Australian Government
Medical Services Advisory Committee

STAKEHOLDER MEETING MINUTES

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

Tuesday 2 November 2021 – 2:00pm to 4:00pm

Attendees

Meeting attendees included members of the Medical Services Advisory Committee (MSAC); clinicians with experience and expertise in neurology medicine, representatives of Ig sponsor companies; a representative of Lifeblood; a representative from a consumer organisation; representatives of the applicant, the National Blood Authority; and representatives from the Department of Health.

1. Meeting open – welcome and introduction

The MSAC Chair opened the meeting at 2:00pm.

The Chair thanked participants for attending and clarified that the stakeholder meeting was not an MSAC decision-making forum. Rather, the aim of the meeting was to obtain further specific clinical information to assist MSAC's future deliberations and advice to the Jurisdictional Blood Committee (JBC) through the National Blood Authority (NBA) related to the issues raised by MSAC at its July 2021 consideration of Application 1564: Review of Immunoglobulin (Ig) for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

The key objectives of the meeting were to seek stakeholder input on issues raised by MSAC relating to Ig use including CIDP diagnosis, thresholds for access to Ig therapy and optimal dose regimens.

The Chair reminded participants that this was a confidential discussion. The outcomes of the meeting will be circulated to the attendees and subsequently published on the MSAC website, but comments will not be attributed to individuals.

Conflicts of interest

The Chair noted the conflicts of interests declared.

2. Background – recent MSAC consideration and issues arising

MSAC first considered Application 1564 for Ig for CIDP at its April 2020 meeting and deferred providing advice on the clinical and cost-effectiveness of Ig in this condition due to the substantial uncertainties in the Departmental Contracted Assessment Report (DCAR). These uncertainties broadly related to: the economic evaluation structure; concerns relating to the discrepancy between epidemiological data on prevalence and Ig usage; and the validity of the criteria for initiation and continuation to identify those patients with the greatest benefit and in whom Ig was cost effective. In its deferral, MSAC requested an update of the systematic literature review on the safety and effectiveness of Ig for CIDP, revised economic

modelling and Ig utilisation data for the management of CIDP addressing specific issues raised by MSAC.

At its July 2021 meeting, MSAC reconsidered application 1564 (and Revised 1564 DCAR) and advised that funding of Ig for CIDP should continue on the basis that it appears safe and is already an accepted first-line treatment in Australia, but further work is needed to manage demand for Ig in this condition. MSAC advised that from the revised cost-effectiveness analysis presented, Ig in this indication does not appear cost-effective and reiterated its concerns about the size of the population receiving Ig therapy for CIDP compared to published estimates of prevalence, and the projected increase in usage in the face of constrained supply.

MSAC recommended that the version 3 of the *Criteria for the clinical use of immunoglobulin in Australia* (Criteria V3) be reviewed to ensure that access to Ig is appropriately maintained for only those patients with a diagnosis of CIDP who are most likely to derive benefit.

MSAC requested that a stakeholder meeting be held to discuss issues relating to CIDP diagnosis and thresholds for initial or continued access to Ig therapy to assist the MSAC refine its advice to the JBC through the NBA as applicant.

MSAC also recommended the BloodSTAR data system be enhanced to help inform an optimum dose regimen in CIDP, and that a separate review of the cost-effectiveness of subcutaneous Ig (SCIg) compared with intravenous Ig (IVIg) should also be explored.

The Public Summary Document (PSD) was circulated to attendees before the stakeholder meeting.

The issues proposed for discussion were:

1. Diagnosis of CIDP with respect to the Criteria V3, and the number of people being treated with Ig for CIDP.
2. Appropriate thresholds for initial access to Ig therapy for CIDP.
3. Reviews and decisions to continue or cease treatment with Ig.
4. Dosing of Ig.
    a. Ig dosing frequency and method of dose calculation.
    b. Equi-effective dosing of IVIg versus SCIg for maintenance therapy.

3. Summary of discussion - Key issues and stakeholder comments

3.1. Diagnosis of CIDP

The Department provided a brief overview of concerns raised by MSAC relating to the large number of patients receiving Ig for CIDP in Australia and the growth in this population over time.

According to NBA data, there is a higher than expected prevalence of CIDP in Australia. MSAC noted 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), nearly four times more patients in Australia received Ig for CIDP than expected.

NBA data indicates that the number of patients receiving treatment for CIDP has increased by 67% from 2011/12 to 2017/18 but the reason for this increase is unclear. The Australian population increased by approximately 10% over the same time period. The revised 1564 DCAR predicted the number of patients receiving Ig for CIDP is projected to increase to approximately 3,133 patients by 2025-2026. Updated data from the NBA on 2020-21 CIDP patient numbers confirmed this modelling is likely to be an accurate prediction.

Table 1: Number of patients with CIDP projected to receive Ig, 2020–21 to 2025–26 (Adapted from 1564 DCAR)

	2020-2021	2021–22	2022–23	2023–24	2024–25	2025–26
Number of patients	2,853 (est) **2,839* (actual)**	2,934	3,003	3,059	3,102	3,133

CIDP = chronic inflammatory demyelinating polyneuropathy; Ig =immunoglobulin.
Source: 'Estimated patient numbers' worksheet in 'MSAC 1564.1 Financials.xlsx' workbook.

It was noted that the disparity between prevalence data and actual Ig use for the treatment of CIDP may be due to prevalence studies using a narrower set of criteria for diagnosis than that used in clinical practice, and patients being misdiagnosed with CIDP such as those with non-CIDP autoimmune neuropathies.

The Criteria V3 states that there is no specific diagnostic test for CIDP, but characteristic clinical and laboratory findings help distinguish this disorder from other immune mediated neuropathic syndromes. The only diagnosis requirements stated in the Criteria V3 are that diagnosis must be made by a neurologist. Participants were asked for their views on the likelihood of over or misdiagnosis of CIDP occurring, and whether there are a minimum set of objective diagnostic requirements that could reasonably be mandated in the Criteria V3 through BloodSTAR to address potential misdiagnosis.

Clinicians acknowledged that overdiagnosis of CIDP in Australia was likely and noted that a Dutch study[1] describing common diagnostic pitfalls demonstrated overdiagnosis of CIDP is also common overseas, as several classical or clinical symptoms are often missed. CIDP may be difficult to diagnose and that tests such as electrophysiological studies need to be rigorously applied. Some clinicians noted that an initial trial of Ig treatment and assessment of patient response has been used as a criterion for determining CIDP. Contributing to the issue of misdiagnosis is that patients without CIDP may also appear to respond to Ig treatment (noting here the impact of placebo effects). Diagnosis of CIDP typically considers clinical symptoms, electrophysiological studies and exclusion of other motor neuropathy conditions. One participant considered the Criteria V3 could potentially mandate some investigations such as MRI studies or nerve ultrasounds, or explicitly mandate the exclusion of non CIDP conditions before a trial of Ig is initiated. A clinician noted there was a Chicago Study[2] similar to the Dutch study that reported approximately 10% of patients misdiagnosed with CIDP had either hereditary or anti-MAG peripheral neuropathy which are not responsive to Ig therapy. These patients can be diagnosed via blood pathology and therefore the Criteria V3 could be refined to exclude this group of patients.

[1] 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
[2] Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology. 2015 Aug 11;85(6):498-504. doi: 10.1212/WNL.0000000000001833. Epub 2015 Jul 15. PMID: 26180143. https://pubmed.ncbi.nlm.nih.gov/26180143/

One participant noted the EAN/PNS Task Force 2021[3] publication suggests not to use MRI in adult patients to diagnose CIDP except in patients fulfilling diagnostic criteria for possible CIDP, and that there is currently no evidence to support MRI in paediatric patients.

Clinicians generally considered the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines were currently the most relevant criteria for diagnosing CIDP. The recommendations for diagnostic criteria in these guidelines were regarded sufficient to diagnose typical CIDP, but clinicians noted that atypical CIDP or variants of CIDP may still be difficult to identify. The diagnosis of some variants such as distal acquired demyelinating symmetric (DADS) neuropathy and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy was often prolonged, slow to respond to treatment, and required a longer trial of Ig to be identified. Attendees considered that the four-month period for initial access to Ig treatment, currently allowed in the Criteria V3, allows sufficient amount of trial time as to not disadvantage patients.

Participants acknowledged that access to specialist diagnostic health services may present an issue in some remote locations, however there is also an issue around the reliability of interpretation of the tests (e.g. MRI and nerve conduction studies). Clinicians noted that approximately 85% of people with CIDP live in capital cities or major centres which is where the majority of overdiagnosis is occurring. This suggests over diagnosis is a systemic issue where there are non-subspecialised (non-neuromuscular) neurologists diagnosing CIDP and MNN.

Clinicians agreed that most CIDP cases have a typical presentation which is easier to diagnose, with atypical variants representing only a small number of cases.

It was noted that access to MBS funded genetic testing for the commonly misdiagnosed disease - Charcot-Marie tooth disease type 1A (CMT1A) is available. The news of the recent MSAC recommendation of Application 1585 for genetic testing for the diagnosis of early-onset or familial neuromuscular disorders for listing on the Medicare Benefits Schedule was welcomed by all. Participants re-iterated that the ordering, interpretation of these genetic tests and genetic counselling was outside the area of expertise of many neurologists and therefore may require referral to a specialist geneticist/clinic. However, the availability of this testing will enable the diagnosis of heritable neuropathies which may mimic the clinical features of CIDP and obviate the use of immunoglobulin as a potential trial therapy.

It was suggested that strict adherence and accountability to the existing Criteria V3 could help target Ig therapy for treatment of CIDP, and a way forward would be to have prescribers provide additional relevant diagnostic test results in BloodSTAR. One clinician clarified that the purpose of the Criteria V3 was to enable access to government funded Ig, rather than to serve as a tool to guide clinicians on diagnosis of CIDP. However, increased prescriber accountability introduced in the Criteria V3 (for example, requirement to provide the name of the diagnosing neurologist) has resulted in fewer initiating patients since its introduction, and a likely reduction in overdiagnosis. Clinicians considered that enhancing the level of prescriber accountability with respect to diagnosis is one potential way to address overprescribing of Ig for CIDP.

[3] Van den Bergh, PYK, van Doorn, PA, Hadden, RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. J Peripher Nerv Syst. 2021; 26(3): 242– 268. https://doi.org/10.1111/jns.12455

3.2. Thresholds for initial access to Ig therapy

The Department provided an overview of the qualifying criteria for initial access to IVIg therapy for CIDP according to the Criteria V3. MSAC previously noted the Criteria V3 do not include a threshold for the Medical Research Council (MRC) sum score for adults or children 10 years or older, or the Six Minute Walk test (6MWT) in children less than 10 years, and that this imprecision may compound poor sensitivity and specificity of the diagnostic criteria. Participants were asked for their insights on appropriate thresholds and if any other metrics of CIDP severity could be included in the Criteria V3.

Clinicians clarified that for adults, the Criteria V3 did not include a threshold for MRC sum scores because it was not intended to provide an assessment of neurological impairment needed for access to Ig therapy. Rather, it was included to capture a baseline clinical assessment upon which future assessments are compared to determine responsiveness to treatment. The measure of baseline impairment needed for access to Ig therapy is captured by the Overall Neuropathy Limitations Scale (ONLS). Participants noted that the MRC sum score assesses weakness only and not the inability to perform tasks requiring finer motor skills due to sensory loss.

Clinicians considered current thresholds in the Criteria V3 appropriate and consistent with international standards, noting that ONLS has a greater sensitivity to change than MRC. Clinicians noted that ONLS is a derivation of the previous Inflammatory Neuropathy Cause and Treatment (INCAT) with additional scoring to assess lower limb disability and is likely to be more sensitive. While there are other scores used in clinical trials, the ONLS was considered the most appropriate for inclusion in the Criteria V3 in favour of allowing different scores to be used.

For the paediatric CIDP population, meeting attendees were informed that at the time of writing the Criteria V3, paediatric neurologists advised that a defined 6MWT value to justify Ig therapy was not appropriate, rather responsiveness should be assessed. Overall, as CIDP in children is rare, clinicians considered it unlikely that Ig would be over prescribed for this population.

3.3. Reviews and decisions to continue or cease treatment with Ig

Participants were directed to the Criteria V3 'Review Criteria for Assessing the Effectiveness of IVIg use for patients with CIDP' that states a review by a neurologist is required after four months of Ig therapy to determine whether the patient has responded. If there is no benefit after this period of treatment, IVIg therapy should be abandoned. Where treatment is continued, a review by a neurologist or general physician is required each 12 months. A trial of cessation should be considered each 12 months in patients in remission on maintenance therapy.

A summary of BloodSTAR data *'Analysis of patients initiating, ceasing and continuing Ig therapy for the treatment of CIDP'* from the Revised 1564 DCAR was presented showing Ig supply for CIDP from initiation to beyond the second clinical review at 16 months. Of the 291 patients who initiated Ig for CIDP during the study period:

- 94 (32%) patients ceased Ig on or before the first clinical review at four months;
- 99 (34%) patients were continuously supplied beyond the second clinical review (16 months) date and without a break in supply;
- A further 39 (13%) patients continued Ig therapy beyond the second review date, but did have at least one break of greater than two months during follow-up; and

- 55 (19%) patients ceased Ig between the first and second clinical review and did not reinitiate in the follow-up period.

Participants considered the results of the analysis reporting '32% of patients ceased Ig on or before the first review at four months' to be encouraging as it appears patients trialling Ig therapy are being ceased if not responding. It was noted that these patients may not have CIDP, or some may have CIDP but not are not responsive to treatment with Ig.

One participant noted that IVIg administration and attendance to hospital to receive infusions is unfavourable to most patients, and they would be unlikely to continue treatment if their condition was not improving. Other participants considered patients are likely to want to continue with Ig due to its appreciable placebo effect, but noted that the objective disability scales included in the Criteria V3 were chosen so that treatment continuation would be based on an objective response rather than subjective patient reported outcomes. It was also noted that patients were more accepting of weaning off Ig therapy rather than ceasing treatment abruptly.

Participants were asked what influences these clinical decisions to wean Ig therapy and if more frequent mandated reviews would be feasible to assist identify patients in remission earlier.

Participants agreed that the decision to continue or cease treatment with Ig was almost entirely a clinical decision based on stable outcome scores, and unlike the initiation of treatment it is not guided by electrophysiological testing or other investigation findings. Clinicians noted that the absence of any deterioration of the patient's clinical status towards the end of the Ig treatment cycle indicates that the patient may be in remission and helps to guide clinicians on when patients should be considered for weaning off Ig.

With respect to mandated review periods to identify patients in remission, participants noted that best practice is for clinicians to review a patient with CIDP receiving Ig therapy every three to six months to assess response to treatment and clinical status, which is more often than the required annual review timeframe outlined in the Criteria V3. Clinicians considered these more frequent reviews are probably already occurring although they are not mandated in the Criteria V3, with the exception of patients living in regional or remote locations who may face difficulties to access a specialised clinician more regularly than the required 12 monthly timeframe for review.

3.4. Dosing of Ig

a. Dosing frequency and method of dose calculation (actual vs ideal body weight (IBW) dosing)

NBA data which was included in the Revised 1564 DCAR, showed there was considerable variation in the Ig doses supplied for patients with CIDP. There has also been increasing use (grams of Ig supplied) per patient/year for CIDP. It was noted there is little evidence to guide frequency and methods of calculating Ig dosing for maintenance treatment of CIDP.

Clinicians' views were sought on how loading doses and frequency of maintenance doses are decided given the range of dose options allowable in BloodSTAR, and views on using ideal body weight (IBW) versus actual body weight when calculating Ig doses for patients with CIDP.

A study by Lunn et al 2016[4] referenced in the DCAR demonstrated that it is possible to taper Ig dosing to identify the optimum individualised dose and dose interval for patients, noting this may result in a temporary deterioration in the patient's clinical condition. According to this dosing algorithm patients were treated with one or two initial IVIg doses of 2gm/kg at an interval of three weeks and their response was assessed. Then a third dose is not administered until the patient's condition deteriorates, allowing a "dose interval" to be set. The dose is then reduced by 20% per course until relapse, allowing dose optimization.

Some clinicians noted that practice in Australia differs because after the initial loading dose, clinicians usually titrate up from the lowest recommended maintenance dose. However, there was some difference in clinical opinion amongst attendees whether dosing should start high and titrate down, or start low and titrate up to determine the appropriate dose.

It was noted that the flexibility afforded to clinicians in determining the appropriate Ig dose for CIDP is not typical for other medicines especially those which are costly, and this approach may result in inefficient use of Ig due to over or under dosing. Therefore, there was general agreement to support the consideration of developing a dosing algorithm to ensure patients receive a therapeutic dose and there is no wastage of Ig. However, some participants acknowledged that there may be different dose considerations in Ig treatments, compared to standardised dosing of non-Ig pharmaceuticals.

Participants acknowledged the lack of evidence to support which method of dose calculation was more effective, based on ideal body weight or bodyweight-based dosing. It was suggested this could be addressed outside the Criteria V3 as an area for potential research although participants acknowledged it may be difficult to recruit sufficient patients to conduct a study in Australia due to the low CIDP prevalence.

With regard to weight-based dosing of Ig, it was noted that BloodSTAR provides the option, rather than a recommendation, to use IBW or actual weight when calculating the Ig dose. Clinicians considered there is conflicting evidence on the relationship between efficacy of weight-based Ig dosing. Some clinicians agreed that IBW should be used as there is no evidence to suggest a difference in efficacy between actual weight-based versus ideal body weight dosing of Ig, but other clinicians noted that randomised controlled trials investigated the safety and efficacy of Ig using actual bodyweight (rather than IBW). Lower effective doses have also been reported to be independent of weight and disease duration[5], and therefore some clinicians considered that a common approach using IBW based-dosing could potentially be used as to help alleviate Ig demand. However, clinicians held different opinions with regards to this. One participant considered that BloodSTAR could be enhanced so that data may be reviewed/analysed for outcomes for those patients whose clinicians chose IBW versus those who use actual weight to calculate Ig dosing.

b. *Equi-effective dosing of IVIg versus SCIg for maintenance therapy*.

SCIg was approved in August 2019 for use for the treatment of CIDP under the National Blood Arrangements and the minimum and maximum dose range in the Criteria V3 are equivalent to the IVIg dose range (IVIg 0.4-2g/kg, 2-6 weekly and SC 0.2-0.5g/kg weekly,

[4] Lunn, MP, Ellis, L, Hadden, RD, Rajabally, YA, Winer, JB & Reilly, MM 2016, 'A proposed dosing algorithm for the individualized dosing of human immunoglobulin in chronic inflammatory neuropathies', J Peripher Nerv Syst, vol. 21, no. 1, Mar, pp. 33-37.

[5]Rajabally YA, Seow H, Wilson P. Dose of intravenous immunoglobulins in chronic inflammatory demyelinating polyneuropathy. J Peripher Nerve Syst 2006; 11: 325– 329. https://pubmed.ncbi.nlm.nih.gov/17117941/

both with a maximum of 2g/kg/4-weeks). The DCAR reported that the dose equivalence of IVIg to SCIg was not well defined. Based on BloodSTAR data it appeared that SCIg administration was associated with increased Ig use rather than decreased use although this observation was considered uncertain.

Pharmacokinetic (PK) information for approved SCIg products showed that the Ig trough concentrations were similar for lower (0.2g/kg/week) and higher dose (0.4g/kg/week) SCIg doses which correlates with the clinical response rates reported in the PATH trial, but not in the PATH trial extension. Clinicians noted that trough Ig concentrations were not usually assessed in practice to guide dosing interval.

Clinician views were sought with regards to the administration of IVIg or SCIg on the equi-effective dose used in clinical practice and what influences the clinician decision-making.

Participants noted it is accepted that patients who are switched from IVIg to SCIg for maintenance treatment are switched using a 1:1 dose ratio, and then dose adjustments would be made depending on patient response. Occasionally a larger dose of SCIg may be required. This is supported by recommendations in the EAN/PNS Taskforce 2021[6] CIDP guidelines.

4. Discussion

Participants noted that patients with CIDP report that access to Ig treatment affords them a better quality of life, less disability and greater capacity to gainful employment. Access to SCIg treatment is beneficial in terms of not having to take leave from work in order to attend hospital for IVIg infusions, especially for patients living in regional or remote areas. It was noted that the ease of implementing SCIg therapy faces different challenges in different jurisdictions depending on whether the consumables were funded by hospitals.

5. Meeting close

The Chair thanked participants for their contributions and valuable insights.

The meeting closed at 4:00pm.

[6] Van den Bergh, PYK, van Doorn, PA, Hadden, RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision. J Peripher Nerv Syst. 2021; 26(3): 242– 268. https://doi.org/10.1111/jns.12455