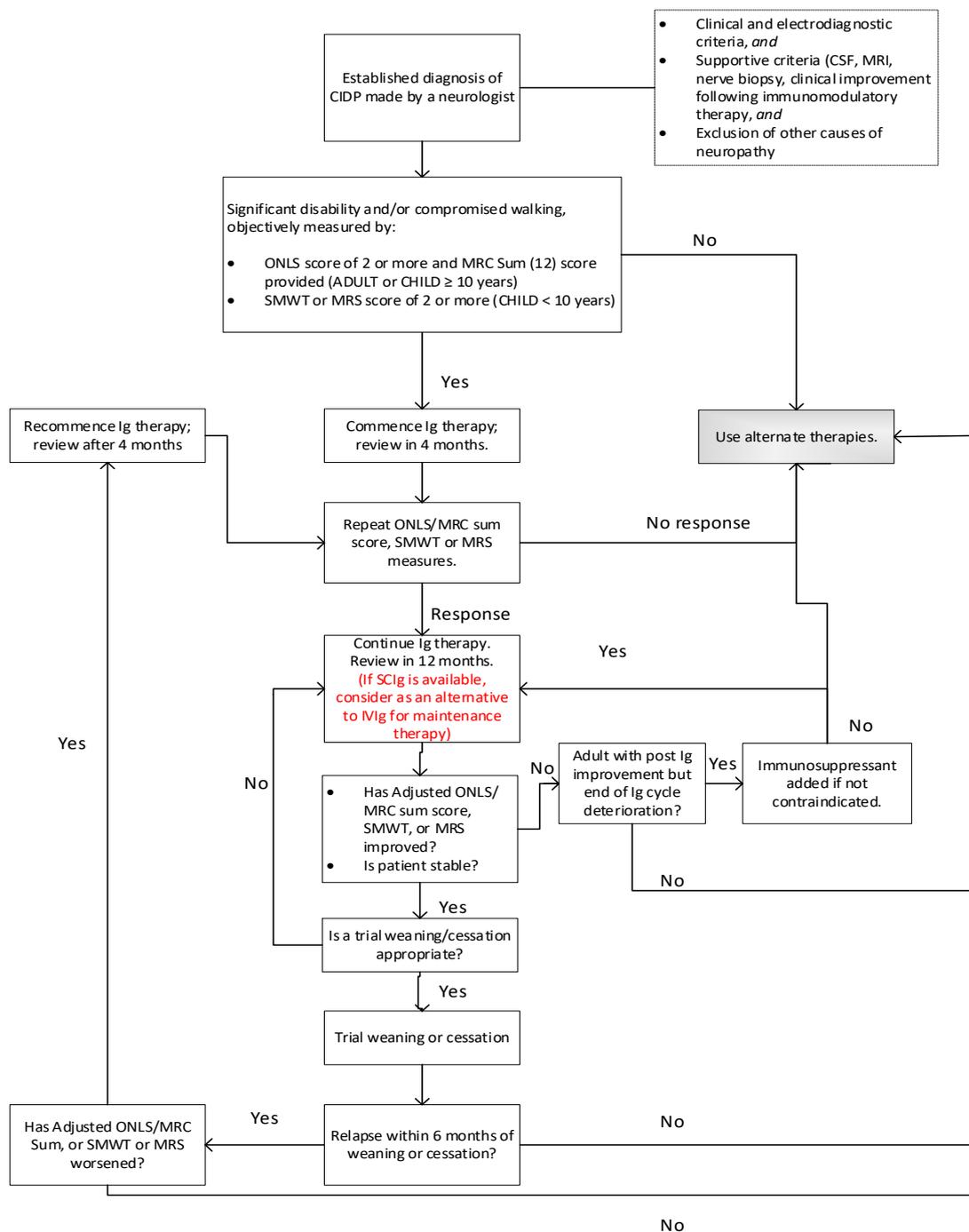


Figure 1 Current management algorithm for CIDP patients eligible for Ig therapy

Source: Contracted Assessment Figure 16 and Ratified PICO.

Abbreviations: ONLS = Overall Neuropathy Limitations Scale, MRC = Medical Research Council, SMWT = Six-minute walking test, MRS = Modified Rankin Scale, Ig = Immunoglobulin, CIDP = Chronic inflammatory demyelinating polyneuropathy, SCIg = subcutaneous immunoglobulin. (12) Hughes, R. A., Bouche, P. et al (2006). 'European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society'. Eur J Neurol, 13 (4), 326-32.

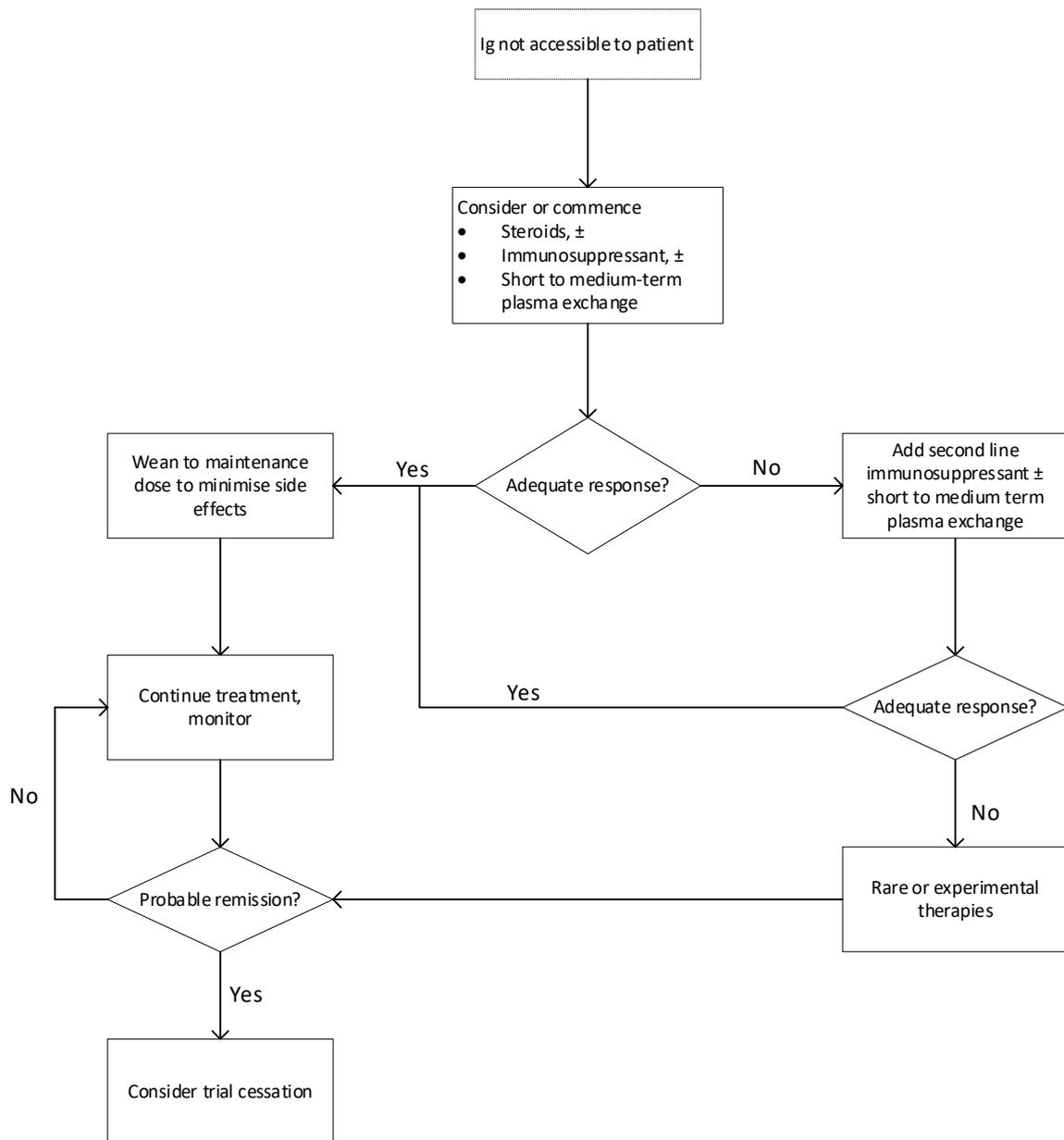


Figure 2 Proposed algorithm for treatment of patients in the absence (or failure) of Ig.

Source: Contracted Assessment Figure 17 and Ratified PICO.

Abbreviations: Ig = Immunoglobulin

Note: this algorithm may also be applicable for any patient not/no longer eligible for Ig under Version 3 of 'the Criteria' (i.e. reach 'use alternate therapies' stage on Figure 1), or for patients in whom Ig is contraindicated

9. Comparator

The comparators to Ig as originally defined in the PICO Confirmation and ratified by the Immunoglobulin Review Reference Group were:

- steroids (oral and intravenous)
- plasma exchange (PE)
- immunosuppressant and/or immunomodulatory drugs and therapies, not including corticosteroids or Ig
- a combination of two or more of the above therapies

- no active treatment, no Ig.

At its April 2020 meeting, MSAC requested the revised DCAR include economic modelling of the following comparisons:

- Main comparison - Ig versus corticosteroids
- Secondary comparison - Ig versus PE
- Tertiary comparison - Ig versus placebo in corticosteroid resistant population

10. Comparative safety

As concluded in the original DCAR, the updated DCAR suggests that relative to the comparator interventions of corticosteroids (oral and IV) and PE, Ig has uncertain safety.

The original 1564 DCAR found the overall rate of serious AEs with any treatment (IVIg, corticosteroids, PE, and immunosuppressant drugs) over the short to intermediate term was low. However, non-inferiority or superiority could not be determined due to the paucity of studies reporting safety outcomes and limitations in trial design.

Evidence from two RCTs (Hartung et al. 2019⁷ PATH study; and, Kuitwaard et al. 2020b⁸ DOSE study) was included to update the review on the safety and effectiveness of Ig for CIDP. Both trials were conducted in patients with CIDP who had been stabilised on IVIg and were assessing Ig as maintenance therapy. The PATH study (assessed as low risk of bias) compared two doses of SCIg with each other and placebo, and found higher treatment related AE rates in patients treated with low or high dose SCIg (30% and 35% of patients, respectively) compared with placebo (18% of patients). The DOSE study (assessed as moderate risk of bias) compared two IVIg dosing regimens in patients on individualised doses and schedules and found the frequency of AEs to be similar between regimens. This study reported no serious AEs.

For the extended assessment of harms, an additional literature search was conducted in a broader population base than CIDP alone. Evidence from nine articles were included in the extended assessment of harms discussed below. AE rates associated with Ig, PE and long-term corticosteroid use were identified, but not directly compared due to the disparate populations from which data were collected and also impacts the applicability of the evidence to the population of interest. Table 1 presents a summary of AEs reported in retrospective cohorts of patients receiving IVIg, PE or corticosteroids⁹.

⁷ Hartung, HP, Mallick, R, Bril, V, Lewis, RA, Sobue, G, Lawo, JP, Mielke, O, Durn, BL, Cornblath, DR, Merkies, ISJ & van Schaik, IN 2019, 'Patient-reported outcomes with subcutaneous immunoglobulin in chronic inflammatory demyelinating polyneuropathy: the PATH study', *European Journal of Neurology*.

⁸ Kuitwaard, K, Brusse, E, Jacobs, BC, Vrancken, AFJE, Eftimov, F, Notermans, NC, van der Kooi, AJ, Fokkink, WJR, Nieboer, D, Lingsma, HF, Merkies, ISJ & van Doorn, PA 2020b, 'Randomized trial of intravenous immunoglobulin maintenance treatment regimens in chronic inflammatory demyelinating polyradiculoneuropathy', *European Journal of Neurology*.

⁹ Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT. Table 25, page 71.

Extended Assessment of harms

Adverse events associated with long-term corticosteroid use

Very few articles in the targeted literature search reported on the long-term safety of corticosteroids in patients with autoimmune neurological diseases, therefore the population was broadened to all autoimmune diseases that are treated with corticosteroids. Evidence was considered from one SR (Rice et al 2017)¹⁰, two large retrospective studies with populations of patients with RA (Huscher et al 2009)¹¹ and giant-cell arteritis (Wilson et al 2017a)¹² and one smaller retrospective study of CIDP patients (van Lieverloo et al. 2018)¹³. All were assessed as moderate risk of bias.

There was considerable variability in the type of AEs reported in the studies, only common AEs were reported (so overall AE rates could not be determined), and AEs were not separated by severity. All AEs relating to corticosteroid use have been previously well characterised over decades of use across indications. The AE with highest incidence for patients taking long-term corticosteroids was serious infection (37.9%), and the AE with highest prevalence was hypertension (> 30%). Frequently reported AEs also included fracture and osteoporosis (prevalence 21% - 30%), diabetes type II (incidence 14.2%) and glaucoma (incidence 10%).

Overall, the rate of AEs associated with long term corticosteroid use was found to be high and dose-related. Several AEs increased linearly in rate with dose including sleep disturbance, ecchymosis and leg oedema. Other AEs demonstrated a threshold effect, including cataracts, weight gain, increased blood pressure and depression.

Severe AEs were reported in only one small study (AE rate of 1.6%, n = 2 patients) and is less certain, although is likely that some of the AEs reported in the other studies may have been severe too. Additionally, as the clinical characteristics of the populations in these studies were diverse, the applicability of these rates of AEs to the population of interest is uncertain.

¹⁰ Rice, JB, White, AG, Scarpati, LM, Wan, G & Nelson, WW 2017, 'Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review', *Clin Ther*, vol. 39, no. 11, Nov, pp. 2216-2229.

¹¹ Huscher, D, Thiele, K, Gromnica-Ihle, E, Hein, G, Demary, W, Dreher, R, Zink, A & Buttgerit, F 2009, 'Dose-related patterns of glucocorticoid-induced side effects', *Ann Rheum Dis*, vol. 68, no. 7, Jul, pp. 1119-1124.

¹² Wilson, JC, Sarsour, K, Collinson, N, Tuckwell, K, Musselman, D, Klearman, M, Napalkov, P, Jick, SS, Stone, JH & Meier, CR 2017a, 'Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis', *Semin Arthritis Rheum*, vol. 46, no. 5, Apr, pp. 650-656.

¹³ van Lieverloo, GGA, Peric, S, Doneddu, PE, Gallia, F, Nikolic, A, Wieske, L, Verhamme, C, van Schaik, IN, Nobile-Orazio, E, Basta, I & Eftimov, F 2018, 'Corticosteroids in chronic inflammatory demyelinating polyneuropathy : A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone', *J Neurol*, vol. 265, no. 9, Sep, pp. 2052-2059.

Adverse events associated with PE

To assess the harms of PE, one SR (Oriz-Salas et al. 2016)¹⁴ and three retrospective observational studies (Basic-Jukic et al. 2005; Mörtzell Henriksson et al. 2016; Nieto-Aristizábal, Vivas, et al. 2020)¹⁵ provided evidence. The studies were conducted in mixed populations with neurological diseases.

Mild to moderate AE rates associated with PE were reported in 2.05% of patients in the SR, and ranged from 4.75% to 8% of procedures in the three retrospective studies. Nieto-Aristizábal, Vivas, et al. 2020 reported an AE rate of 8% in all patients and 7.6% per procedure in CIDP patients (comprising 12.5% of the study population). Mild and moderate AE rates (most commonly hypotension and venous access problems) were reported as 4.75% of patients and 5.31% of PE procedures in the remaining studies. Severe AEs in these studies were reported at rates of 1.68% and 0.12% of procedures and included hypotension, anaphylactic reaction, and death due to neurological disease and septic shock. In general, rates of AEs associated with PE were moderately low; procedures performed by central access were associated with more severe AEs, while peripheral access was associated with more vascular access problems.

Adverse events associated with long-term Ig use

One retrospective study (Waheed et al. 2019)¹⁶ analysed AEs in patients (n=438) with neuromuscular diseases, 50.5% of whom had CIDP (n=221). The median follow-up period was 21 weeks.

AEs occurred in 2.9% of infusions and 16.9% of patients with autoimmune neurological conditions receiving IVIg in an outpatient setting. In a CIDP sub-group, AEs occurred in 1.9% of infusions and 12.2% of patients. The most frequent AEs were headache, hypertension, rash and nausea, but the rates of these were generally low. Serious AEs were rare.

Multivariate analyses found that first lifetime course of IVIg and higher IVIg dose (0.5 – 0.99 g/kg) were found to be associated with a higher risk of some AEs.

Two SCIG doses (0.2 g/kg and 0.4 g/kg) had similar AE rates and serious AE rates over a 24-week randomised trial.

¹⁴ Ortiz-Salas, P, Velez-Van-Meerbeke, A, Galvis-Gomez, CA & Rodriguez, QJ 2016, 'Human Immunoglobulin Versus Plasmapheresis in Guillain-Barre Syndrome and Myasthenia Gravis: A Meta-Analysis', *J Clin Neuromuscul Dis*, vol. 18, no. 1, Sep, pp. 1-11.

¹⁵ Basic-Jukic, N, Kes, P, Glavas-Boras, S, Brunetta, B, Bubic-Filipi, L & Puretic, Z 2005, 'Complications of Therapeutic Plasma Exchange: Experience With 4857 Treatments', *Therapeutic Apheresis and Dialysis*, vol. 9, no. 5, pp. 391-395.

¹⁶ Waheed, W, Ayer, GA, Jadoo, CL, Badger, GJ, Aboukhatwa, M, Brannagan, TH, 3rd & Tandan, R 2019, 'Safety of intravenous immune globulin in an outpatient setting for patients with neuromuscular disease', *Muscle Nerve*, vol. 60, no. 5, Nov, pp. 528-537.

Table 1 Comparison of adverse events reported in retrospective cohorts of patients receiving IVIg, PE or GC

Description	IVIg	PE	GC
Population	Outpatients with autoimmune neurological disorders including CIDP (50.5%) All patients : n = 438 CIDP = 221 Infusions all: 5867 Infusions CIDP: 3256	Patients with malignancy, neurological or haematological disorders	Autoimmune disorders including RA, SLE, GCA, and CIDP; asthma and lung diseases
Observation period Follow-up time	7 months Median follow-up (IQR): 21 (7, 21) weeks	NR	6 months to 5 years
Mild or moderate AEs	16.9% of all patients 2.9% of all infusions 12.2% of CIDP patients 1.9% of CIDP infusions	2.05% of patients 4.75% to 8% of procedures	Up to 37.9% of patients per AE (only most common AEs were reported)
Serious AEs	0.8% of all patients 0.5% of CIDP patients	0.1% to 1.68% of procedures	1.6% of CIDP patients
Most common AEs	Headache Hypertension Rash Nausea	Hypotension Poor venous access Tingling, paraesthesia Infection Urticaria Nausea, vomiting Electrolytic disorder Haematoma	Serious infection Sleep disturbance Hypertension Fracture and osteoporosis Weight gain

Abbreviations: AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; GC = glucocorticoid therapy; GCA = giant cell arteritis; IVIg = intravenous immunoglobulin therapy; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus

SOURCE: Table 25 (**corrected** as per Erratum) of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

11. Comparative effectiveness

The original DCAR found that evidence was of mixed-quality, trials were small, follow-up duration was short, and the relative long-term effectiveness of any of the treatments for CIDP was uncertain. As concluded in the original DCAR, evidence suggests that Ig is: superior to no treatment; at least non-inferior (possible superior) to corticosteroids; and, there is insufficient evidence to determine the relative efficacy to PE or immunosuppressants.

In the revised DCAR, two RCTs (Hartung et al 2019; Kuitwaard et al 2020b) met the inclusion criteria for the update of effectiveness data on IVIg or SCIg.

Hartung et al (2019) reported on patient reported outcomes (PROs) and QoL from an RCT comparing two doses of SCIg (0.2 g/kg or 0.4 g/kg) with placebo (PATH trial). Evidence from the study found that both SCIg doses were more effective than placebo in patients stabilised on IVIg after relapse, for relapse rate, time to relapse, and patient reported measures. Both SCIg doses were more effective than placebo for all domains of health related QoL and overall health, but there was no difference when the two doses were compared. The same trends were seen for treatment satisfaction and work productivity.

The DOSE (Kuitwaard et al. 2020b) RCT was a cross-over study comparing two different IVIg dosing regimens (normal dose and interval, and half dose at half the interval). Both dosing regimens were found to have similar effectiveness in patients who were on individual maintenance regimens. There were no differences found in hand grip strength, disability, fatigue, and overall health.

There was no further evidence identified (from RCTs) comparing the effectiveness of IVIg with PE, corticosteroids, or immunosuppressants.

The revised DCAR notes that the lack of high quality data on Ig should not necessarily be assumed to equate to lack of effect and that real world evidence (e.g. use of registries), may be helpful.

12. Economic evaluation

As requested by MSAC at its April 2020 meeting, three distinct models were developed for the revision of the economic model, one for each of the three comparators – Ig versus corticosteroids; Ig versus therapeutic PE; and second line use of Ig in a corticosteroid-resistant population versus placebo. Consistent with MSAC advice, the first two models are based on the non-inferior efficacy of Ig vs the comparators, but with further investigation of the comparative safety of each of the two therapies for each model. The third model assumes superior effectiveness and likely inferior or non-inferior safety for Ig use.

All models are structured to allow discontinuation of treatment due to remission, in addition to treatment failure. A stepped approach is used to demonstrate the impacts of using the dose and time on treatment likely used in Australian clinical practice (based on BloodSTAR data and clinical opinion), and important structural assumptions.

Table 2 provides a summary of the key characteristics of the economic evaluation, and Figure 3 presents the Markov model structure with allowable transitions between health states.

Table 2 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator(s)	i) Steroids ii) Therapeutic plasma exchange iii) Placebo (in corticosteroids resistant subgroup)
Type of economic evaluation	Stepped cost-utility analysis
Sources of evidence	Systematic review, expert opinion (Ig review reference group) and data provided by NBA and Department of Health
Time horizon	10 years
Outcomes	Cost per QALYs gained
Methods used to generate results	Decision analytic Markov model
Health states	A. Active disease: treatment induction or a relapse after more than 6 months off treatment B. Active but stable disease: maintenance phase (on treatment more than 4 months) C. No active disease: in remission (off treatment) D. Treatment resistant/intolerant disease: best supportive care E. Dead
Cycle length	Four weeks
Discount rate	5%
Software packages used	Microsoft Excel and TreeAge Pro

AE = adverse event; Ig = immunoglobulin; NBA = National Blood Authority; QALY = quality-adjusted life year.

SOURCE: Table 36 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

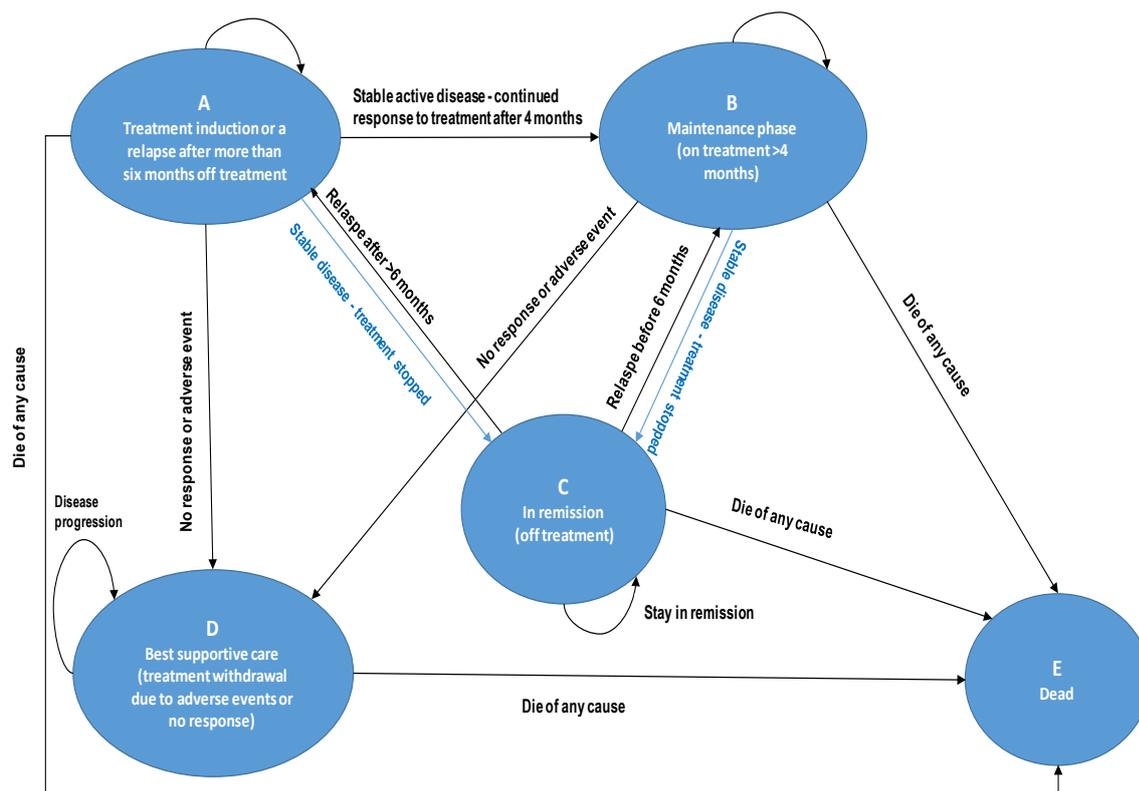


Figure 3 State transition diagram for the Markov model

Each oval (A to E) represents a chance node and the arrows represent the valid transitions between health states. All patients initially enter the Markov model at node “Treatment induction or relapse after six months off treatment”.
 SOURCE: Figure 12 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Results of the modelled base case analysis of each of the three comparisons are summarised in Table 3 below.

Table 3 Results of the modelled base-case economic analysis

Modelled base case economic evaluation	Inc. cost	Inc. QALYs	ICER
<u>Ig versus corticosteroids</u> Applies the dose and frequency based on the Criteria version 3 (2g/kg loading dose and 0.7g/kg maintenance dose for Ig), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39, with the model time horizon of 10 years.	\$137,443	1.1840	\$116,088
<u>Ig versus plasma exchange</u> Applies the dose and frequency based on the Criteria version 3 for Ig and for PE from Gwathmey et al (2020) (Table 28), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39 with the model time horizon of 10 years.	\$68,372	0.5316	\$128,614
<u>Second line Ig versus placebo</u> Applies the dose and frequency based on the Criteria version 3 for Ig and no treatment for placebo, the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39 with the model time horizon of 10 years.	\$159,573	1.7162	\$92,983

ICER = incremental cost-effectiveness ratio; Inc = incremental; Ig = immunoglobulin; PE = plasma exchange; QALY = quality-adjusted life years.

SOURCE: Table 3 (corrected as per Erratum) of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Results of the stepped economic analysis of each of the three comparisons are below:

Ig versus corticosteroids

Table 4 Results of the stepped economic analysis: IVIg vs corticosteroids

	Inc. cost	Inc. QALYs	ICER
Step 1 – Trial-based analysis. Applies the dose (2 g/kg), dose frequency (q4w), non-responder rates, adverse event rates, time horizon (48 weeks) and treatment duration (24 weeks) as per the Nobile-Orazio et al (2012) study.	\$63,315	0.1320	\$479,635
Step 2 – Trial-based dosing, extrapolated outcomes analysis Applies the dose, dose frequency, response rate, adverse event rates from step 1. Relapse rates, and re-remission rates are estimated from the Nobile-Orazio (2015) study, with the model time horizon extrapolated to 10 years.	\$702,576	0.9982	\$703,839
Step 3 – Modelled economic evaluation Applies the dose and frequency based on the Criteria version 3 (2g/kg loading dose and 0.7g/kg maintenance dose for Ig), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 39, with the model time horizon of 10 years.	\$137,443	1.1840	\$116,088

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; QALY = quality-adjusted life years.

SOURCE: Table 45 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Ig versus PE

There was insufficient evidence on the comparison of Ig and PE to support a finding of non-inferiority. The long-term effectiveness of PE treatment for CIDP is uncertain as the evidence was limited and of mixed quality. As such, only exploratory analyses could be conducted for this comparison.

Table 5 Results of the stepped economic analysis: IVIg vs PE

	Inc. cost	Inc. QALYs	ICER
Step 1 – Trial-based analysis. IVIg: 0.4 g/kg/week for first three weeks followed by 0.2 g/kg/week for the next three weeks. PE: Twice per week for three weeks then once a week for next three weeks (Dyck et al. 1994)	-\$5,074	-	-
Step 2 – Modelled economic evaluation Applies the dose and frequency based on the Criteria V3 for Ig and for PE from Gwathmey et al (2020) (Table 28), the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 31, with the model time horizon of 10 years.	\$68,372	0.5316	\$128,614

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; PE = plasma exchange; QALY = quality-adjusted life years.

SOURCE: Table 51 (**corrected** as per Erratum) of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Ig versus placebo in corticosteroid resistant subgroup

There was insufficient evidence on the comparison of Ig and placebo in corticosteroid resistant population. Data from Ig versus placebo study (Hughes et al. 2008) are used for the trial-based analysis.

Table 6 Results of the stepped economic analysis: Ig vs best supportive care

	Inc. cost	Inc. QALYs	ICER
Step 1 – Trial-based analysis. IVIg: Baseline loading dose of 2.0 g/kg over 2–4 d, followed by a maintenance infusion of 1 g/kg over 1–2 d every 3 wk for 24 wk. Placebo (0.1% albumin) (Hughes et al. 2008)	\$40,873	0.1266	\$322,801
Step 2 – Modelled economic evaluation Applies the dose and frequency based on the Criteria version 3 for Ig and no treatment for placebo, the best estimates of transitions for remission, relapse and adverse events as described in section C.3.2 and Table 31, with the model time horizon of 10 years.	\$159,573	1.7162	\$92,983

ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; Inc = Incremental; PE = plasma exchange; QALY = quality-adjusted life years.

SOURCE: Table 56 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Transition probabilities used in the economic models and relevant sources are described in Table 39 Section D.4 of the updated DCAR. Section D.6 presents sensitivity analyses using upper and lower bound of the parameter values found in the studies.

13. Financial/budgetary impacts

The financial implications and predicted use of Ig in patients with CIDP were estimated for a 5-year period from 2021-22 to 2025-26, using a market-based approach. This was based on current utilisation of Ig products in patients with CIDP. As data available on utilisation were only available for use under the Criteria V2 or when patients were transitioning to the Criteria V3, the impact of transitioning to the Criteria V3 could not be captured in the analysis. There is also uncertainty as to whether the trends observed in the past would continue in the future.

The total number of patients with CIDP receiving Ig has increased from 1,551 in 2011–12 to 2,250 in 2015–16 and 2,712 in 2019–20. The rate of growth for CIDP patients were 3.4% and 1.1% for the years 2018–19 and 2019–20 respectively. It is uncertain if this reduction in growth rate can be wholly attributed to the introduction of Version 3 Criteria or if numbers of patient switching from alternate therapies have stabilised.

Consistent with previous Reviews of Immunoglobulin, the cost per gram of Ig used in the base case analysis is \$60.41. This cost was provided by the Applicant to inform the economic and financial analyses and had been estimated retrospectively based on the reported total domestic product cost in 2017/18 (\$195 million) minus domestic SCIg product costs (\$4 million) in that same year, divided by the number of IVIg domestic grams issued (3,161,673) as published in the National Blood Authority (NBA) report on the Issues and Use of Ig in 2017/18 (NBA 2018) (see also Table 80, Appendix G). Additional analyses will be presented assuming:

- The highest cost per gram of Ig (i.e. domestic IVIg, including the cost of plasma fractionation), \$140.18

- The lowest cost per gram of Ig (i.e. imported IVIg), \$44.94
- The weighted average cost per gram of Ig across all indications, \$94.51.

Projected costs of Ig therapy for CIDP are presented in Table 7.

Table 7 Projected cost of Ig for CIDP, 2021–22 to 2025–26

	2021–22	2022–23	2023–24	2024–25	2025–26
Cost per gram of Ig	\$60.41	\$60.41	\$60.41	\$60.41	\$60.41
Total number of patients	2,934	3,003	3,059	3,102	3,133
Total number of Ig grams issued	1,661,542	1,758,705	1,855,868	1,953,031	2,050,194
Total cost of Ig	\$100,373,758	\$106,243,380	\$112,113,002	\$117,982,625	\$123,852,247
Cost of Ig to the Commonwealth ^a	\$63,235,467	\$66,933,329	\$70,631,191	\$74,329,054	\$78,026,916
Cost of Ig to the States ^a	\$37,138,290	\$39,310,051	\$41,481,811	\$43,653,571	\$45,825,331

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin

^a Under the National Blood Agreement, products are funded 63% by the Commonwealth and 37% by the states and territories.

SOURCE: Table 68 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

The net financial implications for government budgets associated with the funding of Ig for CIDP are presented in Table 8.

Table 8 Net financial implications to government associated with Ig for CIDP

	2021–22	2022–23	2023–24	2024–25	2025–26
Cost of Ig	\$100,373,758	\$106,243,380	\$112,113,002	\$117,982,625	\$123,852,247
Cost of Ig to the Commonwealth	\$63,235,467	\$66,933,329	\$70,631,191	\$74,329,054	\$78,026,916
Cost of Ig to the States	\$37,138,290	\$39,310,051	\$41,481,811	\$43,653,571	\$45,825,331
Cost of Ig administration to the States	\$27,807,744	\$28,241,137	\$28,544,731	\$28,721,337	\$28,773,765
Total cost	\$128,181,501	\$134,484,517	\$140,657,733	\$146,703,962	\$152,626,012
Net cost to the Commonwealth	\$63,235,467	\$66,933,329	\$70,631,191	\$74,329,054	\$78,026,916
Net cost to States	\$64,946,034	\$67,551,187	\$70,026,542	\$72,374,908	\$74,599,096

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin.

SOURCE: Table 72 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

Sensitivity analyses exploring uncertainty in the assumptions used to determine the financial implications are presented in Table 9. As expected, the cost of Ig is the main driver in the financial analysis; higher cost per gram of Ig results in higher budget impact and the lower cost of Ig per gram reduces the net cost to the Government.

Table 9 Sensitivity analyses around the financial implication estimates

	2021–22	2022–23	2023–24	2024–25	2025–26
Base case financial implications	\$128,181,501	\$134,484,517	\$140,657,733	\$146,703,962	\$152,626,012
Cost of Ig (base case: \$60.41 per gram)					
High cost of Ig, \$140.18	\$260,722,714	\$274,776,429	\$288,700,345	\$302,497,273	\$316,170,024
Low cost of Ig, \$44.94	\$102,477,445	\$107,277,348	\$111,947,451	\$116,490,566	\$120,909,504
Weighted average of Ig across all indications, \$94.51	\$184,834,531	\$194,450,483	\$203,936,636	\$213,295,801	\$222,530,788
Weighted average across the CIDP, \$71.86 a	\$147,210,848	\$154,626,655	\$161,912,663	\$169,071,683	\$176,106,525
Growth rate of Ig use (base case: average 5.4%)					
5%	\$127,341,007	\$132,751,063	\$138,280,153	\$143,943,530	\$149,757,068
6%	\$129,245,906	\$135,765,589	\$142,520,651	\$149,535,812	\$156,837,108
8%	\$133,109,873	\$141,967,437	\$151,369,135	\$161,371,693	\$172,036,150
Administration cost per IV infusion (base-case: \$693)					
\$214 per infusion b	\$109,646,774	\$116,014,000	\$122,351,118	\$128,654,537	\$134,920,670
Number of patients receiving Ig (base-case: projections assuming curved growth)					
Numbers projected using linear growth	\$129,965,580	\$137,039,285	\$144,090,757	\$151,119,996	\$158,127,003
Switch to SCIg (base-case: 2.5% increase every year)					
Flat 5% SCIg use	\$128,181,501	\$134,703,745	\$141,104,370	\$147,383,377	\$153,540,766
5% increase every year	\$128,181,501	\$134,265,289	\$140,211,096	\$146,024,546	\$151,711,258

^a For estimation of the average weighted price per gram within the CIDP indications see Table 89, Appendix H.

^b Windegger et al reported \$53.54 per week for IVIg ward costs (Windegger et al. 2019), that is \$214 for infusions every 4 weeks.

Ig = immunoglobulin; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin.

SOURCE: Table 73 of Mittal R, Milverton J, Schubert C, Parsons J (2021). Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). MSAC Application 1564.1, Re-submission assessment Report. Commonwealth of Australia, Canberra, ACT

IV and SC administration of Ig

In Australia, the majority of patients receive Ig for CIDP by intravenous infusion but SCIg for the treatment of CIDP was approved in August 2019. The DCAR noted that the impact of dosing route (IV or SC) on total Ig use is uncertain, but it appears more likely that SC administration would be associated with increased Ig use rather than decreased use.

Utilisation data from BloodSTAR (Table 78, Appendix G of the updated 1564 DCAR) shows that the average Ig use per patient is lower when patients receiving SCIg are excluded, suggesting higher doses are used in SCIg patients in Australia. However, this observation is based on a small, non-comparative, short-term dataset and should be interpreted with caution as the higher average dose appears to be driven, at least in part, by the particularly large maximum dose in a single patient.

As stated in the DCAR, the mean dose equivalence of IV and SC Ig in practice is not well defined. In the US a SC:IV dose ratio of 1.37:1 is recommended, whereas the European Union approves a 1:1 ratio. In a small UK study of eight patients with CIDP/ multifocal motor neuropathy (Hadden & Marreno 2015) who switched from IVIg to SCIg, the ratio of mean SCIg to IVIg dose was 1.024:1, and a larger US analysis of real-world data in 278 switching patients (with primary immunodeficiency diseases) indicated a stabilised ratio of 1.05:1, four months after switching.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Does the revised economic model address the concerns previously raised by MSAC?	ESC advises that the specific issues raised by MSAC with respect to the economic model presented in the original DCAR have been addressed in the revised report.
Do the eligibility criteria outlined in the Criteria V3 reflect the currently available evidence and best clinical practice?	ESC considered that the eligibility V3 Criteria reflect the current clinical standard and further evidence would be required to suggest changes to the algorithm. The current eligible population treated with Ig was largely captured in the trials, noting that children were excluded from trials.
The revised DCAR did not identify any additional randomised control trial (RCT) evidence comparing Ig with corticosteroids, plasma exchange (PE), immunosuppressants, or combination therapies for CIDP.	The evidence base for Ig therapy in patients with CIDP was concluded to be very small and of low quality. No additional RCT evidence was identified and there is no change to the clinical claims. ESC considered that funding of RCTs should be explored to assess safety and effectiveness of Ig versus plasma exchange, immunosuppressants / immunomodulatory drugs (excluding corticosteroids) and combination therapy.
There were few differences in effectiveness or safety between the dosing of SCIg 0.2 g/kg and 0.4 g/kg.	MSAC may want to consider whether a recommendation should be made to either: <ul style="list-style-type: none"> • start treatment at the lower SCIg dose (0.2 g/kg) and increase if required; or • start at the higher dose (0.4 g/kg) and reduce the dose when the patient's condition is stable.
Two IVIg dose and interval regimens (normal individualised dose and interval, and half the individualised dose at half the interval) showed similar safety and effectiveness when compared in a cross-over RCT	MSAC may wish to provide advice on whether it is appropriate for more flexible dosing regimens to be offered to patients with CIDP receiving IVIg. The Criteria currently allows for flexibility in dosing between 0.4 and 2.0 g/kg per 6 weeks for IVIg.
Since this revised DCAR commenced, the applicant has procured new contracts for the supply of imported Ig products, affecting the price of Ig.	ESC advised that, should the current prices for Ig be substantially different to those already considered in the DCAR, then MSAC should have visibility of the new prices.
Is Ig a cost-effective treatment for patients with CIDP?	ESC considered the ICER was high and uncertain for the comparison of Ig versus corticosteroids. The cost per gram of Ig remains a key driver in this model, however the base-case ICER in the revised model (\$116,088/QALY) is significantly lower than that in the previous DCAR (\$197,472). This is driven by the assumptions on SAEs associated with long-term corticosteroid use based on a study of patients with giant cell arteritis not CIDP, which ESC considered to be uncertain.

ESC key issue	ESC advice to MSAC
There is wide variability in Ig dosing and continuation rates across individual patients according to BloodSTAR data.	Currently collected or additional patient characteristics recorded in BloodSTAR may be able to further inform sub-groups of patients for whom Ig is more or less clinically effective and cost-effective. If recorded, there is likely be a requirement for data linkage to determine these outcomes.

ESC discussion

Application 1564 requests MSAC **reconsideration** and advice on the supply of immunoglobulin (Ig) therapy under the national blood arrangements for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP). In line with the PICO confirmation, the Department Contracted Assessment Report (DCAR) reviews the available evidence on safety and clinical effectiveness of Ig therapy in this population.

ESC recalled its previous consideration of this application at its February 2020 meeting, and that MSAC had subsequently considered and deferred providing advice on the clinical effectiveness and cost-effectiveness of Ig in the treatment of CIDP. At its April 2020 meeting, MSAC requested that the economic evaluation be revised to include comparisons of Ig versus corticosteroids; Ig versus plasma exchange (PE); and Ig versus placebo (in a corticosteroid resistant population). MSAC also requested an update of the systematic literature review on the safety and effectiveness of Ig for CIDP (including intravenous/IVIg and subcutaneous/SCIg), especially in relation to the safety of comparators.

CIDP is a rare, neurological disorder in which there is inflammation of nerve roots and peripheral nerves and destruction of the myelin sheath. Treatments for CIDP may include Ig therapy, corticosteroids, immunosuppressant drugs and/or plasma exchange. MSAC had previously noted the variability in the incidence and prevalence of CIDP reported across different epidemiological studies. It considered that even with the inclusion of probable and possible cases of CIDP in the estimated prevalence rate of 3 per 100,000 population (Broers 2019), nearly four times more patients in Australia received Ig for CIDP according to NBA data.

The clinical criteria for subsidised access to Ig for CIDP is set out in version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*¹⁷ (Version 3 Criteria). Patients with an established diagnosis of CIDP with significant disability and/or compromised walking, and who meet the specification of Version 3 of ‘the Criteria’ can access Ig as a first-line treatment. Review by a neurologist is required within the first four months, and every 12 months’ thereafter (by a neurologist or general physician). The Criteria also requires that a trial of cessation be considered every 12 months in patients in remission on maintenance therapy. Patients with CIDP who relapse after cessation of Ig therapy may restart treatment with Ig according to the Criteria.

¹⁷ National Blood Authority, 2018, [Criteria for the clinical use of immunoglobulin in Australia](#) (version 3).

ESC recalled that the evidence presented in the original DCAR was based on limited, mixed quality evidence with studies generally small, of short follow-up duration, and often at high risk of bias. Based on the benefits and harms reported in the evidence (April 2020), it was suggested that relative to:

- No treatment: Ig has inferior safety and superior effectiveness; noting that Ig is rarely associated with serious adverse events.
- Steroids: Ig has superior safety and non-inferior effectiveness.
- Plasma exchange, immunosuppressants / immunomodulatory drugs (excluding corticosteroids), and combination therapy: there is insufficient evidence to comment on the relative safety and effectiveness of Ig.

ESC noted that the update of the systematic literature review of comparative safety and effectiveness of Ig for CIDP found no additional randomised control trial (RCT) evidence comparing Ig with corticosteroids, PE, immunosuppressants, or combination therapies for CIDP. The evidence base for Ig therapy in patients with CIDP is very small, and of low quality, as was the evidence base for PE and corticosteroid therapy. ESC agreed that lack of quality data limits the conclusions that can be made about the effectiveness, impact of adverse events (AEs) and long-term safety of Ig compared to PE or corticosteroid therapy in the treatment of CIDP.

Evidence from two RCTs (Hartung et al. 2019 PATH study; and, Kuitwaard et al. 2020b DOSE study) was included to update the review on the safety and effectiveness of Ig for CIDP. Both trials were conducted in patients with CIDP who had been stabilised on IVIg and were assessing Ig as maintenance therapy.

In the RCT evaluating two doses of subcutaneous Ig (SCIg) in stabilised CIDP patients, both SCIg doses (0.2 g/kg and 0.4 g/kg) performed better than placebo for reducing relapse rate; time to relapse; and patient reported outcome scores. The RCT also found there were more AEs associated with SCIg treatment (either dose) than placebo, and found few differences in the effectiveness or safety between the two SCIg doses. ESC advised that MSAC may wish to consider a recommendation for patients to either: start treatment at the lower SCIg dose (0.2 g/kg) and increase if required; or, start at the higher dose (0.4 g/kg) and reduce the dose when the patient's condition is stable.

ESC noted the other RCT by Kuitwaard et al 2005b¹⁸ considered two intravenous Ig (IVIg) dose and interval regimens (normal individualised dose and interval, and half the individualised dose at half the interval) showed similar safety and effectiveness when compared in a cross-over RCT. ESC advised that MSAC may wish to provide advice on whether it is appropriate for more flexible dosing regimens to be offered to patients with CIDP receiving IVIg. The applicant clarified that the Criteria currently allows for flexibility in dosing between 0.4 and 2.0 g/kg per 6 weeks for IVIg, though broader options could be considered if there were evidence to support this.

¹⁸ Kuitwaard, K, Brusse, E, Jacobs, BC, Vrancken, AFJE, Eftimov, F, Notermans, NC, van der Kooi, AJ, Fokkink, WJR, Nieboer, D, Lingsma, HF, Merkies, ISJ & van Doorn, PA 2020b, 'Randomized trial of intravenous immunoglobulin maintenance treatment regimens in chronic inflammatory demyelinating polyradiculoneuropathy', European Journal of Neurology

The Extended assessment of harms in the revised 1564 DCAR was updated to include nine articles. ESC noted that based on evidence found, PE appeared to be a relatively safe treatment with the most common AEs being hypotension and problems with venous access. The frequency of mild or moderate AEs associated with PE was low (2.05%) in one systematic review (SR) in patients with neurological conditions receiving PE. In three other retrospective studies, the frequency of mild or moderate AEs ranged from 5.31% to 8% per PE procedure. ESC noted the erratum ([Attachment A](#)) to the DCAR clarifying the overall AE rate associated with PE in the study by Nieto-Aristizábal et al. 2020 should be reported as up to 40% per patient and 8% per procedure.

For patients taking long-term corticosteroids, the frequency of AEs was found to be high, with the most frequent AEs being serious infection (37% of patients) and hypertension (>30%). However, ESC noted that only the most frequent events were reported, and the widely varying populations included in these studies raises some uncertainty about the applicability of the findings to the population of interest. ESC also noted that AEs associated with corticosteroids appeared to be dose related, with several AEs increasing in rate linearly with dosage. The extended assessment of harms of IVIg reported that the most common AEs were headache, hypertension, rash and nausea although the rates of these were low. AEs occurred in 2.9% of infusions and 16.9% of patients with autoimmune neurological conditions receiving IVIg in an outpatient setting. Within the CIDP subgroup, the AE rates were 1.9% of infusions and 12.2% of patients.

ESC noted that the economic evaluation in the revised 1564 DCAR now presents three distinct models using three different comparators of corticosteroids, PE and placebo. ESC recalled that at its previous consideration of this application in February 2020, the economic model in the original 1564 DCAR presented just one comparison of Ig versus corticosteroids. Overall, ESC considered that specific issues raised by MSAC had been addressed in the new model including: health states allowing patients to cease treatment with Ig or a comparator due to disease remission or treatment failure; base case starting with trial based inputs for efficacy, safety, cessation rates and doses over the trial time horizon; and inclusion of dose and time on treatment informed by BloodSTAR data and/or clinician input to reflect treatment in Australia.

ESC considered the patient profile in the clinical evidence was representative of the demographic characteristics of patients with CIDP in Australia but noted that many trials exclude children. The NBA Annual Report (2017-18) reported that approximately 9% of patients receiving Ig therapy for any medical condition were ≤ 18 years; however, the percentage of children receiving Ig for CIDP was not reported and it was assumed that children comprise only a small proportion of CIDP patients in Australia. ESC also noted some differences between the doses used in trials versus in clinical practice but noted that the model appropriately uses doses used in clinical practice (BloodSTAR data), assuming lower effectiveness with lower doses.

The Criteria V3 and current guidelines recommend that Ig dosing and treatment interval be adjusted based on patient response, as considerable interpatient variability exists. ESC noted that there is little evidence to suggest an optimum dosing algorithm in CIDP patients. A study by Lunn et al proposed a dosing algorithm to standardise the tapering of Ig doses in chronic inflammatory neuropathies based on patient response. Study participants were treated with one or two IVIg doses of 2g/kg three weeks apart, and a third dose was not administered until the patient's condition deteriorated, to establish the dose interval. The dose was then reduced by 20% per course until relapse, allowing dose optimisation. ESC noted the revised 1564 DCAR

tested this 20% dose reduction in a sensitivity analysis which reduced the ICER in the Ig versus corticosteroids comparison by 27% (to \$84,934/QALY).

ESC noted that in the main comparison of Ig versus corticosteroids, the base case ICER was \$116,088 per quality-adjusted life-year (QALY), modelled over a 10-year time horizon. This is significantly lower than the ICER for the same comparison estimated in the original DCAR (\$197,472 per QALY) due to the incorporation of severe and long-term AEs associated with corticosteroid use in the revised model. ESC noted that due to uncertainty in the quality of the effectiveness and safety data (i.e. uncertain estimates for severe AEs associated with corticosteroids), the true ICER may be higher than predicted. ESC queried whether the patient population with giant cell arteritis (GCA) in the study by Wilson et al is representative of a CIDP population, noting that SAE for corticosteroids are duration and dose dependent.

ESC noted results of the secondary comparisons of Ig versus PE and Ig versus placebo produced ICERs of \$128,614/QALY and \$92,983/QALY, respectively.

The financial impacts and predicted Ig use for the treatment of CIDP were estimated using a market-based approach for a 5-year period from 2021-22 to 2025-26. The revised DCAR estimated net government costs for Ig use and delivery for CIDP treatment are projected to be \$128.2 million in 2021-22, increasing to \$152.6 million by 2025-26. The projections are based on the available utilisation data under Criteria V2 or when patients were transitioning to the Criteria V3. ESC considered the methods used and calculations were appropriate but noted there is some uncertainty about whether the trends observed under the V2 Criteria period would continue under the Criteria V3.

ESC noted that consistent with previous reviews of Ig, the cost per gram of Ig used in the base case is \$60.41. This represents the cost per gram of domestic IVIg (excluding the cost of plasma fractionation) and is calculated based on the costs and grams of IVIg issued according to the National Report on the Issue and Use of Ig in 2017/18. Sensitivity analyses were performed using the following prices: highest = \$140.18/g based on the cost of domestic IVIg including the cost of plasma fractionation; lowest price = \$44.94/g based on cost of imported IVIg; and an estimated weighted average price, including plasma fractionation costs = \$94.51/g. Changes to the price per gram of Ig had a large impact on both the ICER and the financial estimates. Therefore, ESC queried whether pricing arrangements to reduce the cost per gram of Ig could be explored by the NBA. It was noted that the applicant recently finalised a procurement process of new national contracts for the supply of imported Ig products. ESC advised that, should the updated prices for imported Ig be substantially different to those already considered in the DCAR, then MSAC should have visibility of the new prices.

15. Other significant factors

Following finalisation of the revised 1564 DCAR, errors were identified in the report which have been corrected in the Erratum to the DCAR ([Attachment A](#)) and updated in this ESC Report.

In the economic model for IVIg versus PE, the calculations of costs associated with central venous access were corrected. A programming error resulted in this cost being repeatedly added for each cycle of PE, rather than as a one-off cost in maintenance phase of treatment, and some repetitions of this cost in the IVIg arm also. The corrected calculations increase the base case ICER from \$94,038 to \$128,614 in this comparison.

The amendments also include a correction to the AE rate reported from the (Nieto-Aristizábal et al. 2020), which should be reported as up to 40% per patient and 8% per procedure, rather than 40% per procedure. This AE value was not incorporated into the economic model.

16. Applicant comments on MSAC's Public Summary Document

The National Blood Authority (NBA) notes MSAC's advice to the NBA and proposed advice to the Minister regarding the funding of Ig therapy for the treatment of CIDP.

The NBA agrees that work needs to continue to manage the access and use of Ig under the national blood arrangements in accordance with the NBA's statutory responsibilities. This work is ongoing through the NBA Immunoglobulin Governance Program, the NBA National Immunoglobulin Advisory Committee (NIGAC), four NIGAC expert Specialist Working Groups, the development, implementation and continuous review of national access criteria to inform clinical decisions to ensure the most appropriate use of this precious and costly blood product, the development and provision of clinical education, and NBA ICT systems that manage product access, use and information nationally. The acquisition and use of blood products is also underpinned by national supply arrangements through the NBA's commercial procurement and contract management activities that deliver the best value for money for governments.

As noted by MSAC in the specific context of CIDP, the growth in the use of Ig is being driven by increased demand. Concurrent with MSAC's consideration of Application 1564, the NBA initiated an external performance review of the NBA Ig Governance Program. This review noted that the NBA has been successful in moderating the overall growth in demand for Ig from almost 12% annually (a growth level in Australia that is consistent with a number of other comparable countries) to 7.3%. The review concluded that, in addition to significant savings already achieved, this reduced level of demand will save governments some \$2.2 billion by 2030-31 compared with costs associated with the unmoderated growth in demand. This moderated growth has been achieved through more targeted and appropriate access to Ig than through access to Ig being ceased for those requiring this treatment.

The NBA will continue this work, including through the current Ig performance improvement program, taking account of MSAC's advice in relation to CIDP. The NBA will continue to pursue improvements in the information and evidence base to ensure Ig therapy for CIDP reflects the most appropriate use. Any material uplift to current activities and systems will require a commensurate increase in funding.

17. Further information on MSAC

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