



**Australian Government**

**Department of Health**

**Application 1564:**

**Chronic Inflammatory Demyelinating  
Polyneuropathy (CIDP)**

**PICO Confirmation**

**(to guide a new referral to MSAC)**

**Summary of PICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)**

| Component    | Description  |
|--------------|--|
| Patients     | <p>Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who are currently eligible for immunoglobulin (Ig) treatment in Australia according to version 3 of the <i>Criteria for the clinical use of immunoglobulin in Australia</i>.</p> <p>Note:<br/>The Reference Group notes that while the above population is appropriate, a broader evidence base should be considered (i.e., entire CIDP population) and evidence of treatment variation then explored.</p>   |
| Intervention | <p>The intervention to be investigated is immunoglobulin (Ig). This may be delivered in one of two forms:</p> <ul style="list-style-type: none"> <li>○ Intravenous Ig (IVIg)</li> <li>○ Subcutaneous Ig (SCIg)</li> </ul>  |
| Comparator   | <ul style="list-style-type: none"> <li>○ Steroids (oral and IV),</li> <li>○ Plasma exchange,</li> <li>○ Immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids)<sup>1</sup>,</li> <li>○ A combination of two or more of the above therapies, or</li> <li>○ No active treatment, No Ig.</li> </ul>   |
| Outcomes     | <p><b><i>The outcomes listed are those identified in the development of the PICO. Additional or more specific outcomes identified during the evaluation process that are considered relevant to the intervention or comparator treatment may be addressed in the evaluation report (Contracted Assessment). Broadly the outcomes identified pre assessment and considered in scope are:</i></b></p> <p><b><i>Safety Outcomes:</i></b></p> <ul style="list-style-type: none"> <li>○ Adverse events including development of disease or side effects (e.g. infections, diabetes, hypertension, cardiovascular disease, prolonged ventilation in ICU)</li> </ul> <p><b><i>Clinical effectiveness outcomes:</i></b></p> <ul style="list-style-type: none"> <li>○ Change in disability: (e.g. Overall Neuropathy Limitations Scale (ONLS) score, Six-Minute Walk Test (6MWT) in children only)</li> <li>○ Change in muscle strength (e.g. Medical Research Council (MRC) Sum (12) in adults, Modified Rankin Scale (MRS) in children)</li> <li>○ Change in quality of life</li> <li>○ Mortality</li> </ul> <p><b><i>Healthcare system resources utilisation</i></b></p> <ul style="list-style-type: none"> <li>● Changes in health system resource utilisation associated with the intervention <ul style="list-style-type: none"> <li>○ Ig products</li> <li>○ Infusion equipment</li> <li>○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig)</li> <li>○ Nursing time (for initiation and monitoring if IVIg)</li> <li>○ Hospitalisation (including use of hospital resources)</li> <li>○ Medication to treat adverse events (e.g. analgesia or antihistamines)</li> <li>○ Training of patient or carer to provide infusions (SCIg only)</li> <li>○ Product dispensing and disposal of any unused product</li> <li>○ Follow-up and/or monitoring visits, including regular neurology visits</li> </ul> </li> </ul> |

<sup>1</sup> In practice, expert advice is that immunosuppressants are used as an add on to steroids (or plasma exchange) rather than as an independent intervention.<sup>1</sup> Expert Neurologist. Personal communication (written feedback received via email 31 January). 2019.

| Component | Description  |
|-----------|--|
|           | <ul style="list-style-type: none"> <li>• Change in health system resource utilisation associated with the comparators <ul style="list-style-type: none"> <li>○ Comparator products</li> <li>○ Resources to deliver the comparator (eg hospital and staff time for IV steroids and plasma exchange, dispensing for oral treatments)</li> <li>○ Hospitalisation</li> <li>○ Management of adverse events</li> <li>○ Follow-up and/or monitoring visits, including regular neurology visits</li> </ul> </li> </ul> |

## PICO rationale for therapeutic medical services

### Population

Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) who are currently eligible for IVIg treatment in Australia make up the proposed population in this PICO Confirmation.

The Reference Group advised that while the above population is appropriate, a broader evidence base should be considered (i.e., entire CIDP population) and evidence of treatment variation then explored. Patients with a CIDP-like neuropathy and an IgG or IgA paraprotein who meet version 3 of the Criteria fall within the scope of the review.

In 2002, a National Blood Agreement was signed by the Federal, state and territory governments.<sup>2</sup> It was agreed that public funding would be available for patients with a clinical need for a blood product. The *Criteria for the clinical use of immunoglobulin in Australia* (hereon known as *the Criteria*) is a framework describing the medical conditions and specific circumstances for which the use of immunoglobulin (Ig) is considered clinically appropriate and for which public funding is available.<sup>3</sup> It was first established in 2007 but has since been updated on two occasions. Version 3 of *the Criteria* came into effect on 22 October 2018 and is accessible online.<sup>4</sup>

Version 3 of *the Criteria* considers the use of Ig to be appropriate for patients diagnosed with CIDP by a neurologist and in whom compromised walking and/or significant disability can be objectively demonstrated (as outlined in Table 1). To be eligible for ongoing maintenance therapy additional review criteria must be met at regular intervals. These are discussed in the Intervention section of this document.

Version 3 of *the Criteria* considers the use of Ig for the following indications:

- CIDP for patients in whom walking is compromised or there is significant disability (treatment-naïve patients).
- CIDP patients who relapse within six months of commencing a trial of Ig therapy.

Expert advice received during the review phase confirmed that version 3 of *the Criteria* intends to restrict Ig access to cases of moderate to severe CIDP via the use of clinically meaningful scales to assess disability. Reserving treatment for moderate to severe cases aligns with established guidelines which recommend that if symptoms are mild, a patient should be monitored without treatment.<sup>1,5,6</sup>

**Table 1 Current initial qualifying criteria for the use of Ig in CIDP in Australia**

| <b>Indication: CIDP patients in whom walking is compromised or there is significant disability</b>  |
|---|
| <p>In adults or children 10 years or older</p> <ul style="list-style-type: none"> <li>Significant disability or compromised walking objectively measured by an ONLS score of at least two points, <b>and</b> the MRC sum score</li> </ul> <p><b>OR</b></p> <p>In children less than 10 years</p> <ul style="list-style-type: none"> <li>Significant disability or compromised walking measured by the 6MWT, <b>and/or</b> an MRS score of at least 2 points</li> </ul> <p>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, Ig therapy should be abandoned.</p>  |
| <b>Indication: CIDP patients who relapse within six months of commencing a trial off Ig therapy</b>   |
| <p>In a previously stable adult or child of at least 10 years of age,</p> <ul style="list-style-type: none"> <li>Deterioration in disability as measured by an increase of at least one point in the Adjusted ONLS, <b>or</b> a reduction in the MRC sum score of at least three points, when compared to the review score before stopping previous treatment</li> </ul> <p><b>OR</b></p> <p>In a previously stable child less than 10 years of age,</p> <ul style="list-style-type: none"> <li>Deterioration in disability as measured by a reduction in the 6MWT <b>or</b> an increase of at least one point in the MRS compared to the review score before stopping previous treatment</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Relapse has occurred within six months of the last Ig dose<br/><i>Ig should be used for a maximum period of four months (induction plus three maintenance cycles) before determining whether the patient has responded. If there is no benefit after this treatment, Ig should be abandoned.</i></li> </ul> |

**Source:** Adapted from Box 1 of the Referral Form, page 27. Originally sourced from the Criteria for the Clinical Use of Immunoglobulin in Australia (version 3), available online.<sup>4</sup> Additional information has been sourced from these Criteria.

**Abbreviations:** **ONLS** = Overall Neuropathy Limitations Scale, **MRC** = Medical Research Council, **6MWT** = Six-minute walk test; **MRS**= Modified Rankin Scale, **CIDP**= Chronic inflammatory demyelinating polyneuropathy.

### Background

CIDP is an acquired autoimmune neuropathy affecting the peripheral nervous system. The condition typically impairs motor and sensory nerves, with patients experiencing weakness and sensory loss in their limbs, commonly in the legs first.<sup>6-8</sup> This weakness is often so severe that a patient is unable to walk unaided.<sup>6</sup> CIDP is a treatable condition; however, repeated or prolonged treatment is often required.<sup>7</sup>

CIDP is believed to occur when the immune system inappropriately attacks peripheral nerve antigens.<sup>9</sup> Inflammation of the peripheral nerves can damage the insulating myelin sheaths, causing demyelination and interfering with signal conductivity.<sup>7</sup> CIDP typically develops slowly, over a period of at least 8 weeks, although there are acute presentations.<sup>1,10</sup> This slow onset helps distinguishes it from Guillain- Barré Syndrome which develops acutely and starts to improve within 2-4 weeks.<sup>1,10</sup>

CIDP is a medical condition which may follow one of multiple courses:<sup>10</sup>

- Relapsing and remitting,
- Chronic progressive, or
- Monophasic.

Expert opinion sought during the review process confirmed that treatment for CIDP, whether it be of a relapsing and remitting or progressive nature, would not differ.<sup>11</sup> Moreover, it was suggested that given improvements in the recognition of this disease, CIDP of a relapsing and remitting course may not have the opportunity to express itself as such.<sup>11</sup>

### Diagnosis

One of the major challenges of this condition is the difficulty in diagnosing CIDP, and as such patients often receive a diagnosis when the condition has become severe (e.g., patients are unable to walk unaided).<sup>11</sup> CIDP is treatable once diagnosed; thus a timely and accurate diagnosis is imperative to ensure the best possible wellbeing for this population.<sup>10</sup>

There is no specific diagnostic test for CIDP; to reach a diagnosis, a physician would typically consider clinical signs and symptoms, evidence of demyelination on electrophysiological or pathological studies and the exclusion of other causes.<sup>7</sup> Response to immunomodulating treatment may further support a diagnosis of CIDP (Referral Form, page 26); as may other tests including cerebrospinal fluid analysis, magnetic resonance imaging (MRI) of spinal nerve roots and nerve trunks, and nerve biopsies.<sup>7</sup>

Multiple diagnostic criteria have been proposed; however, expert opinion sought during the drafting of this PICO Confirmation confirmed that the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines are at present, the most relevant and align with current clinical practice.<sup>11</sup> These guidelines were first compiled in 2006 and have since been updated in 2010.<sup>5, 12</sup>

For the diagnosis of CIDP, the EFNS/PNS guidelines suggest the following investigations (as noted in the Referral Form, pages 25-26):<sup>5</sup>

- Nerve conduction studies
- Cerebrospinal fluid cells and protein
- MRI spinal roots, brachial plexus and lumbosacral plexus
- Nerve biopsy studies
- A supportive criterion is: Objective clinical improvement following immunomodulatory treatment (such as IVIg)

The guidelines also recommend tests to detect concomitant disease and/or hereditary neuropathy.<sup>5</sup>

Under the EFNS/PNS criteria, patients may be classified as having definite, probable or possible CIDP based upon specified clinical, electrodiagnostic and supportive criteria.<sup>5</sup> The Referrer notes a risk that patients may receive Ig for an incorrect diagnosis of CIDP as no specific diagnostic tests are required for a patient to qualify for intravenous Ig in Australia (Referral Form, pages 25- 26). However, the EFNS supportive criterion of improvement following immunomodulatory treatment such as Ig suggests both that this should be done and is normal practice.

Expert advice received during the review phase emphasised the significance of the risk of misdiagnosis; noting that as many as a third of CIDP patients may be misdiagnosed.

## Prevalence of CIDP

Prevalence estimates for CIDP vary considerably, from approximately 1 to 9 per 100,000 (Table 2). Population-based studies have repeatedly demonstrated that men are more commonly affected by this condition and that CIDP becomes increasingly prevalent with age.<sup>7, 13, 14</sup>

**Table 2 Overview of prevalence estimates for CIDP**

| Study (author, year)                     | Country (region)                    | Estimated prevalence (per 100,000) [95% CI]  | Criteria used to classify CIDP patients                        |
|--|-------------------------------------|--|--|
| Lunn et al. (1999) <sup>15</sup>         | England (South East Thames Region)  | 1.00   | AAN*   |
| McLeod et al. (1999) <sup>16</sup>       | Australia (New South Wales)         | 1.9 [1.5-2.2]  | AAN  |
| Mygland and Monstad (2001) <sup>17</sup> | Norway (Vest-Agder)                 | 7.7 [3.2-12.2]   | Albers and Kelly, 1989   |
| Chio et al. (2007) <sup>18</sup>         | Italy (Piemonte and Valle d'Aosta)  | 3.58 [3.02, 4.20]  | AAN  |
| Iijima et al. 2008 <sup>19</sup>         | Japan                               | 1.61   | AAN, Saperstein's modified criteria and INCAT criteria.        |
| Rajabally et al. (2009) <sup>14</sup>    | UK (Leicestershire and Rutland)     | <ul style="list-style-type: none"><li>4.77 [3.49-6.37] using the 2006 EFNS/PNS criteria</li><li>1.97 [1.19-3.08] using the 1991 AAN criteria</li></ul> | EFNS/PNS 2006 (definite, probable or possible), <b>and</b> AAN |
| Lauglin et al. (2009) <sup>20</sup>      | US (Olmsted County, Minnesota)      | 8.9  | Dyck et al. 1975 and Mayo EMG laboratory                       |
| Mahdi-Rogers et al. (2014) <sup>13</sup> | UK (former southeast Thames region) | 2.84 [2.31-3.45]   | EFNS/PNS 2006 (definite, probable or possible)                 |
| Lefter et al. (2017) <sup>21</sup>       | Ireland                             | 5.87 [5.06-6.68]   | EFNS/PNS 2010  |

Source: adapted from Referral Form Tables 2 and 3, Rajabally et al. (2009),<sup>14</sup> Mahdi-Rogers et al. (2014)<sup>13</sup>

**Abbreviations:** **AAN** = American Academy of Neurology, **CIDP** = chronic inflammatory demyelinating polyneuropathy, **EFNS/PNS** = European Federation of Neurological Societies/Peripheral Nerve Society, **INCAT** = inflammatory neuropathy cause and treatment.

Notes: \*in addition to formal AAN criteria fulfillment, "opinion from a consultant neurophysiologist of the presence of a demyelinating neuropathy" was considered sufficient for electrodiagnostic confirmation by these investigators.

Australian data by McLeod et al. (1999) was identified to estimate CIDP prevalence; however, this study used the AAN criteria to classify patients.<sup>16</sup> Rajabally et al. (2009) undertook an epidemiological study using two different criteria: the EFNS/PNS criteria (2006 version), which estimated prevalence as 4.77 per 100,000 (95% confidence interval (CI) [3.49, 6.37]), and the AAN criteria which estimated prevalence as 1.97 per 100,000 (95% CI [1.19, 3.08]).<sup>14</sup> The authors concluded the EFNS/PNS criteria provided a more accurate estimate of CIDP prevalence; studies reporting prevalence figures based on alternate criteria may underestimate the true prevalence of CIDP, by failing to recognise possible or probable cases of CIDP.<sup>10, 14</sup>

### Current usage figures in Australia

As Ig is already funded in Australia, robust usage figures about the use of Ig to treat CIDP are readily available. Information relevant to this PICO Confirmation was recently published in the *National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16* release by the National Blood Authority.<sup>22</sup> This Report provides a comprehensive overview of the number of CIDP patients receiving IVIg therapy in Australia.

Nationwide figures for the years 2011-12 through to 2015-16 and state/territory specific figures for the year 2015-16 are presented in Table 3 and Table 4.

**Table 3 Historical patient numbers using IVIg for CIDP in Australia (total) by year**

| Financial Year | 2011-12 | 2012-13 | 2013-14 | 2014-15 | 2015-16 |
|----------------|---------|---------|---------|---------|---------|
| Patient no.    | 1,551   | 1,753   | 1,903   | 2,054   | 2,250   |

**Source:** Adapted from Table provided by the Referrer, pages 44-45 of the Referral Form. Information was originally sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16 published by the National Blood Authority.<sup>22</sup>

**Table 4 Patient numbers by state/territory using IVIg for CIDP, 2015-16**

| State       | NSW | VIC | QLD | WA  | SA | TAS | ACT | NT | National |
|-------------|-----|-----|-----|-----|----|-----|-----|----|----------|
| Patient no. | 834 | 507 | 648 | 130 | 93 | 36  | 32  | 15 | 2,250    |

**Source:** Adapted from Table provided by the Referrer, page 45 of the Referral Form. Information was originally sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16 published by the National Blood Authority.<sup>22</sup>

Please note that the figures detailed in Table 3 and Table 4 pertain only to the use of IVIg. Subcutaneous immunoglobulin (SCIg) provides an alternate form of delivery for Ig therapy (discussed further in the Intervention section of this document). Its approval for use in CIDP patients is said to be probable in the foreseeable future (Referral Form, page 4). The Reference Group indicated the introduction of SCIg is not expected to greatly increase the number of patients using Ig to treat CIDP.

### Rationale

If evidence is available allowing subgroup analysis the following groups are of interest:

#### Motor, sensory, or sensorimotor

CIDP is a sensorimotor neuropathy; however, the degree to which it affects the motor or sensory peripheral nerves will differ between patients. Treatment recommendations for pure motor CIDP differ from standard recommendations.

The EFNS/PNS guidelines recommend either steroids or IVIg as the first option for patients with moderate to severe CIDP however they do not make a clear distinction which is more appropriate. For pure motor CIDP, the guidelines recommend that IVIg should be the first choice.<sup>5</sup> Expert opinion sought during the drafting of this PICO Confirmation clarified that in cases of pure motor CIDP patients may deteriorate when given steroids. Therefore, IVIg should always be used as the first treatment option (unless contraindicated).<sup>11</sup>

One of the nineteen cases (5%) of CIDP identified in Iceland by Hafsteinsdottir and Olafsson (2016) was the pure motor presentation of the disease.<sup>23</sup> Expert feedback indicated that it was reasonable to assume approximately 5% of Australian CIDP patients have a pure motor form.<sup>1</sup>

The Reference Group noted it was appropriate to treat 'pure motor CIDP' and 'sensorimotor CIDP' as subgroups. However, given the limited evidence base, subgroup analysis should only be considered if it proves to be feasible.

#### IgG and IgA paraproteinemic demyelinating neuropathies

In the current Australian setting, IgG and IgA paraproteinemic demyelinating neuropathies (PDNs) are included as specific conditions within the broader CIDP category.

It has been documented that paraproteinemic neuropathy is a predominantly sensory, chronic neuropathy which, although similar to CIDP, presents with sensory impairment to a relatively greater degree.<sup>24</sup>

The 2010 EFNS/PNS guidelines on paraproteinemic demyelinating neuropathies note that a PDN is often indistinguishable from CIDP and that IgG or IgA PDN may be CIDP with a coincidental paraprotein.<sup>25</sup>

Cochrane reviews have considered treatment for patients with IgG and IgA paraproteinemic neuropathies separately to those with CIDP.<sup>7,24</sup> Expert advice is that treatment for IgG and IgA paraproteinemic neuropathies is the same as for CIDP.<sup>11</sup>

### **Intervention**

The intervention under review is Ig, which is used as an immunomodulation therapy in CIDP (Referral Form, page 2). It may be administered either intravenously (IVIg) or subcutaneously (SCIg).

In general, the overarching clinical goals when treating CIDP are to improve clinical symptoms (e.g., increase strength, decrease sensory loss), improve functional status (i.e., reduce disability) and where possible, achieve remission over the long-term.<sup>8</sup> This is achieved through the use of therapies which suppress the immune system to prevent further inflammation and demyelination of peripheral nerves and, moreover, to avoid secondary axonal degeneration.<sup>26</sup>

The EFNS/PNS guidelines guide the treatment of CIDP.<sup>5</sup> Steroids or IVIg are recommended as first-line treatment options for patients with moderate to severe disability (except for pure motor CIDP where only IVIg is recommended). IVIg is noted as the common first choice treatment as improvement can be fast. SCIg is not discussed in these guidelines; however, recent trials have considered its efficacy, tolerability and effectiveness in CIDP patients.<sup>27,28</sup>

In Australia version 3 of *the Criteria* classifies CIDP as a disease for which IVIg has high quality RCTs demonstrating benefit; IVIg is currently funded publicly for CIDP patients under certain circumstances.<sup>4</sup> IVIg forms a current part of standard care for CIDP patients in Australia. SCIg is considered a suitable alternative to IVIg (and approved for public funding) in certain medical conditions only, of which CIDP is not one.<sup>29</sup> SCIg does not currently form a part of standard care for

this condition in Australia; however, the Referrer has noted that a change is thought probable in the foreseeable future(Referral Form, page 4).

#### Overview of Ig use in Australia

Immunoglobulin is a blood product derived from donated human plasma.<sup>22</sup> It may be employed as either a replacement or immunomodulation therapy across many different disorders, including both antibody deficiencies and autoimmune diseases.

The reliance on donated human plasma may be a limiting factor in the supply of Ig. It is imperative to ensure that supplies are available for patients with the greatest clinical need and for whom there are no safe and effective alternative therapies.<sup>30</sup>

Immunoglobulin supplies in Australia are comprised of both domestic and imported products. CSL Behring Pty Ltd manufactures a domestic supply of Ig from plasma collected by the Australian Red Cross Blood Services (Referral Form page 4). Imported product supply arrangements exist with multiple suppliers (Referral Form page 4). The domestic demand for Ig has been steadily increasing faster than national plasma collections have been increasing. Thus, imports of Ig have had to increase to meet local demand.<sup>30</sup>

#### Immunoglobulin products approved for the treatment of CIDP

The Australian Register of Therapeutic Goods (ARTG) currently lists four Ig products for use in CIDP (Referral Form, page 29). These are Intragam® 10, Privigen® 10%, Hizentra® and Gamunex® 10% (Referral Form, Table 1, page 5). Flebogamma (10% and 5%) are funded by the NBA for use in CIDP however, they are not listed on the TGA for this indication (Referral Form, Table 1, page 5). Furthermore, the Reference Group indicated that Cuvitru should be included in Table 5.

Ig products available to patients in Australia for CIDP are summarised.

**Table 5 Available Ig products for use in CIDP (either TGA approved or NBA funded, or both)**

| Product name and company  | Route of administration | TGA indication for CIDP (y/n) | NBA funded for CIDP (y/n) | NBA price        |
|---|-------------------------|-------------------------------|---------------------------|------------------|
| Intragam® 10<br>CSL Behring Australia P/L<br>(2.5g/25mL to 20g/200mL)<br>DOMESTIC | IV                      | Yes                           | Yes                       | \$146 - \$1,170  |
| Privigen® 10%<br>CSL Behring Australia P/L<br>(5g/50mL to 40g/400mL)<br>IMPORTED  | IV                      | Yes                           | Yes                       | \$255 - \$1,800  |
| Hizentra®<br>CSL Behring Australia P/L<br>(1g/5mL to 10g/50mL)<br>IMPORTED        | SC                      | Yes                           | No*                       | \$57- \$574      |
| Gamunex® 10%<br>Grifols Australia P/L<br>IMPORTED                                 | IV and SC               | Yes                           | No                        | Not funded       |
| Flebogamma 10%**<br>Grifols<br>(5g/50mL – 20g/200mL)<br>IMPORTED                  | IV                      | No                            | Yes                       | \$23 - \$900     |
| Flebogamma 5%**<br>Grifols<br>(0.5g/10mL-20g/400mL)<br>IMPORTED                   | IV                      | No                            | Yes                       | \$225 - \$900    |
| Cuvitru 20%<br>Shire Australia Pty Ltd<br>(1g/5mL to 8g/40mL)                     | SC                      | No^                           | Not yet listed^^          | Not yet listed^^ |

Source: Adapted from Table 2, page 29 of the Referral Form.

**Abbreviations:** CIDP = Chronic inflammatory demyelinating polyneuropathy, IV = Intravenous, NBA = National Blood Authority, SC = Subcutaneous, TGA = Therapeutic Goods Administration.

**Notes:** \* While Hizentra is funded under the National Blood Arrangements for other indications, it is not funded for CIDP. It can be accessed directly from the supplier at the NBA negotiated price if alternative funding can be found (Referral Form, page 29).

\*\* Not listed on the TGA for CIDP. NBA provides these products for CIDP; however, they are not publicly funded.

^ CIDP is not an included indication on either the public ARTG summary or the product information (PI) sheet.<sup>31</sup>

^^ The Reference Group noted that Cuvitru should be added; however, it does not yet appear on the NBA National Product List (as of 1<sup>st</sup> January 2019).<sup>32</sup>

### Current use of Ig for CIDP in Australia (IVIg only)

Expert opinion sought during the drafting of this PICO Confirmation confirmed that IVIg is often a first choice treatment option for patients with moderate to severe CIDP in Australia.<sup>11</sup> As a first-line option, it may be either:

- Trialled alone and if a patient does not respond, stopped and an alternate treatment trialled (e.g., corticosteroids +/- an immunosuppressant drug).<sup>11</sup>

- Used together with, or in rapid sequence with, steroids (where steroids are not contraindicated).<sup>1</sup>

To ensure that only patients achieving a clinical benefit from the use of IVIg consume this resource, version 3 of *the Criteria* specifies certain review criteria that must be met both after an initial trial period and at regular intervals for patients on long-term treatment.<sup>4</sup> In brief, these are:

- An initial review (by a neurologist) is required after 4 months of therapy to determine whether a patient has responded.
- Ongoing reviews (by a neurologist or a general physician) are required annually – clinical effectiveness must be demonstrated for continuation of IVIg therapy.

In accordance with the above described review criteria, authorisation periods for IVIg use are restricted. As specified in version 3 of *the Criteria*, current authorisation periods are:

- Initial authorisation period (max.): 4 months
- Continuing authorisation period (max): 12 months

It is possible for a CIDP patient to be non-responsive to IVIg therapy. Moreover, it is possible for a patient to be misdiagnosed with CIDP or to receive Ig where a neurologist confirms CIDP is probable or possible. Reducing the sustained use of Ig in misdiagnosed patients, or for possible or probable cases CIDP cases, is a key rationale for including a short initial authorisation period.<sup>1</sup>

It is possible for a patient to reach a period of stability at which time a treating physician is encouraged to consider whether the patient continues to need IVIg therapy. Version 3 of *the Criteria* explicitly states that a trial of cessation should be considered at each annual follow-up visit in patients in remission on maintenance therapy.<sup>4</sup>

The review criteria currently applicable in the Australian context are outlined in greater detail in Table 6 and Table 7.

**Table 6 Currently applicable review criteria for initial IVIg therapy in CIDP patients**

|  |
|--|
| <p><b>Initial Review Criteria</b><br/> <i>i.e., on review by a neurologist after initial 4 months of treatment.</i></p>  |
| <p>On review of the initial authorisation period, clinical effectiveness of Ig therapy may be demonstrated by:<br/>           For adults or children 10 years or older</p> <ul style="list-style-type: none"> <li>Improvement in disability as measured by a reduction in adjusted ONLS by at least one point <b>or</b> by an increase in the MRC sum score by at least 3 points as compared to the qualifying assessment.</li> </ul> <p><b>OR</b></p> <p>For children less than 10 years</p> <ul style="list-style-type: none"> <li>Improvement in disability as measured by the 6MWT <b>and/or</b> the MRS as compared to the qualifying assessment</li> </ul>   |
| <p><b>Ongoing Review Criteria</b><br/> <i>i.e., on review by a neurologist or general physician every 12 months</i></p>  |
| <p>On review of a continuing authorisation period, clinical effectiveness of Ig therapy may be demonstrated by:<br/>           For adults or children 10 years or older</p> <ul style="list-style-type: none"> <li>Stabilisation or continued improvement in disease as measured by the ONLS <b>or</b> the MRC sum score compared to the previous review score.</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>For an adult patient with severe disease who continues to report post-infusion improvement that is better or comparable to the level reported at the previous review, with end-of-cycle deterioration and additional immunosuppressant agents having been commenced.</li> </ul> <p><b>OR</b></p> <p>For children less than 10 years</p> <ul style="list-style-type: none"> <li>Stabilisation or continued improvement in disease after previous evidence of deterioration in the 6MWT <b>or</b> the MRS compared to the previous review scores.</li> </ul> <p><b>AND</b></p> <p>A trial of weaning towards cessation of Ig therapy is planned for clinically stable patients to identify those in remission, or a valid reason as to why a trial is not planned or is contraindicated at this time is provided.<br/>           A trial of Ig weaning should be considered annually in stable patients on maintenance therapy to identify patients who are in remission.</p> |

**Source:** Adapted from Box 2a, pages 32-33 of the Referral Form. Information originally sourced from the Criteria for the Clinical Use of Immunoglobulin in Australia, available online.<sup>4</sup>

**Abbreviations:** MRC = Medical Research Council, ONLS = Overall Neuropathy Limitations Scale; 6MWT = Six-minute walking test, MRS = Modified Rankin Scale.

**Table 7 Currently applicable review criteria in CIDP patients returning to treatment following a relapse within six months of ceasing Ig therapy**

|  |
|--|
| <p><b>Initial Review Criteria</b><br/><i>i.e., on review by a neurologist after initial 4 months of treatment.</i></p> <p>On review of the initial authorisation period, clinical effectiveness of Ig therapy may be demonstrated by:<br/>For adults or children 10 years or older</p> <ul style="list-style-type: none"> <li>• Improvement in disability as measured by a decrease of at least one point in the adjusted ONLS <b>or</b> by an increase of at least 3 points in the MRC sum score</li> </ul> <p>For children less than 10 years</p> <ul style="list-style-type: none"> <li>• Improvement in disability as measured by the 6MWT, <b>or</b> a reduction of at least one point in the MRS score</li> </ul> <p><b>AND</b><br/>A trial of weaning towards cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not being planned or is contraindicated at this time</p>   |
| <p><b>Ongoing Review Criteria</b><br/><i>i.e., on review by a neurologist or general physician every 12 months</i></p> <p>On review of a continuing authorisation period, clinical effectiveness of Ig therapy may be demonstrated by:<br/>For adults or children 10 years or older</p> <ul style="list-style-type: none"> <li>• Stabilisation or continued improvement in disease as measured by ONLS score, <b>or</b> the MRC sum score, as compared to the previous assessment</li> <li>• For an adult patient with severe disease who continues to report post-infusion improvement that is better or comparable to the level reported at the previous review, with end-of-cycle deterioration and additional immunosuppressant agents have been commenced.</li> </ul> <p>For children less than 10 years</p> <ul style="list-style-type: none"> <li>• Stabilisation or continued improvement in disease after previous evidence of deterioration in the 6MWT <b>or</b> the MRS score</li> </ul> <p><b>AND</b><br/>A trial of weaning towards cessation of Ig therapy is planned for patients who are clinically stable to identify those in remission or a valid reason provided as to why a trial is not planned or is contraindicated at this time.<br/>Once a patient has relapsed in the first six months of a trial off therapy, a further trial might be considered after at least two years.</p> |

**Source:** Adapted from Box 2b, pages 33-35 of the Referral Form. Information originally sourced from the Criteria for the Clinical Use of Immunoglobulin in Australia, available online.<sup>4</sup>

**Abbreviations:** MRC = Medical Research Council, ONLS = Overall Neuropathy Limitations Scale, 6MWT = Six-minute walking test, MRS = Modified Rankin Scale.

### Dosage and frequency

The IVIg dose range that is permissible under governance arrangements is specified in version 3 of *the Criteria* for both patients commencing initial Ig treatment and patients who have relapsed within six months of a trial off therapy.<sup>4</sup> The dose range that may be prescribed across these two patient groups are the same and are outlined in Table 8. Under the National Policy, clinicians are expected to apply appropriate clinical judgement and use the lowest effective dose that will achieve the appropriate clinical outcome for each patient.

**Table 8 Current effective dosage ranges that may be prescribed for IVIg in CIDP patients in Australia**

|  |
|--|
| <b>Induction dose:</b>   |
| <b>2g/kg</b> in 2 to 5 divided doses (access to a second initial dose should be a rare occurrence) |
| <b>Maintenance dose:</b>   |

#### Induction dose:

Up to **0.4 to 1g/kg**, once every **2 to 6 weeks**. The amount per dose should be titrated to the individual's response and may be reduced while weaning. **A maximum dose of 2g/kg may be given in any 4-week period.** This may be a smaller dose more frequently than fortnightly.

*The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.*

*Once a patient has relapsed when trialled off therapy, a second-line immunomodulatory agent should be strongly considered as an additional therapy*

**Source:** Adapted directly from the Criteria for the Clinical Use of Immunoglobulin in Australia (version 3), available online.<sup>4</sup>

#### Time for infusion

The time required to administer IVIg is patient-dependent. Infusion could occur in a single day or less. For a large dose, administration may be split over consecutive days (Referral Form page 29).

The time required will depend upon the dose required, the patient's weight (dosing is g/kg), the product's advised infusion rate along with the hospital protocol and the patient's response during the infusion (as infusion may be slowed or stopped in the event of an adverse event) (Referral Form, page 29)

#### Setting

The infusion of IVIg may occur in one of many settings (Referral Form, page 31):

- Inpatient private hospital
- Inpatient public hospital (as a private patient)
- Inpatient public hospital (as a public patient)
- Outpatient clinic
- Private same-day infusion facilities, unattached to a hospital

Most patients (approximately 75%), have IVIg delivered in a hospital setting as a day procedure. Expert opinion provided by the Referrer indicated the most common setting for IVIg delivery is the public outpatient setting however it was noted that patients are commonly admitted as a 'same-day' patient (i.e., are considered inpatients). (Referral Form, page 31).

Despite IVIg being an existing therapy for CIDP patients, information regarding patient admission status (public or private; inpatient or outpatient) is not readily available based on publicly available data but the NBA might be able to provide a breakdown of public versus private use (Referral Form, page 31).

#### Personnel and additional services required

Care of a CIDP patient is primarily managed by a neurologist (or possibly, in a regional or rural area, a general physician). (Referral Form, page 30). To be eligible to access IVIg under governance arrangements initially, a registered neurologist must diagnose CIDP in the patient. The review of initial treatment must be undertaken by a neurologist, however the review of continuing treatment may be undertaken by a registered neurologist or general physician (Referral Form, page 31).

IVIg infusion is, generally, initiated by a registered nurse. A patient must be monitored throughout the infusion by a registered or enrolled nurse. On rare occasions, IVIg may be administered by a 'hospital in the home' nurse (Referral Form, page 30).

Analgesia or antihistamines may be required to manage reactions such as headaches, flushes or rashes (Referral Form, page 30).

#### Contraindications

Contraindications to IVIg include absolute IgA deficiency and allergy/anaphylactic response to human immunoglobulins.<sup>8</sup>

#### Length of Ig therapy

It is possible for a CIDP patient being treated with IVIg to achieve remission while on therapy; indeed, this is one of the long-term goals of treatment.<sup>8</sup> However, 75% of neurologists taking part in a recent French study believed that it was common for CIDP patients to require lifetime treatment.<sup>33</sup> Expert advice indicated that remission rate is an important comparative issue between IVIg and corticosteroids (possibly higher in corticosteroids) and moreover, that it remains unclear whether remission rate with IVIg is higher than the natural history remission rate.<sup>1</sup>

Nonetheless, as it is possible for patients to achieve remission, a trial of cessation is recommended in version 3 of *the Criteria* to ascertain remission status. When followed, this recommendation may limit treatment duration to a period during which Ig has a clinical benefit.

However, it cannot be assumed that this recommendation is adequately reflected in clinical practice. It is possible that a trial of cessation is not, or not timely, undertaken and that patients receive ongoing IVIg therapy after remission is achieved (identified as a potential issue by the Referrer, Referral Form, page 45 and the clinical expert consulted for this PICO confirmation<sup>11</sup>).

#### Current usage figures

The National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16 released by the NBA further provides an overview of the weight (in grams) of IVIg used to treat CIDP.<sup>22</sup> Nationwide figures for the years 2011-12 through to 2015-16 and state/territory specific figures for the year 2015-16 are presented in

Table 9 and Table 10.

**Table 9 Australia-wide usage of IVIg (in grams) between 2011-12 and 2015-16**

|                           | 2011-12  | 2012-13  | 2013-14  | 2014-15  | 2015-16    |
|---------------------------|----------|----------|----------|----------|------------|
| Total patient number      | 1,551    | 1,753    | 1,903    | 2,054    | 2,250      |
| Total grams (g)           | 677,458g | 758,271g | 857,533g | 974,258g | 1,071,135g |
| Ave grams per patient (g) | 437g     | 433g     | 451g     | 474g     | 476g       |

**Source:** Adapted from Table provided by the Referrer, pages 44-45 of the Referral Form. Information was originally sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16 published by the National Blood Authority.<sup>22</sup>, or estimated from this data by the Referrer (average gram per patient estimate only).

**Note:** rounding errors were corrected as appropriate.

**Table 10 IVIg usage (in grams) by each state/territory, 2015-16**

| State                          | NSW     | VIC     | QLD     | WA      | SA     | TAS    | ACT   | NT    | National  | Fold Variation |
|--------------------------------|---------|---------|---------|---------|--------|--------|-------|-------|-----------|----------------|
| Patients                       | 834     | 507     | 648     | 130     | 93     | 36     | 32    | 15    | 2,250     |                |
| Total grams (g)                | 363,767 | 248,735 | 277,894 | 104,920 | 40,008 | 19,413 | 9,843 | 6,557 | 1,071,135 |                |
| Grams/episode (g)              | 39      | 38      | 34      | 64      | 45     | 39     | 32    | 42    | 39        |                |
| Grams/patient (g)              | 436     | 491     | 429     | 807     | 430    | 539    | 308   | 437   | 476       |                |
| Grams per 1,000 population (g) | 47      | 41      | 58      | 40      | 23     | 38     | 25    | 27    | 45        | 2.5            |

**Source:** Adapted from Table provided by the Referrer, page 45 of the Referral Form. Information was originally sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16 published by the National Blood Authority.<sup>22</sup> or estimated from this data by the Referrer (grams per patient estimate only).

**Note:** Fold variation calculated by dividing the largest grams/1,000 population by the smallest g/1,000 population using only data from the five largest states (NSW, VIC, QLD, WA and SA). This figure was corrected based on what was provided in the original source.

### Overview of SCIg

#### Dosage and frequency

For SCIg, more frequent infusions (usually twice weekly) are required (Referral Form, page 28).

Unlike for IVIg, version 3 of *the Criteria* provides no current dose range for SCIg, and its use as a treatment for CIDP is not yet funded by the NBA. SCIg dosing is not considered in the current EFNS/PNS guidelines.

Clinical trials have been undertaken in CIDP populations and report the following Ig regimens:

- Van Shaik et al. (2018) compared two alternate dosing regimens to placebo – 0.2g/kg per week or 0.4g/kg per week given weekly over one or two consecutive days in two sessions for 24 weeks.<sup>27</sup> They concluded that both were efficacious and well-tolerated as a maintenance therapy for CIDP patients.

- Markvardsen et al. (2017) compared SCIg at a dose of 0.4g/kg/week given as 2 to 3 infusions per week for 5 weeks to IVIg given at a dose of 2g/kg as 0.4g/kg/day doses given over 5 consecutive days.<sup>28</sup>

### Setting

SCIg would be delivered in a patient's home. (Referral Form, page 32).

### Personnel and additional services required

When administered subcutaneously, the responsibility of administration is delegated to a patient or carer (Referral Form, page 30). The patient or carer is trained how to administer the SCIg by a qualified nurse or technician and ongoing support is provided by a registered nurse (Referral Form, pages 30-31). SCIg would only be available where a patient is treated in a hospital participating in the National SCIg Program and can meet the governing requirements for a hospital-based SCIg program..

### Rationale

Currently in Australia, Ig for use in CIDP is only funded by the NBA where the intravenous route of administration is used.

The nature of administration varies considerably depending on whether an intravenous or a subcutaneous route is used (an overview of SCIg is provided below). Differences in response rates, health outcomes such as adverse events, improvement in disability and venous damage and health resource consumption (i.e., costs) between IVIg and SCIg are possible (Referral Form, page 4).

The Reference Group advised that a head to head comparison of SCIg and IVIg is not necessary noting that the differential budget impact of SCIg and IVIg should be considered.

### **Comparator**

In consultation with the Reference Group, the following comparative treatments for CIDP patients have been identified:

1. Corticosteroids
2. Plasma exchange
3. Immunosuppressant and immunomodulatory drugs and therapies (not including corticosteroids)
4. Combinations of two or more of the above therapies, or
5. No treatment.

Expert opinion noted that immunosuppressant and immunomodulatory drugs and therapies are an add on to corticosteroids rather than an independent comparator.<sup>1,11</sup> The Reference Group noted that it was important to consider any evidence comparing Ig directly against non-steroid immunosuppressants. They also acknowledged the value in searching for evidence comparing Ig to combination therapies.

The comparators may be used either independently of, or in combination with, the intervention, immunoglobulin. The approach taken varies between practitioners with some rarely using Ig in combination with any of the comparators while others consider Ig and corticosteroids in combination as relatively common.<sup>1,11</sup> The Reference Group noted that the combined use of Ig and corticosteroids was relevant.

### Corticosteroids

Corticosteroids are a first-line treatment for CIDP,<sup>34</sup> it is estimated that 50 per cent of Australian patients not receiving Ig therapy will receive corticosteroids (Referral Form page 34). The class of steroid used for treatment of CIDP is the glucocorticoids which are known to inhibit immune responses and have an anti-inflammatory effect.<sup>35</sup> Four glucocorticoids; prednisone, prednisolone, dexamethasone and methylprednisolone have been listed as relevant to this Referral (page 34) all of which are listed on the Pharmaceutical Benefits Scheme (PBS) (Table 11, reproduced from Referral Form pages 35-37).

**Table 11 Corticosteroids listed on the PBS and subsidised for CIDP**

| Generic name  | PBS subsidised for CIDP | PBS restriction | PBS item numbers  |
|---|-------------------------|-----------------|---|
| Prednisone<br>(brand names: Panafcort, Sone)  | Yes                     | Unrestricted    | 1936X (25 mg tablet, 30)<br>1935W (5 mg tablet, 60)<br>1934T (1 mg tablet, 100)   |
| Prednisolone (brand names: Panafcortelone, Solone)  | Yes                     | Unrestricted    | 1916W (25 mg tablet, 30)<br>1917X (5 mg tablet, 60)<br>3152X (1 mg tablet, 100)   |
| Dexamethasone<br>(brand names: Dexamethasone Mylan, Dexamethsone)                           | Yes                     | Unrestricted    | 2507Y (4 mg tablet, 30)<br>1292B (0.5 mg tablet, 50)  |
| Methylprednisolone<br>(brand names: SoluMedrol, Methylpred, Methylprednisolone, Alphapharm) | Yes                     | Unrestricted    | 1928L (40 mg/mL injection, 5 x 1 mL vials)<br>2981X (40 mg injection, 5 vials and inert diluent)<br>5148Y (40 mg/mL injection, 5 x 1 mL vials)<br>5263B (40 mg powder for injection, 5)<br>5264C (1000 mg powder for injection) |

**Source:** Reproduced from Referral Form pages 38 and 39. Original source: PBS website.<sup>36</sup>

**Abbreviations:** CIDP = Chronic inflammatory demyelinating polyneuropathy; PBS = Pharmaceutical Benefits Scheme.

Corticosteroids have been used to treat CIDP for more than 40 years;<sup>37</sup> however, their use is not supported by large scale clinical trials and there is a lack of consensus in the optimum dosing regimen.<sup>8,37</sup> No information on dosing was reported in the Referral Form and expert advice is that no standard dosing regimen exists.<sup>11</sup> An example of a steroid prescription of CIDP in Australia would likely involve initial high doses ( e.g., prednisone at 40 mg per day for two months) with a gradual reduction in dose until the minimum effective dose is reached.<sup>11</sup> Alternate dosing regimens are

reported in the literature: for example; van Lieverloo et al. (2018) detail three regimens; daily oral prednisone or prednisolone (1-1.5 mg/kg for 6 weeks, tapering to zero over at least 8 months); oral pulsed dexamethasone (40 mg per day for 4 consecutive days per month for 6 months); or, IV pulsed methylprednisolone (500 mg per day for 4 days followed by 1-2 g per month for at least 2 months).<sup>38</sup>

Long-term use of corticosteroids is associated with a number of potentially serious side effects including metabolic changes, increased susceptibility to infection, hypertension and impaired wound healing.<sup>8</sup> Due to these effects, corticosteroids are therefore poorly suited to long-term continuous therapy; hence the requirement for dose tapering and the development of pulse regimens. Expert advice is that, in Australia, corticosteroids are used in conjunction with steroid-sparing therapy in the form of immunosuppressants.<sup>11</sup> The types of immunosuppressants used in Australia are discussed below.

Corticosteroids are, generally, not a suitable treatment strategy for patients who have a pure motor form of CIDP (muscle weakness with no sensory loss), although there may be exceptions.<sup>1, 11, 39</sup>

Expert advice indicated that in the absence of Ig, a first-line treatment for patients with pure motor CIDP may be plasma exchange.<sup>1</sup>

### Plasma exchange

The Referral Form (page 37) states that plasma exchange is the next most common comparator treatment for CIDP (following corticosteroids); with the clinical pathways on page 42 of the Referral Form specifying that this would be a short/medium term treatment. Plasma exchange involves the removal and centrifuge or filtering of a patient's blood. The red blood cells are reinfused, and the plasma is replaced with a plasma substitute (usually saline with human albumin).<sup>40</sup> The beneficial effect of plasma exchange is purported to be due to the removal of humoral factors, such as immunoglobulins, autoantibodies and pro-inflammatory cytokines.<sup>8</sup> Plasma exchange has been reported as a treatment for CIDP since the 1970s.<sup>41</sup>

A single exchange removes three to five litres of plasma and reduces IgG levels by 45 per cent. Between three and five exchanges are required to reduce IgG by 90 per cent.<sup>8</sup> The American Society for Apheresis guidelines recommend 1 to 1.5 total plasma volume (TPV) exchanges two to three times per week until improvement; with tapering of the exchange schedule as tolerated.<sup>42</sup> Guidelines from the American Academy of Neurology and the European Federation of Neurological Societies/Peripheral Nerve Society do not recommend any particular exchange schedule.<sup>5, 12, 43</sup> Other exchange schedules have been reported, for example Gorson et al. (2012) state patients with severe CIDP may be treated with five exchanges over 7 to 10 days; while patients with moderate CIDP may receive two to three exchanges over two to three weeks, followed by one to two weekly exchanges for a further three weeks.<sup>8</sup> For both groups, plasma exchange should be repeated as necessary to maintain improvement. The addition of corticosteroids or other immunosuppressants may increase the duration between required exchanges.<sup>8</sup>

Plasma exchange requires adequate venous access for the collection and return of fluids; inadequate blood flow may result in longer procedure times and procedure cessation before the target plasma

exchange volume has been reached.<sup>44</sup> To achieve adequate venous access, patients may have large-bore peripheral cannulation or insertion of a central venous catheter. For longer-term treatment, such as required for CIDP patients, implantation of an arteriovenous fistulae (a surgically created connection between an artery and a vein) may be the most appropriate option.<sup>44, 45</sup> The Referral Form notes that MBS item 13750 is available for therapeutic haemapheresis, and MBS items 34112 (updated to correct item number) and 34121 are available for arteriovenous fistula creation and that the NBA does not fund any procedure required for plasma exchange. Expert advice identified that plasma exchange requires volume replacement, most commonly with albumin, which is provided and paid for by the NBA.<sup>1</sup>

Expert advice is that plasma exchange is only provided in major teaching hospitals and therefore is now only used in Australia for patients who do not respond to first-line treatments (IVIg or corticosteroids). The risks of plasma exchange are substantially different if done via a central catheter (greater risk of infection) or via peripheral vascular access (less risk).

There is no standardised plasma exchange schedule in Australia; however, expert advice suggested that five exchanges trialed over 7 to 11 days would be the most common approach. Plasma exchange may be administered in either an outpatient, day stay, or inpatient setting.<sup>1</sup>

In the absence of Ig therapy as many patients as currently receive IVIg could, in theory, be treated with plasma exchange instead although, this is difficult to predict. Moreover, such a large uptake of plasma exchange could not occur without substantial changes to the current supply.

Expert opinion suggested that while some patients may receive long-term plasma exchange; this would most commonly be provided in combination with an immunosuppressant.<sup>1</sup>

#### Immunosuppressants (other than corticosteroids)

Immunosuppressive drugs have been used successfully as treatments for other autoimmune conditions; leading to their investigation as a treatment for CIDP.<sup>46</sup>

The Referral Form lists nine immunosuppressants as being relevant to this application (Table 12, adapted from the Referral Form pages 37 to 40). Expert advice is that mycophenolate (or azathioprine) would be used as second-line immunosuppressant therapies.<sup>1</sup> Fingolomad (Gilenya) and Rituximab (Mabthera) are not PBS subsidised for CIDP and are listed as “authority required, CIDP not included.” Fingolomad (Gilenya) is not approved for CIDP and expert advice is that it is unlikely that anyone still receives this treatment for CIDP. Rituximab (Mabthera) is however commonly used for CIDP when patients have failed other immunosuppressant therapy, with the cost often being borne by hospital drug committees.<sup>1</sup>

No standardised dosing regimen was reported in the Referral Form; varying dosages have been reported in the literature (reproduced in Table 12).<sup>46</sup>

**Table 12 Immunosuppressants listed on the PBS and subsidised for CIDP treatment**

| Generic name   | PBS restriction  | PBS item numbers  | Dosage information  |
|--|--|---|---|
| Azathioprine<br>(Brand names: APO-Azathioprine, Azathioprine GH, Azathioprine Sandoz, Imuran)  | Unrestricted   | 2688L (25 mg tablet, 200)   | 3 mg/kg/day or 100-200 mg/day   |
| Ciclosporin<br>(Brand names: Neoral (25, 50 or 100), Cyclosporin Sandoz)   | Unrestricted for General Schedule listings only (S100 CIDP not included)                     | 8657P (10 mg capsule, 60)<br>8659Q (25 mg capsule, 30)<br>8659Q (50mg capsule, 30)  | 10 mg/kg/day tapering to 2 mg/kg/day beyond 3 months or 3-5 mg/kg/day or 100-300 mg/day |
| Cyclophosphamide<br>(Cyclonex, Endoxan)  | Unrestricted   | 1266P (50 mg tablet, 50)<br>4327R (injection, 2,800 mg)<br>7226H (injection, 2,800 mg)  | 2-4 mg/kg/day or 50-100 mg/day or 200 mg/kg/day (for 4 days) or 1g/m2/month             |
| Fingolimod*<br>(Brand names: Gilenya)  | Authority required and CIDP not included   | N/A   | NR  |
| Methotrexate**<br>(Brand names: Methoblastin, Methotrexate Accord, Hospira, Methotrexate Ebewe, Pfizer Australia)  | Unrestricted   | 1622J (2.5 mg tablet, 30)<br>2272N (10 mg tablet, 15)<br>1623K (10 mg tablet, 50)<br>1818Q (injection, 50 mg in 2 mL)<br>2396D (injection, 50 mg in 2 mL)<br>2395C (injection, 50 mg in 2 mL)<br>4502Y (injection 1 g/10 mL, 500 mg/20 mL, 5 mg/2 mL, 1 g/10 mL, 50 mg/2 mL, 5 g/50 mL, 1 g/10 mL)<br>7250N (injection 1 g/10 mL, 500 mg/20 mL, 5 mg/2 mL, 50 mg/2 mL, 1 g/10 mL, 5 g/50 mL, 1 g/10 mL) | NR  |
| Mycophenolate mofetil**<br>Brand names: Ceptolate, Myfortic, APO-Mycophenolate, CellCept, Mycophenolate Sandoz, Pharmacor<br>Mycophenolate (AN, 250, 500), | Unrestricted for General Schedule listings only (S100 CIDP not included)                     | 8651H (powder for oral liquid, 1 g/5 mL)<br>1836P (capsule, 250 mg, 50)<br>2150E (enteric tablet, 180 or 360 mg, 120)<br>8649F (capsule, 250 mg, 100)<br>8650G (Tablet, 500 mg, 50)   | 1 g twice daily or 1-2 g/day  |
| Rituximab*<br>(Mabthera)   | Authority required and CIDP not included   | N/A   | 375 mg/m <sup>2</sup> /week or 900 mg/week or 700 mg/3 weeks, or 1 g/2 weeks            |
| Tacrolimus<br>(brand names: ADVAGRAF XL, Prograf, Tacrolimus Sandoz, Pacrolim, Pharmacor<br>Tacrolimus, Tacrograf, TACROLIMUS APOTEX)                      | Unrestricted for General Schedule listings only (S100 authority required, CIDP not included) | 5300Y (MR capsule, 1 mg, 60)<br>10870D (capsule, 0.75 mg, 100)<br>5451X (MR capsule, 5 mg, 30)<br>8647D (capsule, 1 mg, 100)<br>10871E (capsule, 2 mg, 100)<br>8646C (capsule, 0.5 mg, 100)<br>8648E (capsule, 5 mg, 20)<br>5299X (MR capsule, 0.5 mg, 30)  | NR  |

**Source:** Adapted from pages 39 and 40 for the Referral Form; original source: PBS website<sup>36</sup> Dosage information from Mahdi-Rogers et al. (2017)<sup>46</sup>

**Note:** \* = not PBS subsidised for CIDP; \*\* only formulations that could be funded for CIDP included (i.e., where no authority required or where authority includes CIDP patients)

**Abbreviations:** CIDP = Chronic inflammatory demyelinating polyneuropathy, MR = Modified release, NA = Not applicable, NR = Not reported, PBS = Pharmaceutical Benefits Scheme.

The Referral Form (page 38) notes that, in addition to the treatments listed in Table 12, Alemtuzumab and tacrolimus (with cyclosporin) are also used for CIDP; however, their use is rare and only when other therapies are unsuitable or unavailable. Similarly, autologous transplant; involving the harvesting of a patient's own bone marrow stem cells followed by immune system ablation and reconstitution with the stored stem cells, is a rarely used treatment for CIDP. Expert opinion suggested that these do not need be included as comparators in the review given their rarity.<sup>1</sup>

Expert advice is that immunosuppressants are not used in Australia as a stand-alone treatment for CIDP; rather they are initiated alongside corticosteroids (although they may be continued following tapering of steroid dosage). This is reportedly due to the long onset period before immunosuppressants provide effective therapy against CIDP in comparison to the short mode of action associated with corticosteroids.<sup>11</sup> Nonetheless, the Reference Group noted that any information comparing Ig directly against non-steroid immunosuppressants would be of interest and should be included in the review.

#### No treatment

In addition to the above listed active comparators, the review should also investigate the comparison between Ig and no treatment (No Ig-controlled trials).

#### Rationale

The Referral Form lists Etanercept and Interferons as comparator treatments which are excluded from the review as they have an established lack of efficacy for CIDP (Referral Form page 38).

The Referral Form lists Fc receptor (FcRn) inhibitors as a potentially emerging treatment for CIDP. FcRn inhibitors are monoclonal antibodies that inhibit the FcRn responsible for recycling IgG and keeping IgG circulating. Inhibition of FcRn is therefore hypothesised to lower IgG levels.<sup>47</sup> A targeted search of the literature found that does not yet appear to be trialled as a treatment for CIDP.

## Outcomes

The outcomes identified by the Referrer (Referral Form, page 43) are as follows:

### Patient relevant

***The outcomes listed are those identified in the development of the PICO. Additional or more specific outcomes identified during the evaluation process that are considered relevant to the intervention or comparator treatment may be addressed in the evaluation report (Contracted Assessment). Broadly the outcomes identified pre assessment and considered in scope are:***

#### *Safety outcomes:*

- Adverse events including development of disease or side effects (e.g. infections, diabetes, hypertension, cardiovascular disease)

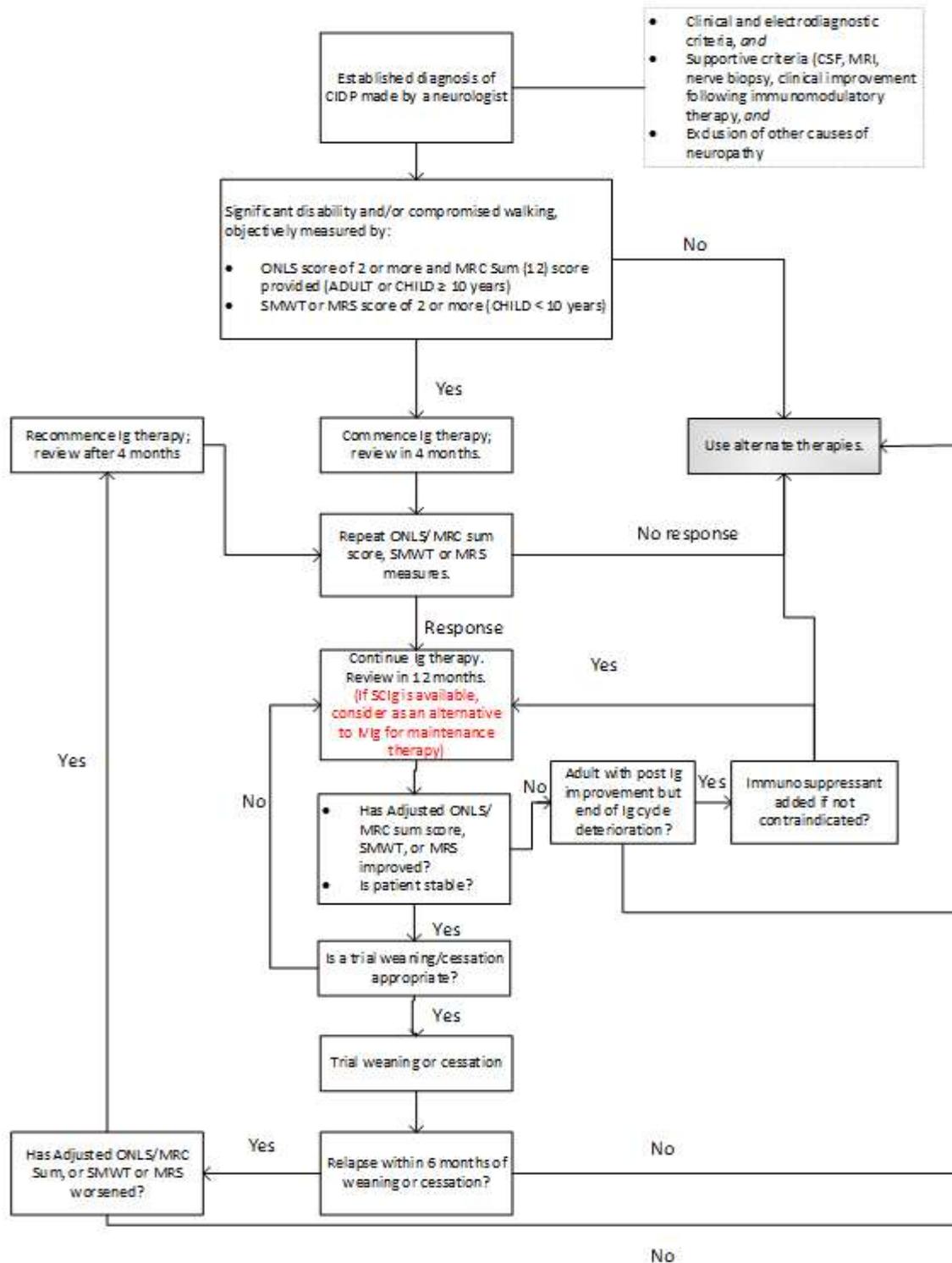
#### *Clinical effectiveness outcomes:*

- Change in disability: (e.g. Overall Neuropathy Limitations Scale (ONLS) score, Six-Minute Walk Test (6MWT) in children only)
- Change in muscle strength (e.g. Medical Research Council (MRC) Sum (12) in adults, Modified Rankin Scale (MRS) in children)
- Change in quality of life
- Mortality

#### *Healthcare system resources utilisation*

- Changes in health system resource utilisation associated with the intervention
  - Ig products
  - Infusion equipment
  - Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig)
  - Nursing time (for initiation and monitoring if IVIg)
  - Hospitalisation (including use of hospital resources)
  - Medication to treat of adverse events (e.g. analgesia or antihistamines)
  - Training of patient or carer to provide infusions (SCIg only)
  - Product dispensing and disposal of any unused product
  - Follow-up and/or monitoring visits, including regular neurology visits
- Change in health system resource utilisation associated with the comparators
  - Comparator products
  - Resources to deliver the comparator (eg hospital and staff time for IV steroids and plasma exchange, dispensing for oral treatments)
  - Hospitalisation
  - Treatment of adverse events
  - Follow-up and/or monitoring visits, including regular neurology visits

## Current clinical management algorithm when IVIg is used



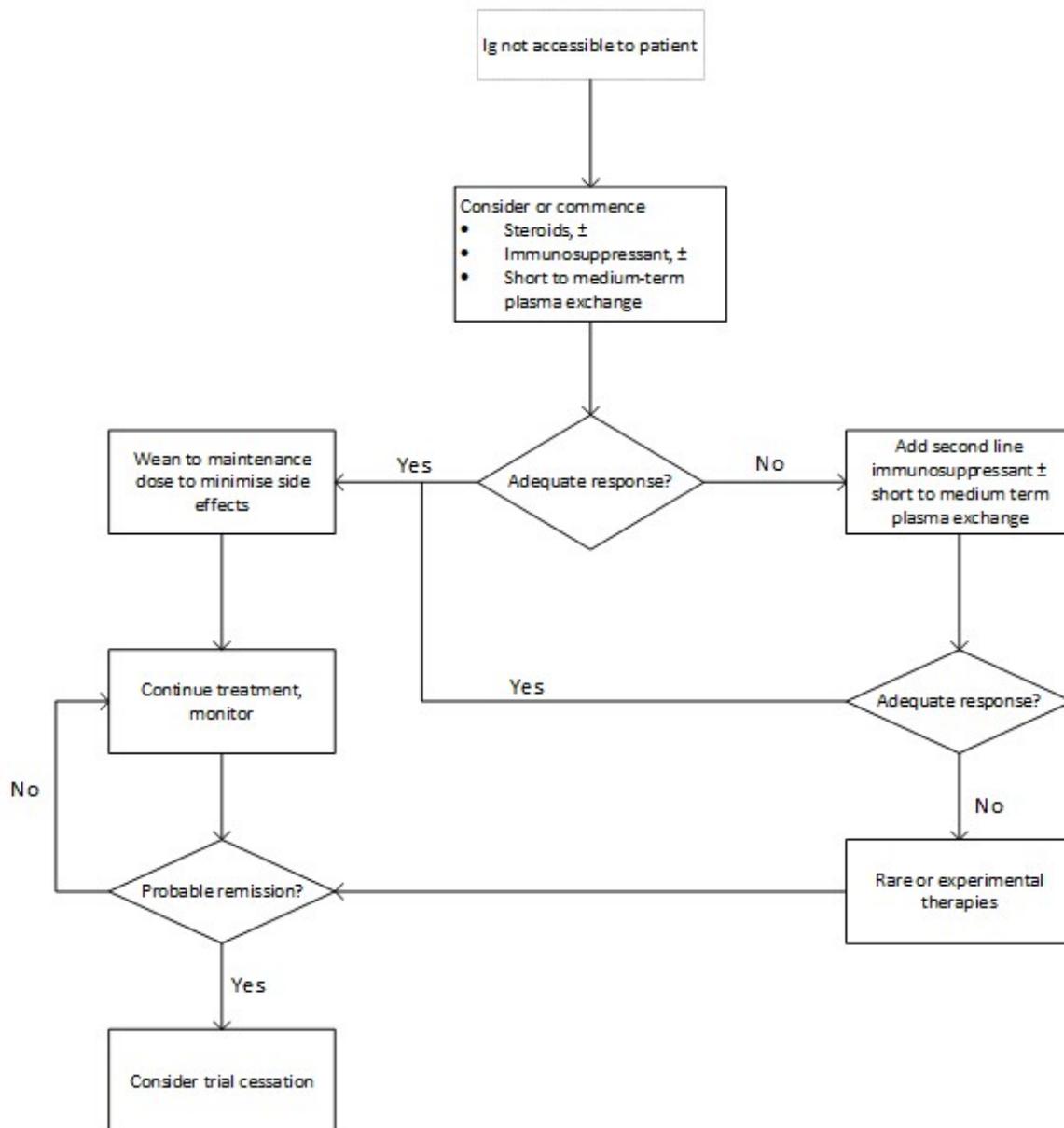
**Source:** Reproduced from Figure 1, page 28 and Figure 2, page 36 of the Referral Form.

**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

### Clinical management algorithm when IVIg is not a treatment option

Note: this algorithm may also be applicable for any patient not/no longer eligible for IVIg under version 3 of the *Criteria* (i.e., reach 'use alternate therapies' stage on **Error! Reference source not found.**), or for patients in whom IVIg is contraindicated.

Figure 1 Proposed algorithm for treatment of patients in the absence (or failure) of Ig



Source: Reproduced from Figure 3 page 42 of the Referral Form.

Abbreviations: Ig = Immunoglobulin.

## Proposed economic evaluation

Ig is claimed to have superior safety and non-inferior effectiveness. The basis of this claim is two small, short-term clinical trials which compared Ig to prednisolone and plasma exchange.<sup>50, 51</sup> In addition, the Referrer notes that (Referral Form, pages 42-43):

- Ig and plasma exchange both require venous access; however, longer-term plasma exchange may require more permanent venous access, increasing the risk of adverse events.
- Long-term steroid use poses many potential risks including the development of disease (e.g., hypertension, cardiovascular disease) and metabolic changes.
- Adverse events associated with IVIg are often associated with the rate of infusion, which can be slowed as required.

Assuming non-inferior effectiveness and superior safety, a cost effectiveness or cost-utility analysis will be required.

**Table 13 Decision algorithm for undertaking an economic evaluation in the setting of the Ig Review.**

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

**Source: Table produced by Adelaide Health Technology Assessment (AHTA) and included with permission on Reference Group advice.**

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

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

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

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

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

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

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

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