Immunoglobulin for chronic Inflammatory Demyelinating Polyneuropathy

November 2019

MSAC application no. 1564

Assessment report

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**ISSN (Online) 1443-7139**

**Internet site** http://www.msac.gov.au/

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

**MSAC’s advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.**

This report was prepared by Research and Evaluation, incorporating ASERNIP-S of the Royal Australasian College of Surgeons. Clinical advice was provided by the Ig Review Reference Group. The report was commissioned by the Australian Government Department of Health.

The suggested citation for this document is:

(2019) *Immunoglobulin for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)*. MSAC Application 1564, Assessment Report. Commonwealth of Australia, Canberra, ACT.

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# Executive Summary

| Main issues for MSAC consideration |
| --- |
| * Utilisation of Immunoglobulin (Ig) for chronic inflammatory demyelinating polyneuropathy (CIDP) is increasing, both in terms of the number of patients receiving the treatment annually and the quantity of Ig used per patient. In 2011/12, 1,551 patients received Ig for CIDP at an average amount of 437g per patient. In 2017/18, 2,595 patients each received an average amount of 497g of Ig. It is not known how utilisation of Ig will change under Version 3 of *The Criteria for the Clinical Use of Immunoglobulin in Australia*, released in 2018*.* Data on utilisation under Version 3 were not available at the time of preparing this Assessment. * The number of patients with CIDP in Australia is unclear. National Blood Authority (NBA) data indicates that 2,595 patients received Ig for CIDP in 2017/18. This is higher than expected based on published prevalence data for CIDP. The European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) prevalence rates suggest the number of Australians with CIDP would be in the range of 578 to 1,593 using upper and lower confidence interval bounds from Rajabaly et al. (2009) and Mahdi Rogers et al. (2014) and including possible, probable and definite cases. * Ig appears to be an efficacious treatment for CIDP (compared to no active treatment) and limited evidence indicates that Ig has at least non-inferior effectiveness to steroids in this population. * Safety and effectiveness findings for all treatments are limited by short follow-up and small patient numbers in the included studies. Safety data, in particular, were poorly reported in the randomised controlled trials (RCTs). * Overall, the rate of serious adverse events associated with any treatment for CIDP over the short to intermediate term is low. Adverse events associated with Ig were typically mild and transient, whereas extended steroid treatment is known to be associated with a range of serious adverse events including psychiatric disorders, metabolic complications, infections and gastrointestinal disorders. * The Reference Group suggested the adverse event profile associated with steroid use in patients with giant cell arteritis reported in the publication by Wilson et al. (2007) is applicable to the Australian CIDP population. Results from this publication are included in Section B6. * The modelling in this Assessment generated a 10-year incremental cost-effectiveness ratio (ICER) of $197,472 per quality-adjusted life-year (QALY), and a 6-month ICER of $269,038 per QALY when comparing Ig to steroids. Assumptions about the utility gain associated with Ig use, the amount of Ig used, and the price paid for Ig are key drivers of the model results. The base case assumes 497g of Ig per patient per year, a price per gram of $60.41, and a utility gain of 0.12 over six months of Ig treatment. * The EFNS/PNS guidelines recommend either steroids or Ig as the first option for patients with moderate to severe CIDP. The PICO noted that, in Australia, Ig can be a first-choice treatment option for patients meeting the requirements set out in Version 3 of *The Criteria*. The degree to which Ig is being used as a first option is difficult to quantify. * Section E estimates of Ig usage for CIDP over the next 5-years are based on the linear trend in Australian utilisation reported from 2012-2018. Ig costs increase from $88.1 to $108.8 million per year between 2020 and 2024. When PBS, Medicare Benefits Schedule (MBS) and state hospital costs are considered, Ig use and its delivery are projected to generate net costs to government of $103.6 million in 2020, increasing to $127.9 million by 2024. |

## Chronic Inflammatory Demyelinating Polyneuropathy

This Contracted Assessment examines the evidence on Ig for the management of CIDP as part of the Review of Immunoglobulin use in Australia.

Alignment with agreed PICO Confirmation

This Assessment addresses all the PICO[[1]](#footnote-2) elements pre-specified in the PICO Confirmation ratified by the Immunoglobulin Review Reference Group.

### Proposed Medical Service

The intervention under review is Ig therapy. Immunoglobulins are antibodies that have been purified from the plasma of healthy blood donors. In Australia, Ig is provided by the NBA and is sourced from plasma collected by the Australian Red Cross Blood Service, from plasma fractionation by CSL Behring Pty Ltd and from imported supplies (Referral Form, page 4).

At the commencement of this Review only intravenous Ig (IVIg) was funded for CIDP. The Reference Group advised that funding for subcutaneous Ig (SCIg) was probable in the foreseeable future. The specific conditions relating to Ig use, the qualifying criteria, and recommended dosages for CIDP were developed by the NBA (NBA Criteria outlined in Version 3 of *The* *Criteria for the clinical use of Immunoglobulin in Australia) (NBA 2018)*. IVIg is most often infused in the public ‘day-case’ setting. It may also be administered to private patients in public hospitals and in private same-day infusion facilities unattached to a hospital.

### Population

The population for this Assessment is patients with CIDP eligible for Ig treatment under Version 3 of *‘The Criteria’*. CIDP is a neurological autoimmune disorder whereby the body’s immune system attacks and damages the myelin sheath of the peripheral nerves causing electrical impulses to be slowed or lost. If left untreated irreversible damage to the nerve axons can occur. Early symptoms include sensory symptoms of tingling or loss of feeling in the toes and fingers, and/or weakness in the arms and hands or legs and feet. Estimates indicate that the cumulative disability caused by untreated CIDP can lead to wheelchair dependence in approximately one-third of patients.

Diagnosis of CIDP is difficult, as there is no definitive test and the symptoms are often vague and match those of several other diseases. Diagnosis is based on a combination of clinical, electrodiagnostic and laboratory investigations (cerebrospinal fluid, magnetic resonance imaging, nerve biopsy) as well as treatment response as outlined in the EFNS/PNS) guideline on CIDP.

Estimated CIDP patient numbers in Australia range from 578 to 1,593 using upper and lower confidence interval bounds from Rajabaly et al. (2009) and Mahdi Rogers et al. (2014) and including possible, probale and definite cases (see Section A.4 and C for more detail). Data from the NBA shows that in the 2017/18 financial year 2,595 patients in Australia received Ig for CIDP (Table 1).

Table 1 Change in number of patients using IVIg for CIDP in Australia over time

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Financial year** | **2011–2012** | **2012–13** | **2013–14** | **2014–15** | **2015–16** | **2017–18** |
| Patient number | 1,551 | 1,753 | 1,903 | 2,054 | 2,250 | 2,595 |
| Total Ig (grams used) | 677,458 | 758,271 | 857,533 | 974,258 | 1,071,135 | 1,290,730 |

Source: annual report by the National Blood Authority on the issue and use of Ig (NBA 2019b)

The difference between prevalence data and Ig usage figures may be due to prevalence studies using a narrower set of criteria for CIDP diagnosis than that used in clinical practice, and patients being misdiagnosed with CIDP, such as those with non-CIDP autoimmune neuropathies being labelled as having CIDP. This issue is further discussed in Section C of this Assessment. Further, expert advice from the Reference Group is that “prevalence studies only take research level proven diagnoses, whereas many patients are diagnosed at the clinical level without tests meeting full research criteria.”

### Comparator Details

Comparators to Ig agreed upon in the PICO are:

* Steroids (oral and IV)
* Plasma exchange
* Immunosuppressant and/or immunomodulatory drugs and therapies not including Ig or steroids (this comparator is referred to as immunosuppressants or by specific drug name in this report)
* A combination of two or more of the above therapies
* No active treatment, No Ig

A description of each comparator is provided in Section A.5 of this Assessment.

### Clinical management algorithm(s)

The current clinical management algorithm is described in Figure 1 (Section A.6). Patients with an established diagnosis of CIDP with significant disability and/or compromised walking, and who meet the specification of Version 3 of ‘*the Criteria*’ can access Ig as a first-line treatment. Treatment response is reviewed four months after commencing therapy, and if the minimum response outlined in Version 3 of *‘the Criteria’* is achieved, Ig treatment is continued. If these criteria are not met, then alternate therapies (steroids, plasma exchange, immunosuppressants) or combination therapies are trialled.

### Key Differences in the Delivery of the Medical Service and the Main Comparator

Treatments for CIDP differ in their mode of action, speed of control, degree of invasiveness, side effect profile and costs. Ig is currently administered intravenously, usually in a hospital setting. Steroids and immunosuppressants can be prescribed orally for use at home or provided intravenously in either an outpatient or day-care setting. Plasma exchange is provided in major teaching hospitals as an outpatient, day stay or inpatient setting. A more detailed description of treatment differences is provided in Section A.7.

Patients receiving steroids require closer monitoring than do patients receiving Ig, needing regular (at least 6-monthly) reviews for blood pressure, blood sugar, weight, skin integrity, infectious complications and dental review. Patients prescribed immunosuppressants also require close surveillance (weekly blood tests initially, then every 1-3 months).

Clinical Claim

Ig has at least non-inferior effectiveness and superior safety than the comparator interventions of steroids (oral and IV), plasma exchange, and immunosuppressants (individually or in combination) in the management of CIDP.

Ig has superior effectiveness but inferior safety to the comparator treatment of no active treatment.

### **Approach T**aken to the **E**vidence **A**ssessment

The medical literature was searched on 25 March 2019 to identify all relevant studies on the treatment of CIDP published to date. Studies were screened by a single reviewer for title and abstract, with all exclusions checked by a second reviewer. Full-text selection was performed independently by two reviewers.

### **Characteristics of the Evidence Base**

Reviews identified 22 publications reporting 14 RCTs that investigated treatment of CIDP in patients with active disease characterised by presence of significant disability. Risk of bias in the RCTs was high in most studies. Typically, this was due to deviation from the intended intervention and missing outcome data. Overall, the studies were generally limited to short-term (≤ 6 months) outcomes. Despite these limitations, the evidence base appears to be applicable to the intended population of this Assessment.

Five additional trials were identified that assessed treatment maintenance in patients who were in remission or currently responding to treatment.

### Results

#### Safety

The evidence reviewed in this Assessment indicates that the overall rate of serious adverse events with any treatment over the short to intermediate term is low. Ig and steroids were the treatments for which most evidence was available. Other active treatments (plasma exchange, immunosuppressants) were associated with small study cohorts and low confidence in safety reporting. A formal test of non-inferiority or superiority of IVIg relative to any other comparator could not be applied owing to the paucity of studies reporting safety outcomes and limitations in trial design. Most patients with CIDP will require long-term treatment and may require multiple therapies over the course of their disease, thereby being exposed to a range of harms.

##### Adverse events associated with Ig

In a total of 1,108 patients treated with Ig, the most frequently reported adverse event was headache, reported in 155 patients. Next most frequent was general disorders and administration site conditions (n = 80), which included fever, chills and flu-like reaction. Gastrointestinal disorders (n = 55), skin disorders (n = 31, predominantly rash) and infections (n = 46) were also common. Less frequent but serious events were vascular disorders and blood and lymphatic system disorders, namely deep vein thrombosis (n = 3), cerebrovascular events (n = 2) and haemolysis (n = 11). The data reviewed on patients with CIDP treated with IVIg shows an adverse event profile consistent with the broad literature on the safety of IVIg.

##### Adverse events associated with steroids

Corticosteroids resulted in a similar proportion of patients experiencing adverse events. Steroids were associated with psychiatric disorders, metabolic complications, infections and gastrointestinal disorders. A total of 358 patients were included in studies reporting safety outcomes. The most commonly reported adverse events were insomnia (n = 35), mood changes (n = 23), Cushingoid appearance (n = 20), indigestion (n = 23), hypertension (n = 14) and infection (n = 15). Events classified as serious (by the study authors) included gastritis (n = 1), psychosis (n = 1), Cushingoid appearance (n = 3), gastrointestinal bleeding (n = 2), infectious complications (n = 3) and one death in a patient with urinary sepsis.

The safety profile of steroids is understood to be related both to dose and duration of treatment. Higher-doses and extended treatments carry a higher risk for serious adverse events such as cardiovascular and metabolic adverse events (Rice et al. 2017). Cocito et al. (2012) and Nobile-Orazio et al. (2012b) followed patients for 52 weeks. A subsequent publication with 4.5 years of follow-up identified no new cases of diabetes or glaucoma or other serious adverse events not identified in the 52 week analysis. However, clinical feedback indicates this may not represent the true harms profile of steroids.

Within the RCT evidence, corticosteroids are started on a high dose (oral or IV) and then tapered over a period (usually no longer than six months). However, population based studies reveal that if steroids are used in a chronic fashion or patients receive multiple rounds of pulsed strategies, patients may be at higher risk of adverse events including hypertension; bone fracture; cataract; nausea, vomiting and other gastrointestinal conditions; metabolic issues (eg weight gain, hyperglycemia and type 2 diabetes); and cardiovascular adverse events (Rice et al. 2017). It is not clear from the peer-reviewed literature whether chronic steroid treatment is prevalent in this population.

The Reference Group noted that the evidence on the adverse events of steroids in CIDP patients did not adequately capture the safety profile. Expert advice from the Reference Group is that a publication on the adverse events experienced by patients with giant cell arteritis provided a more applicable safety profile of steroids (Wilson et al. 2017). The rationale provided by the Reference Group for citing this paper is that patients with giant cell arteritis did not usually have treatemt options other than steroids during the period that data was collected and that the use of steroids in this population was applicable to CIDP patients in Australia. Wilson et al. (2017) found steroid use is associated with increased risk of diabetes (incidence rate ratio (IRR) 1.4, 95% CI [1.2, 1.7]), osteoperosis (IRR 2.4, 95% CI [2.1, 2.8]), fractures (IRR 1.4, 95% CI [1.2, 1.6]), glaucoma (IRR 2.0, 95% CI [1.6, 2.5]) and serious infection (IRR 1.5, 95% CI 1.3, 1.7]).

##### Adverse events associated with plasma exchange

Adverse events with plasma exchange were poorly reported but included difficulty accessing veins (n = 3) and deficiency of coagulation factors (n = 1); myocardial infarction (n = 1); cerebrovascular event (n = 1); and septicaemia associated with a tunnelled catheter (n = 1). However, relative to the experience with steroids and IVIg, the total number of patients in studies reporting issues of safety with plasma exchange was small (n = 104). In the broader literature, plasma exchange is observed to carry a small risk of cardiovascular, respiratory and anaphylactic events. Some complications of central venous catheters may be avoided by the use of peripheral veins (Fridey and Kaplan 2019), however, this issue has not been investigated in the literature on CIDP.

##### Adverse events associated with other treatments

Section B.7. of this report also includes studies reporting on the experience of patients with CIDP receiving azathioprine, cyclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab and immunoadsorption. However, the quantity and quality of evidence identified was poor, with total patient numbers typically less than 100. All of these interventions were associated with adverse events. Notable or severe complications included the development of lymphoma in a patient receiving rituximab[[2]](#footnote-3), thrombotic events with immunoadsorption, and significant nephrotoxicity in patients receiving cyclosporin. Azathioprine, methotrexate and mycophenolate mofetil were also associated with adverse events such as nausea.

Considering the above information, IVIg can be considered a relatively safe intervention with serious adverse events infrequent and common adverse events typically being transient and mild.

#### Effectiveness

##### Effectiveness of Ig compared to no treatment

The evidence reviewed in this Assessment indicates that Ig likely has superior effectiveness relative to no treatment. Ig therapy was found to elicit a clinically meaningful response in approximately 50% of patients receiving the treatment, and thus is likely to be a beneficial treatment option for patients with CIDP.

##### Effectiveness of Ig compared to steroids

Two RCTs directly compared Ig to steroids for CIDP treatment (Hughes et al., 2001, Nobile-Orazio et al., 2012b).

In Nobile-Orazio et al. (2012b), for the composite outcome of discontinuation (any cause), steroid use was associate with higher risk of discontinuation than Ig (relative risk (RR) 0.54, 95% CI [ 0.34, 0.87]). Eleven patients (52%) in the steroid arm discontinued; five due to progressive worsening, three due to failure to improve, one for adverse events (gastritis) and two for reasons unreported. Three patients (12.5%) discontinued Ig therapy; two because of progressive worsening and one due to failure to improve. It is not known what the RR would be if only discontinuations due to inefficacy were considered. Following cessation of treatment, patients treated with methylprednisolone remained in remission longer than those treated with Ig.

The authors reported no difference between Ig and methylprednisolone with respect to secondary outcomes of Medical Research Council (MRC) score, grip strength, Overall Neuropathy Limitations Scale (ONLS), SF36, ISS and W10M tests.

Hughes et al. (2001) reported no difference between IVIg and oral prednisolone with respect to Inflammatory Neuropathy Cause and Treatment (INCAT), 10MWS and 9HPB outcomes.

##### Effectiveness of Ig compared to plasma exchange

Evidence on the comparison of Ig and plasma exchange was limited. Results from a single trial support a finding of non-inferiority.

##### Effectivenes of Ig compared to immunosuppressants

Available evidence indicates that there is little short-term (≤ 6 months) benefit from the addition of immunosuppressants to Ig or steroids (specific to the drugs and dosages used in the RCTs). No long-term data was available.

##### Limitations of the evidence base

These findings are based on limited, mixed-quality evidence. Generally, trials were small and follow-up duration was short. Risk of bias was ‘high’ in 11 of the 20 identified RCTs and a ‘concern’ in a further three. The relative long-term effectiveness of any of the treatments for CIDP is therefore uncertain.

Table 2 Balance of clinical benefits and harms of intervention (Ig), relative to comparator (no treatment or steroids), as measured by the critical patient-relevant outcomes in the key studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcomes  Follow-up | Participants (studies) | Quality of evidence (GRADE) a | Risk with no treatemt | Risk difference with Ig |
| Relative to no treatment | | | | |
| INCAT follow-up: median 6 months | 117 (1 RCT) | ⨁⨁⨁◯ MODERATE a | The mean change in INCAT was -0.3 | mean change 0.7 lower (1.3 lower to 0.2 lower) |
| MRC follow-up: range 3 weeks to 24 weeks | 145 (2 RCTs) | ⨁⨁⨁◯ MODERATE b | Change in MRC favoured Ig in both RCTs with different magnitude (study 1: n = 117, mean change 3.1, p = 0.001 and study 2: n = 18, mean change = 0.29, p = NR) | |
| Clinically meaningful response follow-up: range 3 weeks to 24 weeks | 255 (4 RCTs) | ⨁⨁⨁◯ MODERATE a | Clinically meaningful response was higher in the Ig group in ¾ studies. Rates of response ranged from 13% to 63% in the Ig group and 10% to 23% in the no treatment group | |
| **Relative to steroids** | | | | |
| INCAT  follow-up: 6 weeks | 42  (1 RCT) | ⨁⨁⨁◯ MODERATE a | The mean INCAT was **0** | MD **0.22 lower** (0.62 lower to 1.06 higher) |
| Discontinue treatment  follow-up: 6 months | 45  (1 RCT) | ⨁⨁⨁◯ MODERATE a | 524 per 1,000 | 241 fewer per 1,000 (from 346 to 68 fewer, RR = 0.54) |
| MRC  follow up: 6 months | 45  (1 RCT) | ⨁⨁⨁◯ MODERATE a | Mean change in MRC was 1.8 ± 11.64 | Mean change in MRC was 4.7 ± 7.69 (p = 0.0929) |

Source: GRADE Working Group grades of evidence (Guyatt et al., 2013)  
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.   
⨁⨁⨁⨀ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.   
⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

INCAT = Inflammatory Neuropathy Cause and Treatment; MD = mean difference; MRC = Medical Research Council Sum Score; RCT = randomised controlled trial.

a. Assessed using the Cochran Risk of Bias tool, b. Inconsistent findings in the two trials

On the basis of the benefits and harms reported in the evidence base (summarised in Table 2), it is suggested that; relative to:

* No treatment, Ig has inferior safety and superior effectiveness; noting that Ig is rarely associated with serious adverse events.
* Steroids, Ig has superior safety and at least non-inferior effectiveness. The Reference Group noted that the largest trial may support a finding of superior effectivenss based on non-significant improvements in various disability measures and a statistically significant difference in discontinuations favouring Ig. Discontinuations was a composite endpoint of discontinuations due to inefficacy and intolerance.
* Plasma exchange, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.
* Immunosuppressants, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.
* Combination therapy, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.

Note the Reference Group agreed that it was not appropriate to perform a GRADE summary for safety outcomes due to the different safety profiles of the intervention and comparators.

### Translation Issues

Three key issues arise in translating the evidence provided in Section B to an economic model presented in Section D. The first relates to the applicability of the populations in the pivotal trials to clinical practice in Australia. The second relates to the selection of utilities, and the third to the extrapolation of trial evidence. The key trials presented in Section B align reasonably well with New South Wales (NSW) data, with similar patient age of around 50-60 years, gender, setting for Ig delivery, and disability eligibility criteria.

Participating patients in key trials had varying degrees of steroid resistance (defined as patients contraindicated to steroids and patients for whom steroids did not elicit a therapeutic response). Optimal treatment varies for steroid-resistant and non-resistant sub-groups, whereas trial results have been typically presented for comparator groups as a whole. The types of CIDP evident in trial participants is varied and there is limited data about the characteristics of patients being treated with Ig in Australia. Key assumptions were varied in sensitivity analyses to gauge how model results vary according to the value of these assumptions. The key parameters for extrapolation include longer-term corticosteroid adverse events, Ig relapse, immunotherapy non-response, progression to disability in non-responsive patients and mortality. Modelling results were separated into 6-month (length of available RCT data for Ig versus steroid comparison) and 10-year analyses, given the uncertainty surrounding longer term costs and outcomes.

Much of the health benefit estimated in the model is generated by the 0.12 utility gain assumed for patients receiving Ig over steroids. This assumption was used in the Canadian study by Blackhouse et al. (2010) and was derived from the small short-term trial described by McCrone et al. (2003). The study combined 6-week physical disability scores and EQ-5D scores for 25 patients (78% of participants), along with 6-week treatment costs. The difference between Ig and steroid health utility is assumed to be stable over the extrapolated analysis, which is uncertain given the short-term nature of the evidence. Ig patients are assumed to transition to steroids due to Ig non-response, therefore an averge patient does not capture the 0.12 utility gain for the entire projection. The Reference Group noted that that in McCrone et al. (2003) health-related quality of life (or the utility difference) was not significantly different for IVIg compared to steroids. The effect of the utility gain was tested in sensitivity analyses.

### Economic Evaluation

A cost-utility analysis was undertaken to determine the value of Ig against steroids. A summary of the key characteristics of the economic evaluation is provided in Table 3.

Table 3 Summary of the economic evaluation

|  |  |
| --- | --- |
| **Perspective** | This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients. |
| **Intervention** | * Intravenous Ig (IVIg) |
| **Comparator** | * Corticosteroids |
| **Type of economic evaluation** | Cost-utility analysis |
| **Sources of evidence** | * Blackhouse et al. (2010) Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of CIDP in Canada. * Trials outlined in Section B. * Clinical feedback during preparation of Contracted Assessment. |
| **Time horizon** | 6-month trial and 10-year extrapolated time horizon  Sensitivity analyses include a time horizon of 5 years |
| **Outcomes** | Quality-adjusted life-years (QALY) / life-years (LY) |
| **Methods used to generate results** | Cohort expected value analysis |
| **Health states** | * Ig (Initial treatment and responder) * Corticosteroids (no adverse events) * Fracture * Diabetes * Glaucoma * Cataract * Infection * Corticosteroids non-responder + azathioprine * Azathioprine non-responder * Disabled * Death |
| **Cycle length** | 1 week |
| **Discount rate** | 5% used for base and 0% and 7% sensitivity analyses |
| **Software packages used** | Microsoft Excel 2010 |

Abbreviations: CIDP = Chronic Inflammatory Demyelinating Polyneuropathy, Ig = Immunoglobulin, MBS = Medicare Benefits Schedule, QALY = quality-adjusted life year.

The incremental costs and the incremental effectiveness of IVIg versus corticosteroids for an average patient are presented in Table 4. The ICER is presented as the incremental cost of achieving an additional QALY (Quality-Adjusted Life Year). The trial period ICER is $269,038 per QALY at average Australian Ig use (497 g) and $742,576 per QALY at Ig use of 1,430 g per patient per year based on an estimated trial maintenance dose. The 10-year ICER is $197,472 per QALY at average Australian Ig use (497 g) and $549,897 per QALY at Ig use of 1,430 g per patient per year based on an estimated trial maintenance dose using a base cost of $60.41 per gram of Ig. Sensitivity analyses are undertaken using high and low Ig costs of $140.18 and $44.94 per gram. The 10-year ICER varies between $445,370 and $149,397 using these Ig costs.

Table 4 Incremental cost-effectiveness ratio of IVIg versus corticosteroids (average-patient)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cost ($)** | **Incremental cost ($)** | **Effectiveness (QALYs)** | **Incremental effectiveness** | **ICER ($)** |
| **Trial period** |  |  |  |  |  |
| Ig, 497g per patient per year | $16,808 | $14,459 | 0.35 | 0.05 | $269,038 |
| Ig, 1,430 g per patient per year | $42,257 | $39,907 | 0.35 | 0.05 | $742,576 |
| Corticosteroids | $2,349 |  | 0.30 |  |  |
| **10-year** |  |  |  |  |  |
| Ig, 497g per patient per year | $174,469 | $130,714 | 5.10 | 0.66 | $197,472 |
| Ig, 1,430 g per patient per year | $407,752 | $363,997 | 5.10 | 0.66 | $549,897 |
| Corticosteroids | $43,755 |  | 4.44 |  |  |

ICER = Incremental Cost-Effectiveness Ratio, QALY = quality-adjusted life year

Assumptions about price paid for Ig product and assumed dosing are key drivers of the model results, which are summarised in Table 5.

Table 5 Drivers of the economic model

| Description | Method/Value | Impact |
| --- | --- | --- |
| Utilities for Ig responders and steroids | The utility gain of 0.12 employed in Blackhouse et al. (2010) was used to estimate the difference between Ig and steroids. It was based on the small study by McCrone et al. (2003). A more recent study by Nobile-Orazio found no utility gain, however there were high drop-outs in study arms, which confound generalisability of results. | Large. Decreasing this value has a large impact on estimated ICER. The Reference Group noted that that in McCrone et al. (2003) health-related quality of life (or the utility difference) was not significantly different for IVIg compared to steroids |
| Cost of Ig | The cost of Ig accounts for more than 80% of intervention costs. Correspondingly, variation in this cost has a large impact on the estimated ICER. | Large. Lower Ig price reduces the ICER. Sensitivity analyses are undertaken using high and low Ig costs of $140.18 and $44.94 per gram. The 10-year ICER varies between $445,370 and $149,397 |
| Ig dosing | Induction and maintenance dosing frequencies and grams per dose have a large impact on the estimated ICER. The grams of Ig included in this study of 497 g are less than that of Blackhouse et al. (2010). | Large. The estimated ICER of $197,472 per QALY in this analysis is far less than Blackhouse et al. (2010) of$Canadian 670,396 per QALY ($Australian 732,344 at current exchange rate of 1.09) gained due to lower Ig use. Australian average Ig use of 497g per patient per year versus initial treatment provided as two 1g/kg doses and maintenance treatment as a single 1g/kg dose every three weeks in the Canadian study (around 1,447 g in the first year) |
| Steroid non-response probability | The model is based on assumptions from trials with steroid-resistant and -responsive patients. The Thai economic study (Bamrungsawad et al. 2016) demonstrated that Ig is cost-effective in steroid-resistant populations as patients transition to disability and costs of treatment are higher than steroids alone. | Possibly Large. The ICER for Ig is less in steroid-resistant patients, as disability has a large disutility. For steroid-resistant patients alone, an ICER of $125,260[[3]](#footnote-4) per QALY gained is estimated |

AE = adverse event

### Estimated Extent of Use and Financial Implications

Prevalence estimates for CIDP using the EFNS/PNS criteria for diagnosis vary considerably, ranging from 1.19 per 100,000 to 6.37 per 100,000 (discussed in Section C.2). Based on these rates, estimated CIDP patient numbers in Australia in 2018 vary from 493 to 1,593. This is fewer than the total of 2,595 CIDP patients treated with Ig as reported by the NBA in 2017/18. NBA data indicates that the number of patients receiving treatments has increased by 67% from 2011/12 to 2017/18. The reason for this increase is unclear. The Australian population increased by approximately 10% over the same time period (ABS 2019). Further, the Ig use in grams increased by 91% over the 11/12 to 17/18 period, this continued increase in number of g per patient was not modelled; however, if continued would further increase the ICER and financial costs associated with Ig use.

The EFNS/PNS guidelines recommend either steroids or IVIg as the first option for patients with moderate to severe CIDP. The PICO noted, however, that in Australia IVIg is often a first-choice treatment option for patients with moderate to severe CIDP. The degree to which Ig is being used as a first option is difficult to quantify. The budget impact examines financial costs to the Commonwealth and State governments over the forward estimates (2020 – 2024) assuming a linear rate of increase in CIDP patients using Ig of around 5% per annum, based on the trend of increase in patients using Ig between 2012-2018. Results are summarised in Table 6. Ig costs increase from $88.1 ($55.5 million Commonwealth and $32.6 million state/territoryState government) to $108.8 million per year between 2020 and 2024. When PBS, MBS and state hospital costs are considered, Ig use and its delivery are projected to generate net costs to government of $103.6 million in 2020, increasing to $127.9 million by 2024.

Table 6 Net government costs associated with Ig for CIDP patients, 2020-2024

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Total net government costs** | Unit | **2020** | **2021** | **2022** | **2023** | **2024** |
| Projected Ig patients | No. | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 |
| **Ig costs for CIDP** |  |  |  |  |  |  |
| Commonwealth Ig costs | $ | 55,531,665 | 58,786,392 | 62,041,118 | 65,295,845 | 68,550,572 |
| State Ig costs | $ | 32,613,835 | 34,525,341 | 36,436,847 | 38,348,353 | 40,259,860 |
| **Commonwealth MBS and PBS Costs** |  |  |  |  |  |  |
| MBS-supported service delivery | $ | -1,274,602 | -1,349,307 | -1,424,012 | -1,498,717 | -1,573,422 |
| PBS costs | $ | -1,441,924 | -1,526,435 | -1,610,947 | -1,695,458 | -1,779,970 |
| **State/Territory Hospital Costs** |  |  |  |  |  |  |
| Ig delivery, nurse and adverse events | $ | 18,205,039 | 19,272,041 | 20,339,044 | 21,406,046 | 22,473,049 |
| **Net Government Costs** |  |  |  |  |  |  |
| **Commonwealth costs** | $ | 52,815,139 | 55,910,649 | 59,006,160 | 62,101,670 | 65,197,180 |
| State/territory costs | $ | 50,818,874 | 53,797,382 | 56,775,891 | 59,754,400 | 62,732,909 |
| Total costs to government | $ | 103,634,012 | 109,708,032 | 115,782,051 | 121,856,070 | 127,930,089 |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. MBS = Medicare Benefits Schedule, PBS= Pharmaceutical Benefits Scheme

### Consumer impact summary

All feedback was broadly supportive of Ig use for CIDP. Noted advantages associated with Ig use were high response rates to treatment and generally high tolerability to treatment.

Noted disadvantages of Ig use included adverse events associated with treatment, requirement for in-hospital treatment, and acess-to-treatment issues arising from increasing demand for Ig.

Sponsor companies were also invited to provide submissions to the development of this contracted assessments and four responded with comments that have been considered in this report. Sponsor feedback is summarised in Section A.10 of this report.

# Acronyms and Abbreviations

**Acronym/abbreviation Meaning**

AAN American Academy of Neurology

ACD Anticoagulant citrate dextrose

AE Adverse event

AHPRA Australian Health Practitioner Regulation Agency

AIHW Australian Institute of Health and Welfare

ARTG Australian Register of Therapeutic Goods

CADTH Canadian Agency for Drugs and Technologies in Health

CERA Centre for Eye Research Australia

CI Confidence interval

CIDP Chronic Inflammatory Demyelinating Polyneuropathy

CTCAE Common Terminology Criteria for Adverse Events

EDSS Expanded Disability Status Scale

ENMC European Neuromuscular Centre

HAD Hospital Anxiety and Depression

HRQoL Health-related quality of life

HSCT Haemopoeitic stem cell transplant

HTA Health technology assessment

ICER Incremental cost-effectiveness ratio

INCAT Inflammatory Neuropathy Cause and Treatment

ITP Immune thrombocytopenic purpura

IV Intravenous

LFT Liver function test

LY Life-years

MBS Medicare Benefits Schedule

MD Mean difference

MMP Mucous membrane pemphigoid

MRC Medical Research Council

MRS Modified Ranking Scale

MSAC Medical Services Advisory Committee

NBA National Blood Authority

NHMRC National Health and Medical Research Council

NSW New South Wales

ODSS Overall disability sum score

ONLS Overall Neuropathy Limitations Scale

OMA Opsoclonus-myoclonus ataxia

PASC PICO Confirmation Advisory Sub-Committee of the MSAC

PBS Pharmaceutical Benefits Schedule

PDN Paraproteinaemic demyelinating neuropathy

PGIC Patient global impression of change

PICO Population, Intervention, Comparator and Outcomes

PTP Post-transfusion purpura

PV Pemphigus vulgaris

QALY Quality-adjusted life year

QoL Quality of life

RACS Royal Australasian College of Surgeons

RHS Rotterdam Handicap Scale

RR Relative risk

SAE Serious adverse event

SCIg Subcutaneous Immunoglobulin

SD Standard deviation

TGA Therapeutic Goods Administration

# Section A Context

This Contracted Assessment of IVIg and SCIg for the management of patients with CIDP is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is being sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, utilising reviews of the scientific literature and other information sources, including clinical expertise.

Research and Evaluation, incorporating ASERNIP-S of the Royal Australasian College of Surgeons, has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of Ig for the management of patients with CIDP. This Assessment has been undertaken as part of the review of Ig use in Australia.

The use of Ig in Australian clinical practice was outlined in a PICO Confirmation that was ratified by the Ig Review Reference Group and is available on the relevant MSAC website.

Appendix A provides a list of the people involved in the development of this Assessment report.

## Items in the agreed PICO Confirmation

This Contracted Assessment of Ig addresses all of the PICO elements pre-specified in the PICO Confirmation.

## Medical Service

The intervention under review is Ig therapy using antibodies (Ig) that have been purified from the plasma of healthy blood donors. In Australia, Ig is provided by the NBA, sourced from plasma collected by the Australian Red Cross Blood Service, plasma fractionation by CSL Behring Pty Ltd and through imported supplies (Referral Form, page 4). Ig can be administered intravenously (IVIg) or injected subcutaneously into the tissue under the skin (SCIg) or into the muscle (Davies 2009).

Ig is used for immunomodulating therapy for CIDP, an autoimmune disorder where the body’s immune system attacks its own tissues. The exact mode of action of Ig in immunomodulation is not clear, but it is thought that Ig contains random sets of antibodies that neutralise immune factors causing damage to the peripheral nerves in CIDP (Lewis 2018; Nagelkerke and Kuijpers 2014). Advice from the Ig Review Reference Group is that Ig may:

* contain anti-idiotype antibodies that neutralise immune factors that damage the peripheral nerves
* interact with regulatory Ig receptors on antigen-present cells and adaptive immune repertoire
* act by Ig complex on innate immune cytotoxic response
* increase recycling of pathogenic antibodies.

The use of IVIg for the management of CIDP is currently funded in Australia by the NBA. This current Assessment is not about whether Ig treatment of CIDP should be funded, but is a review of its clinical and cost-effectiveness compared to other treatment options (MSAC 2019).

Although MSAC has not considered an application relating to the use of Ig for CIDP it has previously considered an application to add SCIg to the National Products Price List under the National Blood Agreement. This application (1334) was submitted by Octapharma Australia Pty Ltd (for Gammanorm®) and by CSL Ltd (for Evogam®). In the public summary document, MSAC noted that the NBA had prepared a Cycle 1 Assessment for the two applications and had sought comment from the Evaluation Sub-Committee of MSAC and from MSAC. MSAC’s advice to the Minister, Commonwealth representative of the Jurisdictional Blood Committee and the NBA was as follows (MSAC 2016):

* Comparative health gain should be rated as “no impact”
* Comparative safety gain should be rated as “no impact”
* Comparative cost-effectiveness should be rated as “uncertain”
* Financial implications for the national blood budget should be rated as “uncertain”
* Financial implications for government health budgets should be rated as ‘uncertain’
* Clinical need should be rated as “moderately positive”

The specific conditions relating to Ig use, the qualifying criteria, and recommended dosages are outlined in Version 3 of ‘The *Criteria for the clinical use of Immunoglobulin in Australia (the Criteria)’* developed by the NBA *(NBA 2018).* The section specifically relating to CIDP defines conditions for which IVIg has an established therapeutic role. The use of IVIg and SCIg are funded for management of CIDP patients meeting Version 3 of ‘*the Criteria’*. When this Assessment was commenced, SCIg was not funded for the management of CIDP; funding commenced on 1 August 2019. The Reference Group advised that funding for SCIg was probable in the foreseeable future (DoH 2019a). Therefore, this Assessment considered evidence on both IVIg and SCIg, but is written from the perspective that only IVIg is funded for CIDP management.

According to the Applicant (Referral Form, page 31), infusion of IVIg may occur in any of the following settings:

* 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

The Referral Form (page 31) notes that Clinical Advisors on the Review Group observed that IVIg is predominantly infused in the public outpatient setting. However, they commented that due to funding incentives, patients were often admitted on a ‘same-day care’ basis and counted as ‘inpatients’. They estimated that 75% of infusions were given in this setting.

### Marketing status of device / technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if the device is not listed on the ARTG. Items on the ARTG relevant to this application are shown in Table 7. It should be noted that of the four Ig products listed on the ARTG and indicated for CIDP (Intragram 10, Privigen, Hizentra and Gamunex), only two of them, Intragam 10 and Privigen, are funded by the NBA for the management of CIDP. According to the Applicant, Hizentra is funded under the National Blood Arrangements for several indications, but CIDP is not one of them. Gamunex is not currently contracted and funded under the National Blood Arrangements. The Applicant also reported that in addition to Intragam 10 and Privigen, the NBA funds another three Ig products for CIDP: Flebogamma 5%, Flebogamma 10% and Intragam P. These products are listed on the ARTG but are not indicated for CIDP. The Applicant notes that Intragam P will be removed from the NBA product list once current stocks expire as it has been replaced by Intragam 10 (DoH 2019b). In summary:

* Only two Ig products are listed on the ARTG with an indication for CIDP and are funded by the NBA for CIDP (Intragam 10 and Privigen)
* Two Ig products are listed on the ARTG with an indication for CIDP but are not funded by the NBA for CIDP (Hizentra and Gamunex)
* Three Ig products listed on the ARTG are not indicated for CIDP but are funded by the NBA for CIDP (Flebogamma 5%, Flebogamma 10% and Intragam P)
* All Igs funded by the NBA for CIDP are IVIgs. No SCIgs are currently funded by the NBA for CIDP. Two Igs that can be administered subcutaneously are listed on the ARTG with an indication for CIDP (Hizentra and Gamunex)[[4]](#footnote-5). One of these (Hizentra) is funded under the National Blood Arrangement and is on the National Product List (NBA 2019c) but according to the Applicant it is only for a limited number of indications, CIDP not being one of them.

Table 7 Igs listed on the ARTG and indicated for CIDP

| ARTG no. | Product description | Product category | Sponsor |
| --- | --- | --- | --- |
| 207383 | Hizentra human normal Ig 20% solution for subcutaneous injection 20ml vial | Medicine | CSL Behring Australia, Pty Ltd |
| 207384 | Hizentra human normal Ig 20% solution for subcutaneous injection 50ml vial | Medicine | CSL Behring Australia, Pty Ltd |
| 207385 | Hizentra human normal Ig 20% solution for subcutaneous injection 10lL vial | Medicine | CSL Behring Australia, Pty Ltd |
| 207386 | Hizentra human normal Ig 20% solution for subcutaneous injection 5ml vial | Medicine | CSL Behring Australia, Pty Ltd |
| 285344 | Hizentra human normal Ig 20% solution for subcutaneous injection 5ml pre-filled syringe | Medicine | CSL Behring Australia, Pty Ltd |
| 285345 | Hizentra human normal Ig 20% solution for subcutaneous injection 10ml pre-filled syringe | Medicine | CSL Behring Australia, Pty Ltd |
| 162486 | INTRAGAM 10 normal Ig (human) 2.5g/25ml solution for injection vial | Medicine | CSL Behring Australia, Pty Ltd |
| 162487 | INTRAGAM 10 normal Ig (human) 5g/50ml solution for injection vial | Medicine | CSL Behring Australia, Pty Ltd |
| 162488 | INTRAGAM 10 normal Ig (human) 10g/100ml solution for injection vial | Medicine | CSL Behring Australia, Pty Ltd |
| 162489 | INTRAGAM 10 normal Ig (human) 20g/200ml solution for injection vial | Medicine | CSL Behring Australia, Pty Ltd |
| 219160 | Privigen normal Ig (human) 40g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 143368 | Privigen normal Ig (human) 20g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 143337 | Privigen normal Ig (human) 10g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 143273 | Privigen normal Ig (human) 5g (100 g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 306801 | CSL EU Privigen normal Ig (human) 100g/L solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 269691 | CSL USA Privigen normal Ig (human) 40g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 269690 | CSL USA Privigen normal Ig (human) 10g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 269689 | CSL USA Privigen normal Ig (human) 5g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 265147 | CSL USA Privigen normal Ig (human) 20g (100g/L, 10%) solution for intravenous infusion | Medicine | CSL Behring Australia, Pty Ltd |
| 117240 | GAMUNEX normal Ig (human) 20g/200ml intravenous solution vial\* | Medicine | Grifols Australia Pty Ltd |
| 117239 | GAMUNEX normal Ig (human) 10g/100ml intravenous solution vial\* | Medicine | Grifols Australia Pty Ltd |
| 117238 | GAMUNEX normal Ig (human) 5g/50ml intravenous solution vial\* | Medicine | Grifols Australia Pty Ltd |
| 117237 | GAMUNEX normal Ig (human) 2.5g/25ml intravenous solution vial\* | Medicine | Grifols Australia Pty Ltd |
| 116689 | GAMUNEX normal Ig (human) 1g/10ml intravenous solution vial\* | Medicine | Grifols Australia Pty Ltd |

Source: Therapeutic Goods Administration, accessed 13th February 2019.

CIDP: chronic inflammatory demyelinating polyneuropathy, Ig: Immunoglobulin, USA: United States of America

\*Note: while the product summary for GAMUNEX states “normal immunoglobin intravenous solution vial”, the route of administration states both intravenous and subcutaneous

### Other Indications

Besides CIDP, Ig are used for numerous other medical indications in Australia(NBA 2018). A report by the NBA reviewing the use of Ig from 2008/2009 to 2015/2016 noted that the conditions listed in Table 8 accounted for 88.9% of all Ig supplied. The top ten conditions accounted for 75.1% and CIDP accounted for the greatest use of Ig (NBA 2019b).

Table 8 Top 20 indications for Ig by level of use in Australia based on a review of data 2008/2009 to 2015/2016 by the National Blood Authority

|  |  |
| --- | --- |
| **Top 20 conditions by use of Ig** | **% of total Ig use** |
| Chronic inflammatory demyelinating polyneuropathy | 22 |
| Common variable immunodeficiency disease | 12 |
| Myasthenia gravis | 8 |
| Chronic lymphocytic leukaemia | 7 |
| Non-Hodgkin lymphoma | 7 |
| Multifocal motor neuropathy | 6 |
| Multiple myeloma | 6 |
| Polymyositis | 3 |
| Secondary hypogammaglobulinaemia (excludes haem malignancies) | 3 |
| Guillain-Barré syndrome | 3 |
| Kidney transplantation post-transplant | 2 |
| Other relevant haematological malignancies | 2 |
| ITP refractory | 2 |
| Specific antibody deficiency | 1 |
| ITP in specific circumstances (surgery, corticosteroids contraindicated, chronic ITP) | 1 |
| Dermatomyositis | 1 |
| Inclusion body myositis | 1 |
| HSCT - post | 1 |
| ITP with life-threatening haemorrhage | 1 |
| X-linked agammaglobulinaemia | 1 |

Source: National Blood Authority (NBA 2019b)

HSCT: haematopoietic stem cell transplantation, ITP: immune thrombocytopenic purpura

Other medical conditions listed in the Version 3 of *‘the Criteria’* for which Ig are noted as having an ‘emerging therapeutic role’ include: autoimmune encephalitis mediated by antibodies targeting cell-surface antigens (AMAE), bullous pemphigoid (BP), cicatricial pemphigoid (CP) or mucous membrane pemphigoid (MMP), haemophagocytic lymphohistiocytosis, IgM paraproteinaemic demyelinating neuropathy, immune thrombocytopenic purpura (ITP) (in children 15 years and younger), opsoclonus-myoclonus ataxia (OMA), pemphigus foliaceus (PF), pemphigus vulgaris (PV), post-transfusion purpura (PTP), secondary hypogammaglobulinaemia unrelated to haematological malignancy or haemopoeitic stem cell transplant (HSCT), solid organ transplantation, specific antibody deficiency, and toxic shock syndrome (TSS) (NBA 2018).

### Current funding arrangements

The supply of blood products in Australia falls under the control of the NBA. Public funding for Ig use is available for those patients whose medical conditions meet the requirements set out in Version 3 of *‘the Criteria’*(NBA 2018). The use of Ig for CIDP is supported for the following specific indications:

* Treatment of CIDP for patients in whom walking is compromised or there is significant disability
* Relapse of CIDP patients within six months of commencement of trial off Ig therapy

Ig for the management of CIDP patients who meet these specific indications is wholly government funded with no direct cost to the patient (no co-payments). Costs are shared between the Federal and state/territory governments, covering 63% and 37% of the costs respectively (NBA 2016b). More detailed qualifying criteria regarding the indications for CIDP are available (NBA 2018).

NBA procurement of Ig is via competitive tendering and negotiation with suppliers. Blood products prices (including Ig) and the suppliers procured by the NBA are listed on the National Product Price List (NBA 2019c). Only those Igs listed on the National Product List are supplied free of charge to the patient. The suppliers and cost to the government of Ig products indicated for CIDP on the most recent National Product Price List (products at 1 January 2019) are outlined in Table 9.

Table 9 Price and suppliers of Ig products on the National Product Price List for plasma and recombinant products and indicated for CIDP as at 1 January 2019

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Product Type** | **Name** | **Presentation** | **Supplier** | **Price** |
| IVIg (plasma derived – domestic) | Intragam P | 3g/50ml | CSL Behring | $175.48 |
| IVIg (plasma derived – domestic) | Intragam 10 | 2.5g/25ml  10g/100ml  20g/200ml | CSL Behring | $146.23  $584.93  $1,1169.86 |
| IVIg (plasma derived – imported) | Privigen | 5g/50ml  10g/100ml  20g/200ml  40g/400ml | CSL Behring | $225.00  $450.00  $900.00  $1,800.00 |
| IVIg (plasma derived – imported) | Flebogamma 5% | 0.5g/10ml  2.5g/50ml  5g/100ml  10g/200ml  20g/400ml  5g/50ml  10g/100ml  20g/200ml | Grifols | $22.50  $112.50  $225.00  $450.00  $900.00  $225.00  $450.00  $900.00 |

Soource: NBA 2019c

While the government only funds Ig use for those medical conditions that meet Version 3 of The *Criteria*, the Applicant noted that “where an Ig product is not funded and supplied under the National Blood Arrangements, access to Ig for particular cases may still be available as a decision of a hospital drug committee or similar, or otherwise through direct order arrangements by some other source of funding” (Referral Form, page 3).

## Proposal for Public Funding

There are no proposed MBS items relevant to this Assessment.

## Population

As advised by the Reference Group, the population in the PICO is all patients with CIDP who are currently eligible for Ig treatment in Australia according to Version 3 of ‘The *Criteria’* (DoH 2019a). However, no study was identified that used the exact specifications outlined in Version 3 of ‘*The Criteria’*, so this was broadened for this review to include patients with CIDP. The applicability of the identified evidence to the population of this review is discussed in Section C of this report.

CIDP is a neurological autoimmune disorder whereby the body’s immune system attacks and damages the myelin sheath of the peripheral nerves. The peripheral nerves extend from the spinal cord to the rest of the body and are responsible for stimulating muscle contraction and transmitting information back to the nervous system. As the role of myelin is to insulate the nerve axon allowing electrical impulses to travel smoothly, damage to myelin caused by CIDP results in electrical impulses being slowed or lost (GBS/CIDP 2019). The cause of CIDP is unknown and no specific predisposing factors have been identified (Lewis 2019a). It can occur at any age and is more common in men than women (Brain Foundation 2019; MDA 2019). There is no cure (GBS NSW 2019). If left untreated, irreversible damage to the nerve axons can occur. It is estimated that cumulative disability caused by untreated CIDP can lead to wheelchair dependence in around one-third of patients (Berman 2019).

Symptoms and the natural history of CIDP vary widely among individuals. Early symptoms include tingling or loss of feeling in the toes and fingers, and/or weakness in the arms and hands or legs and feet. Usually weakness in the legs and arms occurs together. Weakness or lack of feeling in the feet can cause problems with walking. Other symptoms can include fatigue, dizziness and aching pain in the muscles. A tremor may develop as the disease becomes more severe (GBS NSW 2019; Lewis 2018; Shelat 2018). According to the Guillain-Barré Association of the New South Wales (NSW), the progression of the disease can be characterised into the following subcategories (GBS NSW 2019):

* subacute—symptoms progress and worsen for at least four weeks but not more than eight weeks before plateauing or improving
* chronic progressive—symptoms progress and worsen for a period exceeding eight weeks
* chronic relapsing—more than one episode in which symptoms progress and worsen for a period greater than four weeks
* recurrent—each bout has a progressive phase of less than four weeks

Chronic relapsing CIDP with spontaneous improvement of remissions is the most common form, present in about 80% of patients. In a very small number of people CIDP progresses without remission (GBS NSW 2019).

Diagnosis of CIDP is difficult as there is no definitive test and the symptoms are often vague, matching those of several other diseases (GBS NSW 2019). There are also several variants of CIDP characterised by different presentations, which include typical CIDP, multifocal motor neuropathy, Lewis-Sumner syndrome, pure sensory CIDP and pure motor CIDP (GBS/CIDP 2019). EFNS/PNS guidelines on CIDP published in 2010 note that: “CIDP should be considered in patients who have symmetric or asymmetric polyneuropathy in whom the clinical course is relapsing and remitting or progresses for more than two months, especially if there are positive sensory symptoms, proximal weakness, areflexia without wasting, or preferential loss of vibration” (Van den Bergh et al. 2010). Diagnosis is based on a combination of clinical, electrodiagnostic and laboratory investigations (cerebrospinal fluid, magnetic resonance imaging, nerve biopsy) as well as treatment response as outlined in the EFNS/PNS guideline on CIDP. The PICO Confirmation noted that expert opinion confirmed that the EFNS/PNS guidelines are the most relevant at present, and align with current clinical practice (DoH 2019a). The PICO states that: “the Referrer notes that there is 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”. The PICO further stated that expert advice received during the review phase emphasised the significance of the risk of misdiagnosis, noting that as many as one third of CIDP patients may be misdiagnosed. (DoH 2019a).

A recent systematic review on the incidence and prevalence of CIDP reported a pooled crude incidence rate of 0.33 per 100,000 (95% CI: 0.21 to 0.53) and a pooled prevalence rate of 2.81 per 100,000 (95% CI: 1.58 to 4.39) (Broers et al. 2019). An older study investigating the prevalence of CIDP in NSW reported a crude prevalence of 1.9 per 100,000 (McLeod et al. 1999b). The mean age of onset was 47.6 years (range: 3 to 83 years). Fifty-one per cent of patients had a relapsing-remitting course of disease and 49% had a non-relapsing-remitting disease (chronic progressive, stepwise progressive or subacute onset with remission). Disease duration ranged from 1 to 31 years with a mean of 7.1 (SD 7.0) (McLeod et al. 1999b). The Guillain-Barré Syndrome Association of NSW reports an estimated incidence of CIDP of 12 to 15 per year and an approximate prevalence of 600 sufferers in any one year in Australia (GBS NSW 2019).

Advice received for the PICO indicated that prevalence estimates using the EFNS/PNS criteria were likely to be the most relevant to the Australian clinical setting. Thus, estimated CIDP patient numbers in Australia are expected to fall within the range of 578 to 1,593 patients using upper and lower confidence interval bounds from Rajabaly et al. (2009) and Mahdi Rogers et al. (2014) and including possible, probale and definite cases diagnosed using EFNS/PNS criteria.

Since CIDP is already an approved indication for Ig therapy in Australia, data is available on the national use of Ig for CIDP from 2011/2012 to 2017/2018 (Table 10) and for state-by-state use for 2015 to 2016 (Table 11). It should be noted that the Ig data only pertain to IVIg. No data is available for SCIg as this is currently unavailable for CIDP. However, the Applicant stated that approval for SCIg use in CIDP patients is said to be probable in the foreseeable future (Referral Form, page 4). The PICO notes that according to the Reference Group, the introduction of SCIg is not expected to greatly increase the number of patients using Ig to treat CIDP (DoH 2019a).

Table 10 Change in number of patients using IVIg for CIDP in Australia over time

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Financial year** | **2011–2012** | **2012–13** | **2013–14** | **2014–15** | **2015–16** | **2017–18** | **% Change between 2011–12 to 2017–18** |
| Patient number | 1,551 | 1,753 | 1,903 | 2,054 | 2,250 | 2,595 | 67% |
| Total grams Ig used | 677,458 | 758,271 | 857,533 | 974,258 | 1,071,135 | 1,290,730 | 91% |

Source: NBA annual report 2015-16 (NBA 2019b)

Table 11 IVIg supply for CIDP by state/territory 2015 to 2016

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **State** | **NSW** | **VIC** | **QLD** | **WA** | **SA** | **TAS** | **ACT** | **NT** | **National** |
| Patient number | 834 | 507 | 648 | 130 | 93 | 36 | 32 | 15 | 2,250 |
| grams | 363,767 | 248,735 | 277,894 | 104,920 | 40,008 | 196,416 | 9,843 | 6,557 | 1,071,135 |
| grams/episode | 39 | 38 | 34 | 64 | 45 | 39 | 32 | 42 | 39 |
| grams per 1,000 | 47 | 41 | 58 | 40 | 23 | 38 | 25 | 27 | 45 |

Source: Source: NBA annual report 2015-16 (NBA 2019b)

Note: IVIg supply by state for the 2017-18 time period was not available.

There appears to be a discrepancy between the current number of patients using Ig for CIDP (as reported in Table 10) and data on the prevalence of CIDP. Expert advice is that the reason for this is likely multifaceted and may be due to prevalence studies using a narrower set of criteria for CIDP diagnosis than that used in clinical practice, and patients being misdiagnosed with CIDP such as patients with non-CIDP autoimmune neuropathies being labelled as having CIDP (Expert Neurologist 2019). This issue is further discussed in Section C of this Assessment.

## Comparator Details

Comparators to Ig agreed upon in the PICO (DoH 2019a) are:

* Steroids (oral and IV)
* Plasma exchange
* Immunosuppressant and/or immunomodulatory drugs and therapies, not including steroids or Ig (this comparator is referred to as immunosuppressants in this report, or by specific drug name)
* A combination of two or more of the above therapies
* No active treatment, no Ig

### Steroids (oral and IV)

Corticosteroids, which work by suppressing the immune system (Hughes et al. 2017), are frequently used as a first-line treatment of CIDP and have a long history of use in its management (Dyck and Tracy 2018; Ryan and Ryan 2018). A range of corticosteroid types and dosing regimens (e.g. daily and alternate-day oral, weekly pulsed oral, weekly or monthly pulsed intravenous) have been used in the management of CIDP (Lewis 2019b; van Lieverloo et al. 2018). The PICO stated that expert advice indicated no standard dosing regimens exist, however, an example of a steroid prescription for CIDP in Australia would likely involve initial high doses (e.g., prednisone at 40mg per day for two months) with a gradual reduction until the minimum effective dose is reached (DoH 2019a).

The Applicant noted that there are four glucocorticoids relevant for consideration as comparators to Ig: prednisone, prednisolone, dexamethasone and methylprednisolone (Referral Form, page 37). All four are listed on the PBS. Their details, as provided in the PICO, are outlined in Table 12 (DoH 2019a).

Table 12 Corticosteroids listed on the PBS and subsidised for CIDP according to the Applicant

|  |  |  |  |
| --- | --- | --- | --- |
| **Generic name** | **Available brand** | **PBS restriction** | **Code and prescriber number** |
| Prednisone | 1 & 5 mg tablets (Predsone & Panafcort)  25 mg tablet (Panafcort & Sone) | Unrestricted | 1934T (1 mg tablet, 100)  1935W (5 mg tablet, 60)  1936W (25 mg tablet, 30) |
| Prednisolone | 1 mg tablet (Predsolone & Panafcortelone)  5 & 25 mg tablets (Panafcortelone & Solone) | Unrestricted | 3152X (1 mg tablet, 100)  1917X (5 mg tablet, 60)  1916W (25 mg tablet, 30) |
| Dexamethasone | 0.5 mg & 4 mg tablet (Dexmethsone) | Unrestricted | 2507Y (4 mg tablet, 30)  129B (0.5 mg tablet, 30) |
| Methylprednisolone | 40 mg/mL injection, 5 x 1 mL vials (Depo-Nisolone, Depo-Medrol)  40 mg injection, 5 vials & inert diluent (Solu-Medrol)  40 mg powder for injection, 5 vials (Methylpred)  1000 mg powder for injection (Methylpred, Methylprednisolone Alphapharm, Solu-Medrol) | Unrestricted | 5148Y (40 mg/mL injection, 5 x 1 mL vials)  1928L (40 mg/mL injection, 5 x 1 mL vials)  2981X (40 mg injection, 5 vials & inert diluent)  5263B (40 mg powder for injection, 5)  5264C (1000 mg powder for injection) |

Source: Table reproduced from the PICO (page 18)(DoH 2019a)

CIDP: chronic inflammatory demyelinating polyneuropathy

Prolonged use of steroids is linked with serious side effects including osteoporosis, cataracts, diabetes hypertension, obesity and myopathy (GBS NSW 2019). It is noted in the Referral Form (page 37) that the Reference Group clinical expert advised that about 50% of patients not on Ig therapy would be on high-dose steroids, which are inappropriate in the long-term due to adverse events. Owing to these side effects, corticosteroids are used in conjunction with steroid-sparing therapy in the form of immunosuppressants (DoH 2019a). By suppressing the immune system, a lower dose of steroids can be used. The types of immunosuppressants used are discussed below.

The PICO noted a contraindication for corticosteroid use for patients who have a pure motor form of CIDP (muscle weakness with no sensory loss) (DoH 2019a). Other contraindications include peptic ulcer disease, brittle diabetes, refractory hypertension, severe osteoporosis and systemic fungal infections (Lewis 2019b).

### Plasma exchange

Plasma exchange is an alternative first-line treatment to steroids for CIDP. The Referral Form (page 37) states that it is the second most common comparator treatment following corticosteroids. The procedure involves taking blood from a patient, separating the plasma (the fluid component of the blood) from the cellular fraction and replacing it with a plasma substitute (usually albumin), then returning the cells plus plasma substitute to the patient (Oaklander et al. 2017; Ryan and Ryan 2018). This is done via a machine called a Blood Cell Separator. The theory behind plasma exchange is that it removes the antibodies and complement components responsible for damaging the myelin sheath of the peripheral nerves (Lewis 2018). The American Society for Apheresis recommends that patients with CIDP initially receive 1 to 1.5 plasma volume exchanges, two to three times per week until improvement and then taper as tolerated. Maintenance plasma exchange may be required at weekly or monthly intervals to control symptoms (Schwartz et al. 2016). Expert advice provided in the PICO noted that there is no standardised plasma exchange schedule in Australia, however, five exchanges trialled over 7 to 11 days would be the most common approach (DoH 2019b). The Guillain-Barré Association of NSW reports that approximately two or three litres of plasma is exchanged at each session and this is repeated several times over about two weeks (GBS NSW 2019). Expert opinion provided to the PICO was that that while some patients may receive long-term plasma exchange, it would most commonly be provided in combination with an immunosuppressant (DoH 2019a). The Reference Group noted that PE was rarely used as an ongoing treatment due to vascular access issues, and lack of access to centres that provide this service.

Contraindications for plasma exchange include active infections, haemodynamic instability, hypocalcaemia and allergies to heparin or albumin (Stieglitz 2018). One general review noted that plasma exchange is an appealing therapy for patients who have contraindications to other treatments such as those with diabetes mellitus (contraindicated to steroids) or pre-existing renal insufficiency (contraindicated to IVIg) (Gorson 2012).

### Immunosuppressants and/or immunomodulatory drugs (other than steroids)

Several immunosuppressive drugs have been reported to be beneficial for CIDP. The Referral Form lists nine sourced from the EFNS/PNS guideline on management of CIDP (Van den Bergh et al. 2010) and an RCT (Hughes et al. 2018). Table 13, which has been reproduced from the PICO (DoH 2019a), lists these drugs along with their PBS item numbers. Table 16 in Section A.7. outlines recommended dosages of immunosuppressants for treatment of CIDP along with suggested frequency of monitoring during treatment.

Table 13 Immunosuppressants listed on the PBS and subsidised for CIDP treatments

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

Source: Reproduced from the PICO. Adapted from pages 39 and 40 for the Referral Form; original source: PBS website

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)

CIDP: chronic inflammatory demyelinating polyneuropathy; MR: Modified release; NA: Not applicable; NR: Not reported; PBS: Pharmaceutical Benefits Scheme.

The PICO notes that Fingolomad (Gilenya) and Rituximab (Mabthera) are not PBS subsidised for CIDP and are listed as “authority required, CIDP not included”. A literature review on CIDP reported that, historically, azathioprine and cyclophosphamide have probably been the most commonly used drug for CIDP, with azathioprine generally used as a steroid-sparing medication or reserved for patients with mild disease (Lewis 2019b). Expert advice, as reported in the PICO, noted that mycophenolate (or azathioprine) would be used as second-line immunosuppressant therapies. Further advice states that it is unlikely that anyone still receives Fingolomad for CIDP, however, Rituximab (Mabthera) is commonly used for CIDP when patients have failed other immunosuppressant therapy, with the cost often borne by hospital drug committees (DoH 2019a). Azathioprine is the most widely used immunosuppressant in the treatment of CIDP according to the Guillain-Barré Association of NSW information page on CIDP.

The PICO notes that expert advice regarding the use of immunosuppressants for CIDP in Australia is that they not be used as stand-alone treatments but are initiated alongside corticosteroids and continued following tapering of steroid dosage if necessary. The clinical expert to the PICO stated that the reason for this was the longer duration required for immunosuppressants to have an effect in comparison to the short action time associated with corticosteroids (DoH 2019a). A literature review on CIDP noted that a therapeutic response to azathioprine may take greater than six months (Lewis 2019b). Another review on the management of CIDP stated in reference to the use of immunosuppressants drugs as second-line therapies for CIDP, that it is critical to use these alternative drugs for long enough (e.g. azathioprine for at least 12 to 18 months) before concluding that the second-line drug is ineffective and moving on to alternative second-line medication trials (Gorson 2012).

## Clinical management Algorithm(s)

Figures 1 and 2 describe the current management of CIDP in patients for whom Ig therapy is indicated and not indicated, respectively.

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



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.

Figure 2 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

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

## Key Differences in the Delivery of the Medical Service and the Main Comparator

Care and treatment of CIDP patients is primarily managed by neurologists. Patients living in regional or rural areas may have ongoing care provided by a general medicine physician and/or neurologist (Referral Form, page 30).

**Immunoglobulins**

*IVIg*

In order to receive IVIg treatment for CIDP a patient must have received a diagnosis from a neurologist, as specified in Version 3 of *‘the Criteria’* (NBA 2018). IVIg treatment can only be prescribed by a BloodSTAR-registered treating medical officer who is an Australian Health Practitioner Regulation Agency (AHPRA)-registered neurologist. The reviewing medical officer (also BloodSTAR registered) must be an AHPRA registered neurologist or a general physician (Referral form page 31). IVIg is infused through a vein in the patient’s arm.

A list of possible settings where Ig infusion can occur in Australia, as reported in the Referral Form (page 31), include:

* 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

The setting must be accredited to administer blood products under the National Safety and Quality Health Service Standard for Blood Management. According to clinical advisers on the Review Group (Referral Form, page 31), IVIg infusion in Australia predominantly occurs in the public outpatient setting. However, due to funding incentives, patients were often admitted on a ’same-day care’ basis and counted as inpatients. The clinical advisers estimated that 75% of infusions were given in this setting. Inpatient administration of IVIg for CIDP was considered rare in either the public or private hospital setting (Referral Form, page 31).

The dosing regimen and amount of IVIg to be infused and for initial CIDP treatment and for treatment of CIDP relapse is shown in Table 14. Most patients with CIDP would receive treatment every four weeks for 12 months followed by a weaning process to withdraw IVIg completely. Patients who respond well initially and remain stable after 4-6 months, may have infusions spaced out to every six weeks. Conversely, patients with more severe disease, or those who develop weakness in the week prior to their infusion, may have their infusion interval reduced (e.g. every 2 or 3 weeks) (Expert Neurologist 2019).

Table 14 Current specified dosages of IVIg for initial CIDP treatment and for CIDP relapse\*

|  |  |
| --- | --- |
| Induction dose | 2.0g/kg in 2-5 divided doses. |
| Maintenance dose† | 0.4-1.0g/kg, 2–6 weekly. 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 might be by smaller doses more frequently than fortnightly. |

Soource: as defined in Version 3 of ‘the Criteria’(NBA, 2018)

\*Relapse of CIDP patients within six months of commencement of trial off Ig therapy. Once a patient has relapsed when trialled off Ig treatment, a second line immunomodulatory agent should be strongly considered as additional therapy.

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

The infusion is generally administered by a registered nurse, and the patient’s vital signs must be monitored throughout the infusion by a registered or enrolled nurse (Referral Form, page 30). Infusion generally takes about three hours to complete (AAAAI 2019), with the time required for each infusion dependent on the patient’s weight, the dose required, the product’s advised infusion rate, hospital protocol, and the patient’s response during infusion (Referral Form, page 29). If the dose is large (e.g. 2g/kg = 160g for an 80kg patient) it is more likely to be split over consecutive days. Smaller doses (e.g. 0.5g/kg = 30g for a 60kg patient) are more likely to be given over the course of half to one day (Referral Form, page 29).

The frequency with which a patient must be reviewed whilst receiving IVIg is specified in Version 3 of *‘the Criteria’* (NBA 2018). Patients receiving IVIg as first-line treatment for CIDP or following a CIDP relapse within six months of commencing a trial off Ig therapy, must be reviewed by a neurologist after four months of Ig therapy to determine patient response. Those who have responded to IVIg must be reviewed by a neurologist or general physician every 12 months. Repeat nerve conduction studies must be conducted at four months to assess patient response whilst undergoing IVIg treatment, however if patients are clinically improving, these tests may not be required. Blood tests for electrolytes, urea, creatinine, liver function and full blood counts may be ordered every four to six weeks during the first few months of treatment. These parameters are more closely checked with steroid or adjuvant immunosuppression treatment than with IVIg (Expert Neurologist 2019).

*SCIg*

The Referral Form noted (page 31) that while SCIg is not currently funded under the National Blood Arrangements for CIDP, clinicians believed that SCIg use will emerge if it is funded for this indication in future. The NBA advised that SCIg could be funded in the future[[5]](#footnote-6) and thus it should be investigated as part of this Assessment and is here discussed accordingly.

SCIg is administered by injecting purified Ig into fatty tissue underneath the skin in the abdomen, thighs or upper arms. The patient or carer at home uses an infusion pump (spring loaded or battery powered) or injects by hand using a syringe and a rapid push method (ASCIA 2018). Unlike with IVIg there is no need to travel to hospital or take time off school/work and the treatment can be taken along when travelling (ASCIA 2018). According to the NBA, SCIg is initially supplied monthly. The product can be collected at an agreed hospital pharmacy or medical centre that does not have to be the treating hospital, and repeat prescriptions can be accessed without seeing a doctor (NBA 2016a). Some SCIg products require refrigerated transport and storage between 2-8°C. Patients are required to use a diary to keep record of their treatments. (NBA 2016c)

Compared with IVIg, SCIg is administered through several smaller doses delivered via a series of injections. The infusion schedule depends on dosage and tolerance, but is more frequent than for IVIg (e.g. 1-3 times per week) (ASCIA 2018). As treatment of CIDP with SCIg is not currently funded by the NBA, there are no dosing guidelines provided in the current version of ‘*the Criteria*’ (Version 3) nor in the most current EFNS/PNS guidelines on CIDP (Van den Bergh et al. 2010). Pharmokinetic differences between IVIg and SCIg mean that bioavailability is lower after SCIg administration than after IVIg. For this reason, the Food and Drug Administration (FDA) requires manufacturers to calculate a dose-adjustment coefficient to achieve similar total exposure to Ig (Fadeyi and Tran 2013). CSL Behring advises that the recommended dosage for SCIg Hizentra maintenance therapy in adults with CIDP is 0.2g/kg body weight (1ml/kg) per week, to be initiated one week after the last IVIg infusion. The first infusion volume should be ≤20ml/site at a rate of ≤20ml/site/hour. Subsequent infusions can be up to ≤50ml/site at a rate of ≤50ml/site/hour (CSL Behring 2019). Hizentra may be infused into multiple injection sites at least two inches apart. Up to eight infusion sites in parallel may be used with multiple infusion devices in use simultaneously (CSL Behring 2019). Tolerance by the patient is the only limit to the volume infused per site and the number of injection sites per infusion. Thus, SCIg offers patients flexibility in infusion administration, with a greater number of needles and sites per session and fewer infusions per week, or fewer injections per infusion and a greater number of infusions per week to meet the target dose (Berman 2019).

Patients can only source SCIg from a public or private hospital that has established its capability and capacity to manage a hospital-based SCIg program within the governing requirements outlined by the NBA (NBA 2019a). A list of hospitals currently participating in the National SCIg Program (updated 4 March 2019) and their contact details are provided on the NBA website (NBA 2019a).

Prior to using SCIg, patients must participate in a hospital-based education and training program to ensure safe and effective treatment delivery. A training program checklist produced by the Sunshine Coast Hospital and Health Service notes the following with respect to patient SCIg training:

* Training is weekly for the first 2-4 weeks (until the patient is confident and competent), with the first training day requiring a 3-hour booking
* Subsequent training may require 2-hour sessions
* Once training is complete the patient must be booked monthly for 15 to 30 minutes at an appropriate SCIg Infusion Clinic for collection of Ig product and disposables, documentation of previous infusions, and completion of a treatment record sheet (DHHS Vic 2019).

According to the NBA, the responsibilities of hospitals participating in national SCIg programs include (NBA 2019a):

* Education and training of staff and patients to ensure appropriate management and use of SCIg, including transport, storage, equipment use and infusion techniques
* Ongoing clinical oversight and patient support, including community nursing, hospital in the home, or contacts for both routine and emergency support as required
* Ensuring patients have access to all necessary equipment and consumables at no additional cost to the patient
* Regular reviews to assess clinical benefit at periods specified by the responsible clinician in line withVersion 3 of *‘the Criteria’*, and;
* Encouraging patients to maintain a diary to record SCIg use and any adverse reactions.

The Australasian Society of Clinical Immunology and Allergy notes that monitoring, advice and clinical assessment of patients on SCIg should be equivalent to current IVIg therapy standards of delivery, which necessitates regular contact with caregivers in specialist teams (ASCIA 2018).

**Steroids**

Steroid treatment for CIDP can be via oral tablets or IV infusion. Dosing regimens include daily and alternate-day oral prednisone, weekly pulse oral methylprednisolone and weekly or monthly pulse IV methylprednisolone (Lewis 2019b). According to the literature, and the opinion of a clinical expert as reported in the PICO, there are no standard dosing regimens for steroid treatment of CIDP (DoH 2019a; Lewis 2019b). The decision as to which regimen to use and how fast to taper is based on a variety of factors including the patient’s health and the severity and pattern of CIDP (Lewis 2019b).

Oral steroids can be administered by the patient at home and can be obtained with a script at any pharmacy. An example of an oral (daily) steroid prescription for CIDP in Australia, as provided by a clinical expert to the PICO, is an initial high dose (e.g. prednisone at 40mg/day for two months) with a gradual reduction in dose until the minimum effective dose is reached. A second example, provided by another clinical expert is 1mg/kg/day of prednisolone (capped at 100mg) continued for 1-3 months, followed by slow tapering of the dose if the patient is stable (e.g. 5-10mg every 2-4 weeks). These examples are for a ‘typical’ patient, and the initial dose and the level to which it can be tapered is affected by patient characteristics, clinical response, side effects and early use of steroid-sparing agents.

Patients on IV steroids must travel to a hospital to receive treatment, even a small hospital will usually suffice (Expert Neurologist 2019). Each steroid infusion, which occurs through a needle in the arm or hand, takes approximately 30 to 45 minutes. Patients need to be at the hospital for approximately one hour to allow blood tests to be taken prior to infusion for monitoring of blood count, sodium and potassium levels. The patient’s blood pressure and pulse will also be checked. Patients are able to return to normal activities, including driving, after treatment (GWH NHS 2014; WebMD 2017). As stated above, no standardised dosing regimens exist for IV steroid treatment of CIDP. In Australia, oral prednisolone comprises the typical dosing regimen for IV steroid treatment of CIDP (Expert Neurologist 2019). A study by Lopate et a. (2005) reviewing the retrospective medical records of patients undergoing IV methylprednisolone as an initial and long-term maintenance therapy for patients with CIDP, reported that the most typical regimen was an initial dose of 1000mg/day of methylprednisolone on each of 3-5 consecutive days, followed by 1000mg on day one each week for the next month. Dosage was then tapered in frequency and amount over a period of two months to two years (Lopate et al. 2005).

Regular tests are required to monitor patients because of the potential adverse effects that corticosteroids can have on multiple organs (Hsu and Katelaris 2009). Owing to the potential side effects, patients on steroids need to be monitored more closely than do patients on Ig. A patient on long-term steroids needs regular (at least 6-monthly) reviews for blood pressure, blood sugar, weight, skin integrity, infectious complications and dental review etc. If the patient is on steroid-sparing agents, further regular blood tests are required (Expert Neurologist 2019). Specific tests and suggested frequencies are reported in Table 15. It is also recommended that baseline bone mineral density should be measured if corticosteroid therapy is required for more than three months, and that it should be checked every 1-2 years (Expert Neurologist 2019; Hsu and Katelaris 2009). Bone protective therapy should also be commenced at the time of starting steroid therapy in high-risk individuals (e.g. those aged 65 years or over, those with prior bone fragility, and osteopaenic patients) (Hsu and Katelaris 2009). Clinical advice also recommends that proton pump inhibitor therapy (pantoprazole 40mg daily) should be given to patients on long-term steroids for prevention of gastric ulcers, and patients on >20mg prednisolone for more than two weeks should receive additional management for prevention of infectious complications, including testing for latent infection and treatment if detected (Expert Neurologist 2019). Patients should also be screened periodically for diabetes, owing to the effect of steroids on blood glucose (Hsu and Katelaris 2009).

Table 15 Suggested frequency of monitoring during treatment with corticosteroids

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Full blood count** | **Electrolytes, urea, creatinine, fasting glucose liver function tests** | **Liver function tests** | **Calcium magnesium phosphate** | **Fasting lipids** | **Eye review** | **Urinalysis** |
| 3 monthly | 3 monthly | 3 monthly | NR | 6 monthly | If symptomatic | NR |

Source: (Hsu and Katelaris 2009)

NR: not routinely recommended

**Plasma exchange**

Patients undergoing plasma exchange must visit a hospital licensed and accredited to perform apheresis. In Australia, plasma exchange is only provided in major teaching hospitals in an outpatient, day stay or inpatient setting (DoH 2019a).

Laboratory tests to be conducted prior to the first apheresis treatment include a complete blood count, electrolytes and creatinine, calcium, magnesium, phosphate and albumin (Pavenski 2018). At the hospital, the patient is connected to a cell separator via two large-bore needles inserted into the patient’s arms. Whole blood is removed from one arm, blood cells are separated from the plasma in the cell separator, and the blood cells plus albumin and saline are returned to the patient via a needle in the other arm. Patients must endure repeated needle insertions each time they undergo the procedure, unless they have poor peripheral venous access for repeated insertions, in which case they will be required to have a double-lumen, central venous catheter placed (temporary catheter installed for a few weeks, or a permanent catheter) (Lewis 2018). Placement of a central venous catheter comes with associated risks including pneumothorax, catheter site infection and venous thrombosis.

There are no specific guidelines outlining the frequency or schedule of treatment with plasma exchange for CIDP patients (Gorson 2012). Expert opinion provided to the PICO noted that five exchanges over 7-11 days would be the most common approach. This is similar to that reported by the Guillain-Barré Association of NSW, which notes that plasma exchange for CIDP is usually repeated several times over about two weeks, with approximately 2-3 litres of plasma exchanged at each session (GBS NSW 2019). The American Society for Apheresis guidelines recommend 1-1.5 total plasma volume exchanges 2-3 times per week until improvement (Schwartz et al. 2016). Plasma volume is calculated using a standardised formula for sex, height, weight and haematocrit (Pavenski 2018). The British Committee for Standards in Haematology guidelines also state that the optimum treatment volume for each procedure is 100-150% of the patient’s plasma volume. This committee further notes that to avoid excessive hypofibrinogenaemia while maximising removal of the target macromolecule, many centres initially perform a run of five exchanges at 100% plasma volume at daily or alternate-day intervals for the majority of indications (Howell et al. 2015). For indications where maintenance of plasma exchange is required the frequency of exchanges may vary from once every two weeks to once every six weeks, guided by symptoms (Howell et al. 2015).

Each plasma exchange session takes around two hours, depending on the amount of plasma exchanged (American Society for Apheresis 2019). It is recommended that patients do not drive after the procedure nor do any hard physical exercise for the remainder of the day, as the procedure generally makes people feel tired (NHS 2014). Following plasma exchange, patients should be clinically assessed, and post-treatment blood results reviewed. Fibrinogen levels should also be monitored (Howell et al. 2015).

**Immunosuppressants and/or immunomodulatory drugs (other than steroids)**

Immunosuppressants can be delivered in the form of tablets or intravenously. Cyclophosphamide and rituximab are used in aggressive, steroid-refractory cases (Expert Neurologist 2019). A list of immunosuppressants relevant to this Assessment was provided in the Referral Form and is here described in Table 13 (Section A.5.) Possible dosage regimens for some of these immunosuppressants are provided in Table 16.

Table 16 Recommended dosages for immunosuppressants used to treat CIDP

|  |  |  |
| --- | --- | --- |
| **Immunosuppressant** | **Form** | **Dosage** |
| Azathioprine | Oral | 2.0 to 3.0mg/kg/day |
| Oral | Started at 1 mg/kg/day and then titrated up to achieve a response (up to 2.5mg/kg/day). |
| Cyclosporine A | Oral | 5.0mg/kg/day. Provided as two dosages, 12 hours apart. Dose adjustment is made following target blood levels. Once the patient has stabilised the dosage should be titrated to the lowest dose required to maintain improvement. |
| Cyclophosphamide | Intravenous | 1.0g/m2 administered monthly for 6 to 12 months. |
| Oral | 2.0mg/kg/day. |
| Mycophenolate mofetil | Oral | 1.0g twice per day. |
| Oral | 500mg twice per day and titrated up to achieve a response (up to 1500mg twice per day). |

Source: as derived from the literature (Gorson 2012) and from advice provided by a clinical expert.

Owing to the significant adverse effects and toxicity of immunosuppressants, patients need to be under constant surveillance including undergoing various tests, necessitating a partnership between the specialist and a general practitioner (Trevillian 2006). Patients on azathioprine require blood tests every week for two months, then every month thereafter. Those on mycophenolate mofetil require blood tests weekly for one month, twice a month for two months, and then every 1-3 months (Expert Neurologist 2019). The specific tests that patients should undergo when on different immunosuppressants, and their recommended frequency, are shown in Table 17. Surveillance may need to continue long after the treatment with immunosuppressive drugs has ceased (Hsu and Katelaris 2009). For patients receiving cyclophosphamide, for example, it is necessary to monitor for haematuria and check urine cytology every 6-12 months after discontinuation as bladder transitional cell carcinomas can develop up to 15 years after treatment has stopped (Hsu and Katelaris 2009).

Table 17 Suggested frequency of monitoring during treatment with immunosuppressive drugs

| **Immunosuppressant** | **Recommended frequency of monitoring** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Full blood count** | **Electrolytes, urea, creatinine, FG, LFT** | **Liver function tests** | **Calcium magnesium phosphate** | **Fasting lipids** | **Eye review** | **Urinalysis** |
| Azathioprine | 1-3 monthly | 1-3 monthly | 1-3 monthly | NR | 6 monthly | NR | NR |
| Ciclosporin/tacrolimus | 1-3 monthly | 1-3 monthly | 1-3 monthly | 1-3 monthly | 6 monthly | NR | NR |
| Methotrexate | 1-3 monthly | 1-3 monthly | 1-3 monthly | NR | 12 monthly | NR | NR |
| Mycophenolate | 1-3 monthly | 1-3 monthly | 1-3 monthly | NR | 12 monthly | NR | NR |
| Cyclophosphamide | Fortnightly to monthly | monthly | monthly | NR | 12 monthly | NR | 6 monthly |

FG = fasting glucose; LFT = liver function tests; NR = not routinely required.

Source: (Hsu and Katelaris 2009)

Like oral steroids, oral immunosuppressants can be administered by the patient at home and obtained with a script at any pharmacy.

## Clinical Claim

The following clinical claims have been made regarding Ig use for the management of CIDP:

* Ig has superior effectiveness but inferior safety to the comparator treatment of no active treatment
* Ig has non-inferior effectiveness and superior safety than the comparator intervention of steroids
* Ig has non-inferior effectiveness and superior safety than the comparator intervention of plasma exchange
* Ig has non-inferior effectiveness and superior safety than the comparator intervention of immunosuppressant and/or immunomodulatory drugs and therapies (other than steroids)
* Ig has non-inferior effectiveness and superior safety than the comparator intervention of a combination of two or more of the previously mentioned therapies

## Summary of the PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each Assessment. The PICO Confirmation describes current clinical practice and reflects likely future practice with the medical service.

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1 and Box 2.

Box 1 Criteria for identifying and selecting studies to determine the safety of Ig in patients with CIDP

|  |  |
| --- | --- |
| **Selection criteria** | **Description** |
| Population | Patients with chronic inflammatory demyelinating neuropathy (CIDP) |
| Intervention | Intravenous and subcutaneous immunoglobulin (IVIg and SCIg) |
| Comparators | * Steroids (oral and intravenous) * Plasma exchange * Immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids) * A combination of two or more of the above therapies * No active treatment |
| Outcomes | Critical for decision making:  Any adverse events including the development of disease or side effects (e.g. infections, diabetes, hypertension, cardiovascular disease, prolonged ventilation in ICU). |
| **Systematic review question** | What is the relative safety of Ig (IVIg and SCIg) for the management of CIDP? |

CIDP: chronic inflammatory demyelinating neuropathy; ICU: intensive care unit; Ig: immunoglobulin

Box 2 Criteria for identifying and selecting studies to determine the efficacy of Ig in patients with CIDP

|  |  |
| --- | --- |
| **Selection criteria** | **Description** |
| Population | Patients with chronic inflammatory demyelinating neuropathy (CIDP) |
| Intervention | Intravenous and subcutaneous immunoglobulin (IVIg and SCIg) |
| Comparators | * Steroids (oral and intravenous) * Plasma exchange * Immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids) * A combination of two or more of the above therapies * No active treatment |
| Outcomes | Critical for decision making:   * 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 Ranking Scale (MRS) in children) * Change in quality of life * Mortality |
| **Systematic review question** | What is the relative efficacy of Ig (IVIg and SCIg) for the management of CIDP? |

CIDP: chronic inflammatory demyelinating neuropathy; Ig: immunoglobulin

## Consumer impact statement

All feedback was broadly supportive of Ig use for CIDP.

### Targeted Consultation Survey feedback

Feedback to the Targeted Consultation Survey was received from a specialist neurologist and a manufacturer of therapeutic plasma exchange devices.

All feedback noted the advantages associated with Ig, highlighting high response rates to treatment and generally high tolerability of the treatment.

Disadvantages included adverse events associated with treatment, requirement for in-hospital treatment, and issues with acess-to-treatment arising from increasing demand for Ig. It was noted that SCIg may negate the disadvantage of hospital attendance. Both feedback responses noted the financial burden associated with Ig therapy.

The therapeutic plasma exchange device manufacturer recommended that plasma exchange should be considered a first-line treatment for CIDP, noting evidence that Ig and therapeutic plasma exchange are therapeutically equivalent.

### Sponsor comments on the PICO confirmation

On 21 May 2019, sponsors of Ig were contacted and given an opportunity to provide input to the development of this contracted assessment, specifically information relevant to the utilisation, efficacy, safety and cost-effectiveness of Ig. The submissions received from four companies were provided to the contracted HTA group for consideration in the development of this report. Much of this feedback included key trials already identified in this Assessment Report. Sponsors did not provide any unpublished clinical trial data that would furhter inform the contracted assessment. Sponsors also provided comments on management of the Ig supply and access to SCIg, and the process for the Ig Reviews in general. Other feedback advised amending aspects of the PICO Confirmation. Since this has been ratified and cannot be changed, this feedback was noted by the Assessment Group but not reproduced here.

Specific feedback relevant to the Contracted Assessment was:

* Maximum benefit of Ig treatment may occur at 24 weeks
* Diagnosis of CIDP should include testing of four motor nerves and four sensory nerves
* Evidence on the effectiveness of second-line immunomodulatory agents is limited
* Occasional steroids may be used to manage headaches associated with Ig
* EFNS/PNS guidelines are currently being updated and are expected to list SCIg as an alternative to IVIg for maintenance treatment of CIDP
* Published prevalence data should be interpreted with caution as studies used different classification criteria to estimate CIDP prevalence
* The NBA reported average dose of Ig used by patients with CIDP is low, suggesting that neurologists are using the lowest possible dose to achieve remission.

# Section B Clinical Evaluation

## Literature Sources and Search Strategies

The medical literature was searched on 25 March 2019 to identify all relevant studies published to date on the treatment of CIDP. Searches were conducted of the databases and sources described in Appendix B. Search terms are described in Table 18.

Table 18 Search terms used in PubMed (adapted for Embase)

| Element of clinical question | Search terms |
| --- | --- |
| Population | CIDP, Chronic inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy [MeSH Terms] |
| Limits | No limits were applied |

To ensure all relevant data on treatment of CIDP was identified a broad search strategy was employed; including only terms for the population of interest.

Our search strategy was deliberately broad to identify all studies on the treatment of CIDP. Only terms relating to the population were included and no limits were used.

## Results of Literature Search

A PRISMA flowchart (Figure 3) provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al. 2009). A total of 20 randomised controlled trials (RCTs) reported in 28 studies were identified to inform on relative safety and effectiveness. An additional 36 non-randomised comparative and single-arm studies were included in the extended assessment of harms.

Studies were screened by title and abstract by a single reviewer, with all exclusions checked by a second reviewer. Full-text selection was performed independently by two reviewers.

Additional pre-specified criteria for excluding studies are detailed in Table 19. It was our intention to perform a network meta-analysis on all treatments for CIDP relevant to this Assessment: Ig, steroids, plasma exchange, immunosuppressants, any combinations of these treatments (combination therapy) and no treatment (including placebo). With this in mind we included any RCT on the intervention or any of the included comparators. Studies with a lower level of evidence (non-randomised comparative studies and single-arm studies) were included for the extended assessment of harms.

Table 19 Study selection criteria

| Selection criteria | Inclusion criteria | Exclusion criteria |
| --- | --- | --- |
| Population | Any patients with CIDP or IgA and IgG paraprotein neuropathies | Other related immunological conditions (GBS, MS, IgM paraprotein neuropathy)  Studies reporting on more than one type of immune condition where CIDP results were not reported separately. |
| Intervention | Any Ig treatment for CIDP | Nil |
| Comparator | Active comparators:   * plasma exchange * corticosteroids * immunosuppressants including autologous transfer) * any combination of these.   No treatment:   * no active treatment * placebo | Etanercept, Interferons, Fc receptor inhibitors, Ig capture columns.  Note: studies comparing these excluded comparators to either Ig or another active comparator were selected for possible inclusion in the network meta-analysis. |
| Outcomes | Any treatment effect measured  Any safety outcomes | Outcomes not related to effectiveness or safety. |
| Study type | Comparative safety and effectiveness:  Any RCT on the intervention or any comparators  Extended assessment of harms:  Any non-randomised comparative study or case series study on the intervention and/or any comparators | Case reports (<10 patients)  Narrative reviews  Opinion pieces  Letters |

Abbreviations: CIDP = Chronic inflammatory demyelinating polyneuropathy, Ig = immunoglobulin, GBS = Guillain-Barre Syndrome, MS = Multiple sclerosis, RCT = randomised controlled trial.

Studies excluded following full-text review are listed as Excluded Studies in Appendix D. All other studies that met the inclusion criteria are listed in Appendix C.

Figure 3 Summary of the process used to identify and select studies for the Assessment



Abbreviations: CIDP = Chronic inflammatory demyelinating polyneuropathy; RCT = randomised controlled trial.

A: eg refers to narrative reviews, editorials, letters and case reports of ≤ 10 patients.

A profile of each included study is provided in Appendix C, describing the authors, study ID, publication year, study design and quality (risk of bias), study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator, and relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4.

### Appraisal of the evidence

Appraisal of the evidence was conducted in three stages:

Stage 1: Appraisal of the risk of bias within individual RCTs included in the review (Section B.3).

Stage 2: Extraction of the pre-specified outcomes for this Assessment, synthesising to determine an estimate of effect per outcome.

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6-8).

## Risk of Bias Assessment

### Risk of bias in the randomised controlled trials

The risk of bias in the included RCTs was assessed using the Revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2) (Higgins et al. 2016). Studies were assessed by a single reviewer and checked by a second reviewer. The Cochrane risk of bias (ROB) tool assesses bias in five domains:

1. Bias arising from the randomisation process
2. Bias due to deviation from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

The overall risk of bias was deemed to be low in 30% of the studies, of some concern in 15%, and high in in 55% of studies. A summary of the assessment is presented in Table 20.

Table 20 Summary of Cochrane Risk of Bias assessment of the included randomised controlled trials

Quality appraisal of RCTs using Cochran RoB tool.

With respect to the randomisation process, just over half of the studies were deemed to have low risk of bias (55%) and just under half were deemed to have some concerns (40%). The concerns were attributable to the lack of reporting regarding both concealment and/or randomisation. One study (Zinman et al. 2005) scored a high risk of bias for this domain due to concerns over the differences in one of the baseline characteristics (duration of disease) being higher in the IVIg-treated group. The authors noted that owing to the small numbers of patients in the study, “the randomisation process may have resulted in important baseline differences”.

For the domain ‘bias due to deviation from intended interventions’, half of the studies had a low risk of bias. There were ‘some concerns’ in 15% of the studies due to three studies not conducting ‘intention-to-treat’ analyses. They were not graded as ‘high risk’ of bias as it was deemed unlikely that failure to analyse participants in the group to which they were randomised would have had a substantial impact on the results. The remaining seven studies (35%) were all assessed as having a ‘high risk’ of bias. These studies also failed to do ‘intention-to-treat’ analyses and it was deemed that this possibly could have had a substantial impact on the results. Studies varied in terms of blinding of patients and carers. In 11 studies (55%) both the patient and carer were blinded to the assigned intervention. In five studies (25%) both the patient and carer were either probably aware, or were aware, of the assigned intervention.

Missing outcome data was the domain that had the greatest ‘high risk’ of bias among the included studies (40%). This was owing to data not being available for all, or nearly all, of the participants randomised in these studies, and the reason for the missing data being either due, or likely to be due to, its true value. For example, reasons provided for missing data included discontinuation due to lack of effect or poor performance, termination of a treatment due to the patient’s health status (worsening or failure to improve), and patients not being crossed over due to improvement with their first treatment arm. Most of the other studies scored ‘low risk’ of bias for this domain (55%).

For the remaining two domains, all studies were deemed to have a low risk of bias for the ‘measurement of outcome’ domain, and low or some concerns of bias for ‘selection of the reported result’ domain. Two studies were deemed to be of ‘some concern’ of bias in ‘selection of the reported result’ domain. One study was a brief communication in which there was insufficient information to assess whether the data that produced this result was analysed in accordance with a pre-specified analysis plan finalised before unblinded outcome data were available for analysis (Dyck et al. 1985). Another study had randomised patients into three groups, but then had analysed them as two groups because there were not enough patients in the low-dose IVIG group (Zinman et al. 2005). No studies were assessed as being of ‘high risk’ of bias in either of these two domains.

Conflicts of interest are not assessed as part of the Cochrane RoB 2 tool, so this was investigated separately. Of the 20 studies, six did not report conflicts of interest, three specifically reported ‘no conflicts of interest’, and eight declared conflicts of interest. Of the three remaining studies, two did not report conflicts of interest but noted that the Ig was provided by a pharmaceutical company. The third noted that it had received an unconditional grant from Baxter Healthcare to conduct the study.

### Studies included for the extended assessment of harms

The extended assessment of harms includes a large number of studies examining the experience of patients with CIDP receiving a range of interventions in level IV and III-3 comparative studies. These studies lack contemporaneous control groups, suffer from the confounding effects of multiple concurrent interventions, and contain limited detail regarding the nature of adverse events. However, these observational case series make up a substantial proportion of publications on patients with CIDP and typically followed patients for longer than did those enrolled in the RCT evidence. Overall, these studies will under-report the true number of adverse events because the vast majority were retrospective in nature and therefore accuracy of safety reporting will depend on the completeness of medical records. Key limitations of these studies include the following:

* Level IV and III-3 studies do not exclude patients receiving multiple interventions and therefore the attribution of a particular adverse event to the intervention under study may be questionable.
* Studies were overwhelmingly retrospective in nature and therefore adverse event reporting was typically limited to the availability and accuracy of case notes or records.
* The risk of any particular outcomes cannot be estimated from these series as the sample sizes were typically small and the reported rates of adverse events exhibit significant heterogeneity across studies.
* Whether there was consecutive enrolment in studies was typically unclear and the inclusion and exclusion criteria were poorly defined overall. Consequently, selection bias may be significant within this evidence base.
* Adverse events were under-reported in the included evidence as revealed by statements from authors such as: “the most frequent minor side effect was headache, which was easily controlled with symptomatic medications”, wherein the actual number of patients or events was not reported (Jann et al. 2005).

## Characteristics of the Evidence Base

See Appendix C for details on the individual studies included in the evidence base. A summary is provided in Table 21. Two types of study were identified: studies of patients receiving treatment for active disease (treatment studies), and studies of patients who had responded to treatment and required ongoing maintenance (maintenance studies).

Table 21 Key features of the included evidence investigating treatment or maintenance of CIDP

| Trial | I vs C  N | Design/ duration  Risk of bias | Key Inclusion criteria | Key outcome(s) |
| --- | --- | --- | --- | --- |
| **Studies comparing Ig to NT** | | | | |
| Hahn et al. (1996b)(Hahn et al. 1996b) | Ig vs NT (placebo)  30 | R, MC, DB, CO  High | Definite or probable CIDPA. Continually progressive (>8 weeks). Static or recently progressed disease. Muscle weakness interferes with ambulation (NDS ≥ 40). Ig naïve patients. | Treatment  NDS, grip strength, clinical grade,  Isolated AEs: |
| Hughes et al. (2008)(Bril et al. 2009; Donofrio et al. 2010; Hughes et al. 2008; Merkies et al. 2009a; Vanhoutte et al. 2013b) | Ig vs NT (placebo)  117 | R, MC, DB, CO  Low | Adult patients with diagnosed CIDP (motor and sensory dysfunction) with significant disability (INCAT 2-9). Patients treated for CIDP in last 3 months excluded. | Treatment  INCAT, MRC, grip strength, ISS  Any AE  SAE  Discontinuation  Nature of AEs |
| Mendell et al. (2001)(Mendell et al. 2001) | Ig vs NT (placebo)  50 | R, MC, DB  Some concerns | Patients fulfilling diagnostic criteria for definite or probable CIDP. Patients receiving treatment in past 3 months excluded | AMS  Treatment  Discontinuation  Nature of AEs |
| Vermeulem et al. (1993)(Vermeulen et al. 1993) | Ig vs NT (placebo)  28 | R, MC, DB  Low | Newly diagnosed CIDP with progression of weakness over >8 weeks. Disability ≥ 3 on modified Rankin Scale. Treatment naïve. | Treatment  MRC |
| van Schaik et al. (2018)(Mielke et al. 2019; van Geloven et al. 2018) | Ig vs NT (placebo)  172 | R, MC, DB  Low | Patients aged 18 year and over, definite or probable CIDP.C Last IVIg treatment within 8 weeks of study. Ig-dependent disease. | Maintenance  INCAT, MRC, grip strength, I-RODS |
| Markvardsen et al. (2013)(Markvardsen et al. 2013) | Ig vs NT (placebo)  30 | R, MC, DB  High | CIDPC patients aged 18-80 years in maintenance therapy with IVIg. All were Ig responders and received treatment every 3-10 weeks. | Maintenance  MRC, grip strength, ODSS, 40MWT |
| **Studies comparing Ig to St** | | | | |
| Hughes et al. (2001)(Hughes et al. 2001) | Ig vs St  17 | R, MC, DB, CO  High | Diagnosis of CIDP by neurologist, progressive or relapsing motor and sensory dysfunction of >1 limb resulting from neuropathy developing over > 2 months. Significant disability in upper or lower limb functions. Stable or worsening clinical condition | Treatment  INCAT, 10MWS  Any AE  SAE  Discontinuation  Nature of AEs |
| Nobile-Orazio et al. (2012)(Nobile-Orazio et al. 2012b; Nobile-Orazio et al. 2015) | Ig vs St  45 | R, MC, DB  High | Definite typical CIDPC. ONLS or modified Rankin core ≥ 2. Active or stationary disease phase but not in remission. | Treatment  MRC, grip strength, ONLS, SF36, ISS, 10MWT  Any AE  SAE  Discontinuation  Nature of AEs |
| **Studies comparing Ig to PE and Ia** | | | | |
| Dyck et al. (1994)(Dyck et al. 1994) | Ig vs PE  19 | R, CO  High | CIDP diagnosis with static or worsening neurological disability. NDS ≥ 5 points. | Treatment  NDS  Isolated AEs |
| Zinman et al. (2005)(Zinman et al. 2005) | Ig vs Ia  14 | R  High | Patients aged 18-70 years with motor and/or sensory CIDP > 2 months. Patients treated with Ig, Is or PE in last 6 months excluded. | Treatment  Isolated AEs |
| **Studies investigating Is as Ig/St-sparing agents** | | | | |
| Mahdi-Rogers et al. (2009)(R. M. C. Trial Group 2009) | Is vs NT (placebo)  Is as Ig- and St-sparing agent  60 | R, MC, DB  Low | Diagnosed CIDPD with chronically progressive, stepwise, or recurrent weakness of all extremities, developing over ≥ 2 months and present for ≥ 6 months. ONLS ≥ 2 and MRC ≤4. Patients must have responded to and still be receiving stable dose of IVIg (equivalent to at least 0.4 g/kg every 4 weeks and given at least every 8 weeks) or corticosteroids (equivalent to at least 15 mg daily prednisolone). Ig- or steroid-dependent disease demonstrated in last 12 months. | Maintenance  MRC, ODSS, 4MWT |
| Hughes et al. (2018)(Hughes et al. 2018) | Is vs NT (placebo)  Is as replacement for Ig and St  104 | R, MC, DB  High | Patients with typical or atypical CIDPC with INCAT disability score of 1-9, receipt of either IVIg (minimum dose equivalent to 0.4 g/kg every 4 weeks for a minimum of 12 weeks) or corticosteroids (minimum dose equivalent to prednisone 10 mg/day) documented clinically meaningful deterioration on interruption or reduction of therapy in the 18 months before screening. Stable disease without a substantial change in treatment for the 6 weeks before randomisation. | Maintenance  MRC, ALDS |
| **Other comparisons** | | | | |
| Markvardsen et al. (2017)(Markvardsen et al. 2017) | Ig vs Ig  20 | R, CO  High | Patients aged 18-80 with definite or pure motor CIDP naïve to immune modulatory therapy and fulfilling EFN/PNS criteria. | Treatment  MRC, grip strength, 9PHT, 40MWT, ODSS |
| Kuitwaard et al. (2010)(Kuitwaard et al. 2010) | Ig vs Ig  27 | R, MC, DB  Low | Patients aged ≥ 18 with CIDPA. Observed and documented improvement of muscle function after first use of Gammagard S/D; ODSS ≥ 2 or MRC grade ≤ 4 before start of trial or following reduction of IVIg dose within last 12 months. Ongoing intermittent treatment with Gammagard leads to stable condition; stable dose for last 8 weeks. | Maintenance  INCAT, grip strength, ODSS, FSS |
| Dyck et al. (1982)(Dyck et al. 1982) | St vs NT (placebo)  28 | R  High | Patients with CIDP for > 6 months and untreated with immunosuppressive therapy | Treatment  NDS |
| van Schaik et al. (2010)(Eftimov et al. 2012; van Schaik et al. 2010) | St vs St  41 | R, MC, DB  Low | Patients aged ≥ 18 years with newly diagnosed definite or probable CIDPB Required to have signs and symptoms severe enough to warrant treatment. Treatment naïve. | Treatment  INCAT, MRC, grip strength, ALDS, SF36  Discontinuation  Nature of AEs |
| Hahn et al. (1996a)(Ashworth et al. 2000; Hahn et al. 1996a) | PE vs NT (sham)  18 | R, DB, CO  High | Patients aged >18 years with newly diagnosed CIDPA, progressive for 8-104 weeks. Significant muscle weakness (NDS ≥ 50). Treatment naïve. | Treatment  NDS, grip strength  Isolated AEs |
| Dyck et al. (1986)(Dyck et al. 1986) | PE vs NT (sham)  29 | R, DB  Some concerns | Patients with CIDP and a neurologic status that was static or worsening. NDS ≥ 50 points. No change to immunotherapy in preceding six weeks. | Treatment  NDS |
| Dyck et al. (1985)(Dyck et al. 1985) | St + Is vs St  29 | R  High | Static or worsening CIDP with symptoms for ≥ 6 months, NDS ≥ 50 points, no treatment with prednisone or immunotherapy for at least 3 months. | Treatment  NDS, grip strength |
| Lieker et al. (2017)(Lieker et al. 2017) | PE vs Ia | R  Some concerns | Met EFN/PNS 2010 diagnostic criteria for possible, probable or definite CIDP. | Treatment in refractory patients |

R = randomised; DB = double blind; CO = crossover; AE = adverse event; St = steroids, Ig = immunoglobulins; NT = no treatment; Is = immunosuppressants; PE = plasma exchange; Ia = immunoadsorption; MC = multicentred; vs = versus; I = intervention, C = comparator; FSS = fatigue severity score; INCAT = Inflammatory Neuropathy Cause and Treatment; N = number of subjects; MRC = Medical Research Council; ISS = INCAT sensory sum score; SAE = serious adverse event; NDS = neurologic disability score, AMS = average muscle score; RODS = Rasch-built Overall Disability Scale; ODSS = INCAT overall disability sum score; MWT = metre walk test; ALDS = Academic Medical Centre Linear Disability Score; 9PHT = 9 pin-hole test;

Notes: A = 1991 American Academy of Neurology (AAN) diagnostic criteria; B = ENC diagnostic criteria, C = ENFS/PNS criteria, D = diagnosis by consultant neurologist. Treatment = studies of patients receiving treatment for active disease; Maintenance = studies of patients who had responded to treatment and required ongoing maintenance.

Fourteen RCTs were identified that investigated treatment of CIDP in patients with active disease characterised by presence of significant disability. The studies were generally small, with four studies including fewer than 25 patients (Dyck et al. 1994; Hahn et al. 1996a; Markvardsen et al. 2017; Zinman et al. 2005). Nine studies included 25-50 patients (Dyck et al. 1986; Dyck et al. 1985; Dyck et al. 1982; Hahn et al. 1996b; Hughes et al. 2001; Mendell et al. 2001; Nobile-Orazio et al. 2012b; van Schaik et al. 2010; Vermeulen et al. 1993). One study included greater than 100 patients (Hughes et al. 2008). Given that CIDP is a rare disease it is unsurprising that most studies were small, however, whether the studies were sufficiently powered to detect reported outcomes was generally not reported and is therefore unclear. Five studies did perform power calculations to determine the number of patients required for recruitmen (Hughes et al. 2001; Hughes et al. 2008; Markvardsen et al. 2017; Nobile-Orazio et al. 2012b; van Schaik et al. 2010).

All of the studies required patients to have been diagnosed with CIDP, using either American Academy of Neurology (AAN) criteria (Hahn et al. 1996a; Hahn et al. 1996b), ENFS criteria (Markvardsen et al. 2017; Nobile-Orazio et al. 2012b), ENC criteria (van Schaik et al. 2010), or the criteria published by Dyck at al 1975 (Dyck et al. 1975; Dyck et al. 1982). Eight studies did not report the diagnostic criteria used. The type of CIDP was rarely reported. The ratio of progressive to relapsing disease was 1:1 in four studies (Dyck et al. 1982; Hahn et al. 1996a; Hahn et al. 1996b; Nobile-Orazio et al. 2012b) and 1:2 in one study (Hughes et al. 2001). The mean time between CIDP diagnosis and enrolment varied, ranging from less than one year (Hahn et al. 1996a) to greater than three years (Hughes et al. 2001; Nobile-Orazio et al. 2012b).

In addition to diagnosed CIDP, patients were also required to have significant levels of disability for inclusion in most studies. Disability was defined as either: NDS ≥ 40 (Hahn et al. 1996b), NDS ≥50 (Dyck et al. 1986; Dyck et al. 1985; Hahn et al. 1996a), NDS-W >≥5 (Dyck et al. 1994), INCAT 2-9 (Hughes et al. 2001; Hughes et al. 2008), Rankin ≥ 3 (Vermeulen et al. 1993), or ONLS≥ 2 (Nobile-Orazio et al. 2012b). Four studies did not specify a minimum disability level (Dyck et al. 1982; Markvardsen et al. 2017; Mendell et al. 2001; Zinman et al. 2005).

Typically, patients included in the RCTs were middle-aged males with significant levels of baseline disability (see Appendix C for baseline data).

Information about the intervention and comparator used in each study is provided in Appendix C. Nine studies investigated Ig directly: four studies compared to no treatment (placebo arm) (Hahn et al. 1996b; Hughes et al. 2008; Mendell et al. 2001; Vermeulen et al. 1993), two studies compared Ig to steroids (Hughes et al. 2001; Nobile-Orazio et al. 2012b), one study compared Ig to plasma exchange (Dyck et al. 1994), one study compared Ig to immunoadsorption (Zinman et al. 2005), and one study compared two forms of Ig to each other (Markvardsen et al. 2017). Five other studies investigated use of comparators for treatment of CIDP and were included as supplementary evidence (Dyck et al. 1986; Dyck et al. 1985; Dyck et al. 1982; Hahn et al. 1996a; van Schaik et al. 2010).

Three studies administered a single induction dose of Ig (2 g/kg) (Hahn et al. 1996b; Hughes et al. 2001; Vermeulen et al. 1993), three studies reported consistent dosing of Ig at 2 g/kg over six months (Markvardsen et al. 2017; Nobile-Orazio et al. 2012b; Zinman et al. 2005) and one study gave an induction dose followed by an additional dose of 1 g/kg three weeks later (Mendell et al. 2001). One study reported using an induction dose (2 g/kg) followed by lower-dose Ig (0.4 g/kg) given over an extended period (Hughes et al. 2008). One study used a dose of 0.4 mg/kg for three weeks followed by three weeks of treatment at 0.2 g/kg (Dyck et al. 1994). Studies providing only a single dose of Ig had short follow-up periods and thus the applicability of these studies to the long-term management of patients with CIDP is limited. No study reported using doses of Ig that would not be allowed under Version 3 of ‘*the Criteria’*.

The four studies investigating daily use of steroids each included dose tapering over the course of the treatment, consistent with how steroids would be used in clinical practice (Expert Neurologist 2019). Two studies used prednisone at a starting dose of 120 mg, tapering to zero (Dyck et al. 1985; Dyck et al. 1982); two studies used oral prednisolone at 60 mg daily, tapering to zero (Hughes et al. 2001; van Schaik et al. 2010). Two studies investigated a pulsed-steroids regimen where the intervention was given for four days per month (Nobile-Orazio et al. 2012b; van Schaik et al. 2010). Nobile-Orazio et al. (2012) used IV methyl prednisone while van Schaik et al. (2010) used dexamethasone. Experts advise that in Australia, IV methylprednisolone is favoured and dexamethasone would rarely be used for this purpose (Expert Neurologist 2019).

Three studies investigated plasma exchange. One study administered 10 exchanges over four weeks (Hahn et al. 1996a), one used twice weekly exchanges for three weeks followed by weekly exchanges for three weeks (Dyck et al. 1994), and the third study did not report the exchange schedule (Dyck et al. 1986).

Generally, the observation period within the RCTs was short, except for of six studies that followed patients for 6-12 months (Dyck et al. 1985; Hughes et al. 2008; Nobile-Orazio et al. 2012b; van Schaik et al. 2010; Vermeulen et al. 1993; Zinman et al. 2005). A key concern with respect to the comparative safety and effectiveness of interventions for CIDP is the long-term outcome of therapy. But only limited data is available to inform this consideration. Only one of the studies with a longer follow-up compared IVIg to an active comparator currently in use in Australia for CIDP treatment (Nobile-Orazio et al. 2012b). Overall, despite the limitation of short-term outcomes, the evidence base identified on the treatment of CIDP appears to be applicable to the intended population of this Assessment.

An additional five trials were identified that assessed ongoing maintenance in patients who were in remission or currently responding to treatment (Table 21 and Appendix C). Criteria for the diagnosis of CIDP were AAN (Kuitwaard et al. 2010), ENFS/PNS (Hughes et al. 2018; Markvardsen et al. 2013; van Geloven et al. 2018), or were unreported (R. M. C. Trial Group 2009). Generally, patients in the maintenance studies had been diagnosed with CIDP at least two years before enrolment. All patients in these studies had to be currently responding to treatment, consisting of IVIg in three studies (Kuitwaard et al. 2010; Markvardsen et al. 2013; van Geloven et al. 2018) and Ig or steroids in two studies (Hughes et al. 2018; R. M. C. Trial Group 2009).

Patients included in the maintenance studies were generally middle-aged males (Appendix C). Baseline disability was measured as a mean Inflammatory Neuropathy Cause and Treatment (INCAT) of 2-3 in two studies (Hughes et al. 2018; van Geloven et al. 2018), a mean overall disability sum score (ODSS) of 3-4 in two studies (Kuitwaard et al. 2010; Markvardsen et al. 2013), and a mean Overall Neuropathy Limitation Scale (ONLS) score of 4 in one study (R. M. C. Trial Group 2009).

Kuitwaard et al. (2010) investigated disease maintenance with IVIg compared to SCIg (Kuitwaard et al. 2010), while van Shaik et al. (2018) and Markvardsen et al. (2013) investigated treatment maintenance with either SCIg or no treatment (Markvardsen et al. 2013; van Geloven et al. 2018).

Two studies investigated the effectiveness of methotrexate or fingolimod as Ig and steroid-sparing agents for disease maintenance.

One additional trial looked at treatment of CIDP with PE or immunoadsorption in patients refractory to first-line treatment (Ig and/or steroids) (Lieker et al. 2017).

**Studies included for the extended assessment of harms**

Table 99 (Appendix B) summarises the relevant characteristics of the studies included for an extended assessment of harms. These studies comprised 17 case series contributing data on the safety of IVIg or SCIg, five level III-3 studies that were considered as level IV evidence contributing data on the safety of IVIg and other comparators, the RCTs included for comparative safety, and, 14 further case series contributing data on the safety of active comparators. These studies are extremely heterogenous in terms of the completeness of safety reporting. The observation period of patients ranged from very short-term, as in the RCTs, up to seven years (Barnett et al. 1998). However, most studies with IVIg (level III-3 and IV) were consistent, in that patients typically received maintenance treatment over the entire study period unless they were considered to be in remission. While maintenance regimens varied, the uncontrolled trial evidence may be a more accurate representation of the treatment patterns in CIDP patients. Notably, severe adverse events were rare, even in studies that followed patients for extended periods.

## Outcome Measures and Analysis

We had originally planned to conduct a network meta-analysis including all evidence on relevant treatments for CIDP. However, due to heterogeneity in the types of outcomes reported and length of follow-up, it was determined that pooling results would not be appropriate, so results of this review are reported narratively. Outcomes reported in the included trials are discussed below.

Version 3 of ‘*the Criteria’* restricts use of Ig in CIDP patients according to ONLS or MRC Sum Scores. Advice from the Reference Group is that these scales are used as they do not require specialist equipment for patient evaluation. In addition to these; many scales are reported in the literature and thus used in the CIDP studies included in this Assessment. These scales measure a range of outcomes including strength impairment, sensory dysfunction and disability. A list of currently validated scales deemed suitable for use in CIDP studies, their key measures and scoring has been reported by Allen et al. (2017) and is presented in Table 22. Scales used in the studies included in this Assessment that are not on the list of validated scales reported by Allen et al. (2017) are provided in Table 23.

Table 22 List and description of currently validated scales suitable for use in CIDP

|  |  |  |  |
| --- | --- | --- | --- |
| Scale | Scoring Range | Key Measures | Patient or physician reported |
| INCAT\* | 0-10 | Arm and leg disabilities, overall score is sum of the two | Patient |
| ODSS\* | 0-5 (upper limb)  0-7 (lower limb) | Arm and leg disabilities score, overall score is sum of the two | Patient |
| ONLS\* | 0-5 (upper limb)  0-7 (lower limb) | Same as ODSS, but includes “Does the patient have difficulty running or climbing stairs?” | Patient |
| RODS | Raw RODS score (0–48) transformed to final score 0–100 | Upper and lower limb disability, questions range from ability to “read a book”, “eat” or “brush teeth” to “dance”, “stand for hours”, and “run”. Participants are asked to indicate if they can easily perform the tasks, perform it with difficulty, | Patient |
| GAITrite® | Percentage scores recorded | Gait parameters: velocity, cadence, swing phase, double support time, stance phase | Physician |
| TUG | Timed activity test | Time taken to stand up from a chair, walk a short distance, turn around, return and sit down again | Physician |
| 10 metre walk test\* | Timed activity test | Time taken to walk 10 metres | Physician |
| Grip Strength\* | Instrument-based scale | Grip Strength | Physician |
| FSS | 9–63 | Questions relating to fatigue severity and the impact of fatigue on activities and lifestyle | Patient |
| Rasch-based FSS |  | As in FSS but with four response categories | Patient |
| SF-36\* | 8 scaled scores, each directly transformed into a 0–100 scale | Physical functioning (10 items), role functioning – physical (4), role functioning – emotional (3), social functioning (2), body pain (2), mental health (5), vitality (4), general health perception (5) and change in health | Patient |
| CAP-PRI | Single score comprising of 4 domains | Physical function, social function, pain, emotional well-being | Patient |

Source: reproduced from literature (Allen et al., 2017)

\*Outcome scales used in the studies included in this Assessment. CAP-PRI: Chronic Acquired Polyneuropathy Patient-reported Index; CIDP: chronic inflammatory demyelinating polyneuropathy; FSS: Fatigue Severity Scale; ICE: Immune Globulin Intravenous CIDP Efficacy; INCAT: Inflammatory Neuropathy Cause and Treatment; MMN: multifocal motor neuropathy; ODSS: INCAT overall disability sum score; ONLS: Overall Neuropathy Limitation Scale; RODS: Rasch-built Overall Disability Scale; TUG: Timed Up and Go; SF-36: Short-Form-36

Table 23 Outcome scales used in the studies included in this Assessment and NOT included in the list of validated scales for use in CIDP

|  |  |  |  |
| --- | --- | --- | --- |
| Scale | Scoring Range | Key Measures | Patient or physician reported |
| 40 metre walk test | Timed activity test | Time taken to walk 40 metres. | Physician |
| 9 peg hole test (NMSS 2019) | Timed activity test | Measure of upper extremity function. Measures time to place 9 pegs into holes in a block and then remove them, one at a time and place them back into a container. Both hands are tested twice. | Physician |
| ALDS (Met et al. 2009) | Scores are linearly transformed into values between 0 and 100 | Measures disability, as expressed by the ability to perform activities of daily life. Consists of 77 items ranging from very easy to relatively difficult. Each item has 3 response options. | Patient |
| Clinical grade (Hahn et al. 1996a) | 0-10 | Clinical grading scale used for functional assessments. Scores can range from 0 (normal) to 10 (dead). | Physician |
| ISS (NSW ITIM 2019) | 1-75 | Calculated as the sum of the squares of the highest Abbreviated Injury Scale code in each of the three most severely injured ISS body regions (head or neck, face, chest, abdominal or pelvic contents, extremities or pelvic girdle, external). | Physician |
| MRC Sum Score | Total out of 60 | Measure of muscle strength. Each muscle is grade from 0 (no visible contraction) to 5 (normal). The MRC sum score is the sum of MRC scores from six muscles in the upper and lower limbs on both sides (left and right). | Physician |
| NDS (Dyck et al. 1982) | 0-280 | Summation of all neuropathic deficits of weakness. Measures weakness in cranial nerves, muscles, reflexes and finger and toe sensation in both sides of body (35 items). Score of 0 (no deficit) to 4 (complete absence of function) for each item measured. | NR |

Source: reproduced from Allen et al. (2017)

ALDS: Academic Medical Centre Linear Disability Score; ISS: Injury Severity Score; MRC: Medical Research Council Sum Score; NDS: Neurological Disability Score; NR: not reported

While no evidence-based guidelines were identified regarding which outcomes to use when assessing CIDP trials, recommendations were formulated by a group of neuromuscular researchers from eight different countries at the 196th European Neuromuscular Centre (ENMC) workshop on outcome measures in inflammatory peripheral neuropathies (Vanhoutte et al. 2013a). The recommendation for outcome reporting in CIDP trials was that “The minimum core set should include:

* At the impairment level, the Martin Vigorimeter, the Rasch transformed modified INCAT sensory sum score (RT-miSS), and a ‘manual muscle testing’ procedure, not otherwise defined.
* At the activity and participation level, the Rasch-built overall disability scale (R-ODS) and the original INCAT disability score.
* At the quality of life level, the 5-point patient global impression of change (PGIC) and the SF-36 should be used until the data of the PeriNomS study regarding quality of life measures are further analysed.”

A further CIDP recommendation from the ENMC workshop is that the primary outcome for CIDP trials should be the activity and participation level as measured by the R-ODS (Vanhoutte et al. 2013a). The primary outcome in several of the studies included in this Assessment was ‘response rate’, although how response was defined was inconsistent and varied among the studies. A list of the studies included in this Assessment that included response rate as their primary outcome, along with its definition, is provided in Table 24.

Table 24 Studies that included 'response rate' as one of their efficacy outcomes and their definition of 'response'

|  |  |
| --- | --- |
| Study | Definitions of clinically meaningful response |
| Hahn et al. (1996b) (crossover)  Dyck et al. (1982) | >20 point improvement on NDS scale |
| Hughes et al. (2008), Donofrio et al. (2010), Bril et al. (2009), Merkies et al. (2009), Van schaik et al. (2010), Eftimov et al. (2012) and van Shaik et al. (2018) | >1 point improvement on INCAT scale |
| Zinman et al. (2005) | Stabilisation or improvement in two out of four clinical measures with no deterioration in any measure. |
| Vermeulen et al. (1993) | Improvement (defined as at least 1 point decrease on the Rankin Scale) |
| Lieker et al. (2017) | An improvement of 2 or more points on the MRC sum score in two different muscle groups or an improvement of 1 point or more on the INCAT score (except for the changes in upper limb function from 0 to 1) |

INCAT: Inflammatory Neuropathy Cause and Treatment; MRC: Medical Research Council Sum Score; NDS: Neurological Disability Score

**Safety in the randomised controlled trials**

Safety outcomes reported in the RCTs were not suitable for inclusion in a meta-analysis. There was a paucity of studies comparing safety across different interventions, follow-up duration was variable, and interventions were not consistent. Consequently, the approach to comparative safety taken in this Assessment is to provide a narrative and tabular summary of all adverse events, serious adverse events and adverse events leading to discontinuation that were reported in the included studies. Events across studies have been pooled to provide a general indication of the frequency of adverse events with each intervention. But this analysis should be interpreted with caution as the comparability of studies in terms of interventions and follow-up periods is extremely limited. Only one of the included studies performed a formal assessment of comparative safety.

Because the interventions for CIDP are broad ranging in terms of their mechanism of action, mode of delivery, and known adverse event profile, it was considered important to capture the differences in the nature of adverse events with each intervention. For example, long-term use of steroids is known to be associated with a range of psychiatric and metabolic adverse events (Buchman 2001), while plasma exchange may carry a small risk of infectious, cardiovascular, respiratory and anaphylactic events (Sutton et al. 1989). IVIg, on the other hand, is commonly associated with infusion reactions such as fever, chills and rash, with possible long-term complications involving haemolysis and reduced renal function (Levine et al. 2017). In order to investigate the nature of adverse events reported in patients with CIDP receiving IVIg or an alternative treatment, the events occurring within the included studies have been categorised according to the Common Terminology Criteria for Adverse Events (CTCAE), with number of events pooled for each system (NCI 2018). As a result, the same patient may contribute multiple times to the table if that patient experienced multiple adverse events. The intent of this approach is to enable characterisation of the most frequent adverse events associated with each intervention in patients with CIDP.

Table 28 lists all adverse events that occurred in any patient in any treatment arm of the included RCTs. In pooling the results across studies it has been assumed that if an event was not mentioned it did not occur. If a study explicitly reported zero events of that nature, this was recorded in the table. Since these were RCTs with a mandate to assess safety it was considered reasonable to assume that unreported events likely did not occur. Events reported by two studies (Dyck et al. 1994; Zinman et al. 2005) are included within the table but do not contribute to pooled rates because their reporting of safety outcomes was poor. Patient numbers have been pooled across studies to provide a general representation only of the proportion of patients experiencing adverse events with different interventions.

**The extended assessment of harms**

A similar approach was taken for the extended assessment of harms. Data was extracted from the included studies and a list of all adverse events reported with each intervention was generated and categorised according the CTCAE classification. Due to the lower quality of the included studies it was not reasonable to assume that if an event was not reported, that it did not occur. Therefore, data is presented as the number of patients reported to experience the event (n), the number of studies that reported that outcome (k) and the total number of patients in the reporting studies (N).

In the interests of providing a complete picture of the potential harms associated with each intervention, B.7 incorporates outcomes reported by all studies including the RCTs identified in B.6.

## Results of the Systematic Literature review

## Is it safe?

What is the safety of Ig compared to steroids (oral and IV), plasma exchange, immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids), a combination of two or more of the above therapies, or no active treatment?

With respect to comparative safety, the only active comparator for which a direct comparison is available is for IVIg compared to oral prednisolone and IV methylprednisolone, as reported by two RCTs (Hughes et al. 2001; Nobile-Orazio et al. 2012b). Overall, the rate of any adverse event was frequent (40-70%) with both IVIg and steroids, although serious adverse events and discontinuations were rare with either intervention.

Compared to no active treatment (i.e. placebo), more patients receiving IVIg will experience an adverse event relative to placebo (75% versus 45%). However, serious adverse events and those resulting in discontinuation were nevertheless reported in patients receiving placebo (no observable differences between arms) (Hughes et al. 2008; Mendell et al. 2001).

No direct comparisons can be made between the safety of IVIg and plasma exchange, immunoadsorption or alternative immunosuppressive pharmacotherapy (azathioprine, methotrexate, cyclosporin, rituximab etc.) owing to poor reporting and/or a lack of identified studies.

Considering the nature of the adverse events occurring across all of the included studies, the single most frequent adverse event associated with IVIg was headache (33% of all patients), followed by fever (14%), chills (9%), nausea (8%) and rash (5%). Other adverse events occurred in less than 5% of patients. These events were rarely reported as reasons for discontinuation and were typically transient or isolated events. Abnormalities in renal function and haemolysis were not observed in the IVIg arms. However, it should be noted that the longest observation period in any study, including IVIg, was 12 months. The extended assessment of harms (B.7) contains a more complete picture of possible adverse events.

Corticosteroids were associated with a different profile of adverse events (up to 52 weeks of follow-up) including, insomnia and mood changes (both 25%), weight gain (24%), indigestion (20%), increased appetite (19%), Cushing appearance (18%), unspecified (15%), minor infections and hypertension (both 9%), acne and headache (both 8%), skin thinning (6%) and delayed wound healing (5%). The majority of adverse events associated with steroids were reported by one study that followed patients for 12 months (Nobile-Orazio et al. 2012b). The other study reporting adverse events with steroids (Hughes et al. 2001) had a very short follow-up period (approximately eight weeks). Adverse events with placebo were less frequently reported, with the only two consistently reported being headache (15%) and hypertension (5%).

There was insufficient data on other active comparators to characterise the adverse event profiles of these interventions. However, there were isolated adverse events reported in studies on plasma exchange, including one cardiac event (myocardial infarction), one vascular event (stroke) and one infection (of indwelling catheter). The extended assessment of harms provides further detail.

The Reference Group noted that the evidence on the adverse events of steroids in CIDP patients did not adequately capture the safety profile of steroids. Expert advice from the Reference Group is that a publication on the adverse events experienced by patients with giant cell arteritis provided a more applicable safety profile of steroids (Wilson et al. 2017). The rationale provided by the Reference Group for citing this paper is that patients with giant cell arthritis did not usually have treatment options other than steroids during the period that data was collected and that the use of steroids in this population was applicable to CIDP patients in Australia. Wilson et al. (2017) found steroid use is associated with increased risk of diabetes (incidence rate ration (IRR) 1.4, 95% CI [1.2, 1.7]), osteoporosis (IRR 2.4, 95% CI [2.1, 2.8]), fractures (IRR 1.4, 95% CI [1.2, 1.6]), glaucoma (IRR 2.0, 95% CI [1.6, 2.5]) and serious infection (IRR 1.5, 95% CI 1.3, 1.7]).

Five RCTs reported comparative safety adequately (Hughes et al. 2001; Hughes et al. 2008; Mendell et al. 2001; Nobile-Orazio et al. 2012b; van Schaik et al. 2010). Four further studies (Dyck et al. 1994; Hahn et al. 1996a; Hahn et al. 1996b; Zinman et al. 2005) reported isolated events, which are discussed in this summary. Overall, it is important to note the following when considering interpretation of the safety data reported by the RCTs:

* Two studies providing comprehensive reporting employed a crossover study design. Therefore, the same patient could contribute adverse event results for both the intervention and the comparator.
* Many patients treated for CIDP will require long-term treatment, the side effects of which are poorly captured in the available RCTs, owing to their limited follow-up periods and/or crossover study design.
* Only one study made a formal statistical comparison of safety events across arms.
* Due to the paucity of detail regarding safety, serious adverse events may not be adequately captured (i.e. events were not typically reported with a grade).
* No direct comparison was available to inform the safety of IVIg compared to plasma exchange, immunoadsorption or alternative immunosuppressant and/or immunomodulatory drugs (azathioprine, methotrexate, cyclosporin, rituximab etc).

The safety data presented below should be interpreted in light of these limitations.

### IVIg versus steroids

When considering IVIg compared to steroids, two RCTs are relevant (Hughes et al. 2001; Nobile-Orazio et al. 2012b). Hughes et al. (2001) randomised patients to either IVIg 2.0 g/kg over two days (single course) or oral prednisolone 60 mg each morning for two weeks, 40 mg each morning for one week, 30 mg each morning for one week, 20 mg each morning for one week, then 10 mg each morning for one week. After a four-week hiatus, patients then crossed over, with IVIg treated patients entering the prednisolone arm and vice versa. Therefore, a single patient could experience adverse events attributable both to IVIg and prednisolone. Nobile-Orazio et al. (2012b) randomised patients to either IVIg 0.5 g/kg or 0.5g IV methylprednisolone at 250 ml daily for four days and then every 28 days for six months thereafter. Both trials included limited patient numbers. Due to the short follow-up in this study and the crossover design of Hughes et al. (2001), longer term complications of steroids such as weight gain and glucose intolerance are unlikely to have been captured.

Overall, a substantial proportion (40-67%) of patients receiving IVIg and steroids experienced an adverse event in these trials. Hughes et al. (2001) also reported that urticaria led to the discontinuation of one IVIg course and psychosis prompted the discontinuation of one prednisolone course. Nobile-Orazio et al. (2012) reported that one patient in the methylprednisolone group withdrew due to gastritis. Overall, Nobile-Orazio et al. (2012b) reported that the proportion of patients experiencing adverse events did not differ significantly between the two arms.

In terms of serious adverse events, Hughes et al. (2001) reported one case of previously unrecognised cancer in a patient receiving prednisolone, one case of psychosis in a patient receiving prednisolone, and one case of heart failure requiring hospitalisation four weeks after the first IVIg treatment. Nobile-Orazio et al. (2012) reported two deaths in patients treated with IVIg, one due to cardiac arrest one month after the last course of IVIg (patient had hypertension, cardiovascular risk factors and was on oral anticoagulants), and a second in a patient who had received six courses of IVIg after deteriorating after one course of IV methylprednisolone. Three months after the last IVIg course this patient died of respiratory failure. Nobile-Orazio et al. (2012) also reported one case of gastritis resulting in treatment discontinuation in a patient receiving IV methylprednisolone.

The safety profile of steroids is understood to be related both to dose and duration of treatment, with higher-doses and extended treatments carrying a higher risk for serious adverse events such as cardiovascular and metabolic adverse events (Rice et al. 2017). Nobile-Orazio et al. (2012b) followed patients for 52 weeks. A subsequent publication with 4.5 years of follow-up identified no new cases of diabetes or glaucoma or other serious adverse events not identified in the 52-week analysis. However, clinical feedback indicates that this may not represent the true harms profile of steroids.

Studies published from large administrative data sets have identified substantially increased cardiovascular risk in patients taking corticosteroids. However, findings are mixed in disease-specific cohorts (Bruce 2005; Johannesdottir et al. 2013; Kremers et al. 2007; Souverein et al. 2004). Most published studies on steroid safety are retrospective and observational. While it is widely acknowledged that chronic steroid treatment is associated with serious side effects, robust data on the rates of specific events stratified by corticosteroid dose and duration of exposure are still uncertain (Rice et al. 2017). Prospective trials are necessary to explore thresholds for certain side effects and to investigate independent effects attributable to steroids versus underlying disease (Oray et al. 2016). Broadly speaking, it appears that long-term harms with steroids are the most well established in patients taking more than 7.5 mg prednisone or equivalent per day. RCTs of steroid use in CIDP patients typically start patients on a high dose (oral or IV when considering evidence from Van Shaik et al. (2010)) and then taper to 0. Therefore, the success of tapering in clinical practice may affect the side effect profile of this treatment option if patients require chronic steroid treatment. It is not clear from the peer-reviewed literature whether chronic steroid treatment is prevalent in this population.

Table 25 Any adverse or serious adverse event reported in the randomised controlled trials (IVIg vs steroids)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Completeness of safety reporting | Comparison | IVIg  n/N (%)  Any AE  Serious AE | Steroids  n/N (%)  Any AE  Serious AE |
| Hughes 2001 | Moderate  (< 8 weeks) | IVIg versus oral steroids | 18/30 (60%)a  1b/30(3%) | 11/27 (41%)a  1/27a (4%) |
| Nobile-Orazio 2012 | High  (52 weeks) | IVIg versus IV steroids | 11/24 (46%)  2/24 (8%) | 14/21 (66%)  1/21 (5%) |

a reported out of courses not patients, however, most patients received only one course of IVIg, so this is a reasonable approximation of the number of patients.

The Reference Group noted that the evidence on the adverse events of steroids in CIDP patients did not wholly capture the safety profile of steroids. Expert advice from the Reference Group is that a publication on the adverse events experienced by patients with giant cell arteritis provided a more applicable safety profile of steroids (Wilson et al. 2017). The rationale provided by the Reference Group for citing this paper is that patients with giant cell arteritis did not usually have treatment options other than steroids during the period that data was collected and that the use of steroids in this population was applicable to CIDP patients in Australia. Wilson et al. (2017) examined the Health Episode Statistics dataset of patient admissions in NHS hospitals in England between 1997 and 2012. A cohort of 5,011 patients with giant cell arteritis who had a recorded prednisolone prescription within six months of diagnosis were identified and matched 1:1 to a randomly selected group of patients. Patients in both cohorts were required to have at least three years medical history. Data from this study is presented in Table 26.

Table 26 Adverse events associated with steroid use in giant cell arteritis patients

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **GCA cohort** |  | **Non-GCA cohort** |  | **Difference** |
| **Adverse event** | **Number**  **Patient years** | **I/1000 per year (95% CI)**  **Annual probability** | **Number**  **Patient years** | **IR (95% CI)**  **Annual probability** | **IRR (95% CI)**  **Net annual probability** |
| Diabetes | 340  24,017.8 | 14.2 (12.7, 15.7)  1.41% | 254  25,395.7 | 10.0 (8.9, 1.3)  1.00% | 1.4 (1.2, 1.7)  0.41% |
| Osteoporosis | 532  23,203.1 | 22.9 (21.1, 24.9)  2.26% | 246  26,124.4 | 9.4 (8.3, 10.7)  0.94% | 2.4 (2.1, 2.8)  1.32% |
| Fractures | 433  26,227.3 | 16.5 (15.0, 18.1)  1.64% | 340  27,707.9 | 12.3 (11.0, 13.6)  1.22% | 1.4 (1.2, 1.6)  0.42% |
| Glaucoma | 253  24,837.9 | 10.2 (9.0, 11.5)  1.01% | 134  26,451.0 | 5.1 (4.3, 6.0)  0.51% | 2.0 (1.6, 2.5)  0.5% |
| Serious infection | 476  12,559.8 | 37.9 (34.7, 41.4)  3.7% | 346  13,454.1 | 25.7 (23.2, 28.5)  2.5% | 1.5 (1.3, 1.7)  1.2% |

Source: reproduced from Wilson et al. (2017). Annual probabilities calculated by Assessment Group using the formula:

probability = 1- exp^(-rt)

Note: Wilson et al. (2017) also reported hospitalisations; however, as the data allowed for previously reported adverse events to contribute to the number of hospitalisations this outcome has not been reported to avoid double counting.

Based on the data presented in Table 26, steroid use is associated with increased risk of diabetes, osteoporosis, fractures, glaucoma and serious infection.

### IVIg versus placebo

When considering IVIg compared to placebo, only one RCT (Hughes et al. 2008) reported the rate of adverse events overall. A second trial reported the type but not rate of adverse events and is discussed elsewhere (Mendell et al. 2001). Hughes et al. (2008) report that 85 of 113 patients (75%) receiving IVIg (2 g/kg over 2-4 days followed by 1 g/kg over 1-2 days every 3 weeks) experienced an adverse event and 45 of 95 patients (47%) who received a placebo infusion experienced an adverse event. It should be noted that responders to the first treatment were then eligible to be re-randomised into IVIg or placebo arms. Therefore, a single patient could experience adverse events attributable both to IVIg or placebo. Hughes et al. (2008) reported discontinuation due to adverse events in two patients who received IVIg (during the initial or crossover phase) and in two patients who received placebo. In total six patients (5%) receiving IVIg and eight (8%) receiving placebo experienced a serious adverse event. However, the nature of those events is not reported.

Another paper reported on the same patient cohort (Donofrio et al. 2010) but expressed adverse events per 100 infusions. Considering only those that were drug related, the rate of adverse events with IVIg compared to placebo was 46.7 versus 9.3 per 100 infusions during the initiating phase, and 10.1 versus 2.0 during the maintenance phase. A study by Hahn, Bolton et al. (1996b) randomised patients to IVIg or placebo and reported that one patient receiving IVIg developed symptoms resembling aseptic meningitis, but this study did not provide sufficient detail regarding safety outcomes to be formally included.

Table 27 Any adverse or serious adverse event reported in the randomised controlled trials (IVIg vs placebo)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Completeness of safety reporting | Comparison | IVIg  n/N (%)  Any AE  Serious AE | Placebo  n/N (%)  Any AE  Serious AE |
| Hughes 2008 | High  (at least 24 weeks) | IVIg versus placebo | 85/113 (75%)  6/113 (5%) | 45/95 (47%)  8/95 (8%) |

AE: adverse event

### IVIg versus other active treatments

No direct comparisons can be made between the safety of IVIg and plasma exchange, immunoadsorption or alternative immunosuppressive pharmacotherapy (azathioprine, methotrexate, cyclosporin, rituximab etc.) owing to poor reporting and/or a lack of identified studies. The extended assessment of harms contains information on these treatment options.

### Nature of the adverse events reported in any randomised controlled trial

Adverse events occurring within the included studies have been categorised according to the Common Terminology Criteria for Adverse Events classification (NCI 2018). This allows for consideration of all of the high-level evidence associated with each intervention across the RCTs in order to construct adverse event profiles of different interventions. This analysis is provided for information purposes only and no statistical comparison across interventions can be made. Table 28 lists all adverse events that occurred in one or more patients in any treatment arm of the included studies. Events are categorised according to system and the same patient may contribute multiple times to the table if multiple adverse events were experienced.

Considering the nature of the adverse events occurring across the included studies, the single most frequent adverse event associated with IVIg was headache (33% of all patients), followed by fever (14%), chills (9%), nausea (8%) and rash (5%). Other adverse events occurred in less than 5% of patients. These events were rarely reported as reasons for discontinuation and were typically transient or isolated events. Steroids were associated with a different profile of adverse events, typically metabolic or psychiatric in nature. Frequent adverse events included insomnia and mood changes (both 25%), weight gain (24%), indigestion (20%), increased appetite (19%), Cushing appearance (18%), unspecified (15%), minor infections and hypertension (both 9%), acne and headache (both 8%), skin thinning (6%) and delayed wound healing (5%). There was insufficient data on other active comparators to inform this table, however, as noted earlier there were isolated adverse events reported in studies on plasma exchange including one cardiac event (myocardial infarction), one vascular event (stroke) and one infection (of indwelling catheter). Since it was unclear whether these were the only adverse events in these studies or only those deemed notable by authors, no true proportion can be calculated. Adverse events with placebo were less frequently reported, with the only two consistently reported being headache (15%) and hypertension (5%).

The extended assessment of harms section (Section B.7) considers these events in as well as those reported in observational series across a broader range of interventions.

Table 28 Nature of the adverse events reported by the randomised controlled trials

|  |  |  |  |
| --- | --- | --- | --- |
| **System**  AE | **AEs reported in patients receiving IVIg of any dose and frequency**  **Studies = 4, N = 197[[6]](#footnote-7)** | **AEs in patient receiving intravenous methylprednisolone, pulsed dexamethasone or oral prednisone**  **Studies = 3, N = 88** | **AEs in patients receiving placebo**  **Studies = 2, N = 118** |
| **Cardiac disorders** | **2/197 (1%)** | **0** | **0** |
| Cardiac arrest | Nobile-Orazio 2012: 1/24 (4%) *fatal[[7]](#footnote-8)* | Presumed nil | Presumed nil |
| Heart failure | Hughes 2001: 1/30 (4%)[[8]](#footnote-9) | Presumed nil | Presumed nil |
| **Eye disorders** | **0** | **1/88 (1%)** | **0** |
| Increased ocular pressure | Nobile- Orazio 2012: 0/24 (0) | Nobile- Orazio 2012: 1/21 (5%) | Presumed nil |
| **Gastrointestinal disorders** | **28/197 (14%)** | **21/88 (24%)** | **5/118 (4%)** |
| Abdominal/gastric pain | Nobile- Orazio 2012: 3/24 (12.5%) | Nobile- Orazio 2012: 2/21 (9.5%) | Presumed nil |
| Colitis | Nobile- Orazio 2012: 1/24 (4%)[[9]](#footnote-10) | Nobile- Orazio 2012: 0/21 (0) | Presumed nil |
| Gastritis | Nobile- Orazio 2012: 0/24 (0) | Nobile- Orazio 2012: 1/21 (5%) *lead to discontinuation* | Presumed nil |
| Indigestion | Hughes 2001: 6/30 (20%) | Hughes 2001: 4/27 (20%)  Van Shaik 2010a: 8/24 (33%) *1/24 in f/u [[10]](#footnote-11)*  Van Shaik 2010b: 6/16 (38%) *2/16 in f/u* | Presumed nil |
| Nausea | Hughes 2008: 7/113 (6%)  Mendell 2001: 10/30 (33%)^ | Presumed nil | Hughes et al. 2008: 3/95 (3%)  Mendell 2001: 2/23 (9%)^ |
| Vomiting | Nobile- Orazio 2012: 1/24 (4%) | Nobile- Orazio 2012: 0/21 (0) | Presumed nil |
| **General disorders and administration site conditions** | **53/197 (27%)** | **3/88 (3%)** | **1/118 (1%)** |
| Fever | Hughes 2008 15/113 (13%)  Hughes 2001: 5/30 (17%)  Mendell 2001: 10/30 (33%)^ | Hughes et al. 2001: 0/27 (0) | Hughes et al. 2008: 0/95 (0)  Mendell 2001: 0/23 (0) |
| Flu-like syndrome | Nobile-orazio 2012: 3/24 (12.5%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Chills | Hughes 2008: 9/113 (8%)  Mendell 2001: 9/30 (30%)^ | Presumed nil | Mendell 2001: 1/23 (4%)^  Hughes et al. 2008: 0/95 (0) |
| Oedema (limbs/peripheral) | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 2/21 (10%) | Presumed nil |
| Malaise | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Thoracic pain or oppression | Nobile-orazio 2012: 2/24 (8%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| **Infections and infestations** | **11/197 (6%)** | **14/88 (16%)** | **2/118 (2%)** |
| Conjunctivitis | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Cutaneous infection | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Cystitis | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Influenza | Hughes 2008: 6/113 (5%) | Presumed nil | Hughes et al. 2008: 2/95 (2%) |
| Infection of catheter | Dyck 1994: 1/9 (11%) | Presumed nil | Presumed nil |
| Minor infections | Presumed nil | Van Shaik 2010a: 6/24 (25%) 4*/24 in f/u*  Van Shaik 2010b: 2/16 (12.5%) 9*/16 in f/u* | Presumed nil |
| Pleuritis | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Pneumonia | Hughes 2008: 1/113 (<1%)[[11]](#footnote-12)  Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Pharyngitis | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Sepsis | Hughes 2008: 1/113 (<1%)[[12]](#footnote-13) |  | Presumed nil |
| Sinusitis | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| **Injury, poisoning and procedural complications** | **0** | **21/88 (24%)** | **0** |
| Investigations | Presumed nil | Presumed nil | Presumed nil |
| Laboratory abnormalities | Mendell 2001: 0/30 (0) | Presumed nil | Mendell 2001: 0/23 (0%) |
| Weight gain | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 2/21 (9.5%)  Van Shaik 2010a: 10/24 (42%) *3/24 in f/u*  Van Shaik 2010b: 9/16 (56%) *0/16 in f/u* | Presumed nil |
| **Metabolism and nutrition disorders** | **1/197 (1%)** | **22/88 (25%)** | **0** |
| Diabetes | Presumed nil | Van Shaik 2010a: 1/24 (4%) *0/24 in f/u*  Van Shaik 2010b: 3/16 (19%) *2/16 in f/u* | Presumed nil |
| Cushing appearance | Presumed nil | Van Shaik 2010a: 6/24 (25%) *2/24 in f/u*  Van Shaik 2010b: 10/16 (63%) *3/16 in f/u* | Presumed nil |
| Hyperglycaemia | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 2/21 (9.5%) | Presumed nil |
| **Musculoskeletal** | **9/197 (5%)** | **1/88 (1%)** | **7/118 (6%)** |
| Arthralgia | Presumed nil | Presumed nil | Hughes et al. 2008: 1/95 (1%) |
| Back pain | Presumed nil | Presumed nil | Hughes et al. 2008: 3/95 (3%) |
| Limb pain | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Weakness (Asthenia) | Hughes 2008: 9/113 (7%) | Presumed nil | Hughes et al. 2008: 3/95 (3%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **2/197 (1%)** | **1/88 (1%)** | **0** |
| Carcinoma of the bronchus | Hughes 2001: 1/27 (4%)[[13]](#footnote-14) | Presumed nil | Presumed nil |
| Rectum polyp | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Uterine leiomyoma | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| **Nervous system disorders** | **77/197 (39%)** | **11/88 (13%)** | **19/118 (16%)** |
| Dizziness/light headedness | Hughes 2008: 7/113 (6%)  Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 2/21 (10%) | Hughes et al. 2008: 1/95 (1%) |
| Headache | Hughes 2008: 36/113 (32%)  Hughes 2001: 10/30 (33%)  Mendell 2001: 20/30 (67%)^  Zinman 2005: 2/8 (25%)  Nobile-orazio 2012: 1/24 (4%) | Hughes 2001: 7/27 (25%)  Nobile-orazio 2012: 0/21 (0) | Hughes et al. 2008: 8/95 (8%)  Mendell 2001: 10/23 (44%)^ |
| Neuralgia | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Paraesthesia | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Tremor | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| **Psychiatric disorders** | **0** | **50/88 (57%)** | **0** |
| Anxiety | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Agitation | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Delirium | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Depression | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Insomnia | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%)  Van Shaik 2010a: 9/24 (38%) *2/24 in f/u*  Van Shaik 2010b: 12/16 (75%) *2/16 in f/u* | Presumed nil |
| Mood changes | Presumed nil | Van Shaik 2010a: 10/24 (42%) *4/24 in f/u*  Van Shaik 2010b: 12/16 (75%) *1/16 in f/u* | Presumed nil |
| Psychosis | Presumed nil | Hughes 2001: 1/27 (4%) | Presumed nil |
| Visual hallucinations | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| **Respiratory, thoracic and mediastinal disorders** | **2/197 (1%)** | **1/88 (1%)** | **0** |
| Asthma | Presumed nil | Presumed nil | Presumed nil |
| Cough | Presumed nil | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Dyspnoea | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Respiratory failure | Nobile-orazio 2012: 1/24 (4%) *fatal[[14]](#footnote-15)* | Presumed nil | Presumed nil |
| **Skin and subcutaneous tissue disorders** | **11/197 (6%)** | **16/88 (18%)** | **2/118 (2%)** |
| Acne vulgaris | Presumed nil | Van Shaik 2010a: 4/24 (17%) *0/24 in f/u*  Van Shaik 2010b: 3/16 (19%) *0/16 in f/u* | Presumed nil |
| Rash | Hughes 2008: 8/13 (7%)  Hughes 2001: 2/30 (6%)  Zinman 2005: 2/8 (25%) *resulting in discontinuation* | Presumed nil  Hughes et al. 2001: 0/27 (0) | Hughes et al. 2008: 1/95 (1%)  Mendell 2001: 1/23 (4%) *dropped out due to urticaria on 1st infusion* |
| Delayed wound healing | Presumed nil | Van Shaik 2010a: 1/24 (4%) *3/24 in f/u*  Van Shaik 2010b: 3/16 (19%) *0/16 in f/u* | Presumed nil |
| Dermatitis | Nobile-orazio 2012: 1/24 (4%) | Nobile-orazio 2012: 0/21 (0) | Presumed nil |
| Skin thinning | Presumed nil | Van Shaik 2010a: 2/24 (8%) *2/24 in f/u*  Van Shaik 2010b: 3/16 (19%) *0/16 in f/u* | Presumed nil |
| **Vascular disorders** | **6/197 (3%)** | **9/88 (10%)** | **6/118 (5%)** |
| Cerebrovascular event | Presumed nil | Presumed nil | Presumed nil |
| Deep vein thrombosis | Presumed nil | Presumed nil | Presumed nil |
| Flushing/blushing | Nobile-orazio 2012: 0/24 (0) | Nobile-orazio 2012: 1/21 (5%) | Presumed nil |
| Hypertension | Mendell 2001: 3/30 (10%)^  Nobile-orazio 2012: 2/24 (8%)[[15]](#footnote-16) *lead to discontinuation in both* | Nobile-orazio 2012: 3/21 (14%)  Van Shaik 2010a: 3/24 (12.5%) *3/24 in f/u*  Van Shaik 2010b: 2/16 (12.5%) *2/16 in f/u* | Hughes et al. 2008: 4/95 (4%)  Mendell 2001: 2/23 (9%)^ |
| Hypotension | Hughes 2001: 1/30 (3%) | Hughes et al. 2001: 0/27 (0) | Presumed nil |
| **Unspecified** | **0** | **30/88 (34%)** | **0** |
| Increased appetite | Presumed nil | Van Shaik 2010a: 9/24 (38%) *3/24 in f/u*  Van Shaik 2010b: 8/16 (50%) *1/16 in f/u* | Presumed nil |
| Other | Presumed nil | Van Shaik 2010a: 7/24 (30%) 1*/24 in f/u*  Van Shaik 2010b: 6/16 (38%) *1/16 in f/u* | Presumed nil |

AE: adverse event; NR: not reported.

Explanatory notes:

1. Where an AE was explicitly reported as not having occurred this was recorded as 0. When the event was not mentioned in the text it was presumed not to have occurred
2. Events are classified according to the CTCAE definitions
3. The same patient could experience multiple events and therefore will be counted multiple times within the table
4. ^ indicates that the n/N back-calculated from % owing to a paucity of follow-up data
5. Van Shaik 2010a: oral dexamethasone
6. Van Shaik 2010b: oral prednisolone

## Is it effective?

What is the efficacy of IVIg compared to steroids (oral and IV), plasma exchange, immunosuppressant and/or immunomodulatory drugs and therapies (not including steroids), a combination of two or more of the above therapies, or no active treatment?

Ig appears to have superior short-term effectiveness compared to no treatment. Three out of four RCTs reported an improvement in disability measures. A higher proportion of patients receiving Ig had a clinically meaningful response compared to patients receiving no treatment (48% vs 18%).

In the long term, continued Ig use appears to maintain a response in a greater number of patients than those receiving no continuing treatment. However, mixed results were reported with respect to the difference in disability (two RCTs found a significant reduction in disability while one RCT found no difference).

Compared to steroids, Ig appears to have at least non-inferior effectiveness in the short-term. Nobile-Orazio et al. (2012b) included 45 patients. For the composite outcome of discontinuation (any cause), steroid use was associated with higher risk of discontinuation than Ig (relative risk (RR) 0.54, 95% CI [ 0.34, 0.87]). It is not known what the RR would be if only discontinuations due to inefficacy were considered. Following cessation of treatment, patients treated with methylprednisolone remained in remission longer than those treated with Ig. The authors reported no difference between Ig and methyl prednisolone with respect to secondary outcomes of MRC, grip strength, ONLS, SF36, ISS and W10M tests. Hughes et al. (2001) included 42 patients and reported no difference between IVIg and oral prednisolone with respect to INCAT, 10MWS and 9HPB outcomes.

The Reference Group noted that the results from Nobile-Orazio et al. (2012b) may support a finding of superior effectiveness based on non-significant improvements in various disability measures and a statistically significant difference in discontinuations favouring Ig. Discontinuations was a composite endpoint of discontinuations due to inefficacy and intolerance.

A single RCT of 38 patients reported no difference in Ig and plasma exchange.

No evidence comparing Ig to immunosuppressants was identified. Two studies reported no short-term effect from immunosuppressants used as Ig- or steroid-sparing agents.

The evidence base is limited by small studies, usually with short follow-up durations. Each study used different disability measurements and different definitions for a clinically meaningful response, which prevented any meta-analysis of results.

Comparative effectiveness results for Ig are summarised in Table 29 and Table 30 and described narratively below.

### Ig vs no treatment

Three out of four studies comparing Ig to no treatment (placebo) found that Ig was more effective with respect to change in NDS (Hahn et al. 1996b), change in grip strength (Hahn et al. 1996b; Hughes et al. 2008), change in MRC (Hughes et al. 2008), and change in INCAT score (Hughes et al. 2008). Hahn et al. (1996b) and Mendell et al. (2001) had short follow-up periods (4 weeks and 6 weeks, respectively) and gave only a single induction dose of Ig or an induction dose and a single follow-up. However, Hughes et al. (2008) provided six months follow-up with ongoing Ig usage during this period. The number of patients whose response was defined as clinically meaningful was higher for patients receiving Ig in all three of these studies.

Conversely, Vermeulen et al. (1993) found no difference between Ig and placebo treatment after a single Ig infusion and three weeks follow-up.

Hughes et al. (2008) also investigated treatment maintenance using Ig. Patients who responded to Ig were randomised to receive continued Ig or a placebo and were monitored for an additional six months. Relapse was less frequent on continued Ig (4/31 vs 11/26, p = 0.011), however no difference in disability measures (INCAT, MRC, ISS and grip strength) were observed in the maintenance phase of the trial.

Two additional studies randomised IVIg responsive patients to either SCIg or placebo. Both studies reported that SCIg was better than no treatment for ongoing disease maintenance.

Based on these results, it is likely that Ig is superior to no treatment for initial treatment and ongoing maintenance of CIDP. This conclusion is based primarily on the study by Hughes et al. (2008), which included greater than 100 patients, was adequately powered to detect a difference between the two groups. It was considered at low risk of bias and included up to 12 months follow-up. The consistency of the rest of the evidence base (with the exception of Vermeulen et al. (1993)) supports the finding of superiority.

### Ig vs Steroids

Two RCTs directly compared Ig to steroids for CIDP treatment (Hughes et al. 2001; Nobile-Orazio et al. 2012b).

Hughes et al. (2001) reported no difference between IVIg and oral prednisolone with respect to INCAT, 10MWS and 9HPB outcomes. Patients received either a single dose of Ig (2 g/kg over two days) or daily prednisolone (60 mg tapering to zero).

Nobile-Orazio et al. (2012) administered monthly Ig (2 g/kg) for six months or monthly IV methylprednisolone (2g over four days). The primary outcome of the study was the number of patients discontinuing treatment. Treatment was discontinued due to inefficacy (absence of improvement or worsening), side effects or intolerance. For the composite outcome of discontinuation (any cause), steroid use was associate with higher risk of discontinuation than Ig (relative risk (RR) 0.54, 95% CI [ 0.34, 0.87]). Eleven patients (52%) in the steroid arm discontinued; five due to progressive worsening, three due to failure to improve, one for adverse events (gastritis) and two for reasons unreported. Of the eight patients discontinuing due to static or worsening CIDP, seven subsequently improved with Ig treatment. Three patients (12.5%) discontinued Ig therapy; two because of progressive worsening and one due to failure to improve. All three of these patients improved on methylprednisolone. It is not known what the RR would be if only discontinuations due to inefficacy were considered.

The authors reported no difference between Ig and methyl prednisolone with respect to secondary outcomes of MRC, grip strength, ONLS, SF36, ISS and W10M tests.

Following cessation of treatment, patients treated with methylprednisolone remained in remission longer than those treated with Ig. Following cessation of Ig, 17 of 21 responders worsened at a median of six months while 8 of 10 initial responders to methylprednisolone worsened at a median of 12 months (p = 0.0295).

Overall, the study found that there was no difference in rates of response (p = 0.858) when using either Ig or methylprednisolone as an initial treatment with the other used as a rescue in case of non-response.

Based on this data, the claim that Ig is at least non-inferior to steroids appears to be reasonable. However, this conclusion is limited by the small number of trials, the small number of patients included in those trials, limited follow-up by Hughes et al. (2001), and the fact that both trials were considered to be at high risk of bias. Advice from the Reference Group is that the evidence may support a finding of superior effectiveness based on the relative number of patients discontinuing treatment over six months reported in Nobile-Orazio et al. (2012).

### Ig vs plasma exchange?

A single study of 19 patients investigated the relative effectiveness of Ig and plasma exchange. Dyck et al. (1994) found no difference in change in NDS between the two treatments. However, this small study had limited follow-up (6 weeks) and was at high risk of bias. This limited evidence of the non-inferior effectiveness of Ig compared to plasma exchange, is supported by an informal indirect comparison of trials comparing Ig to no treatment and plasma exchange to no treatment. As discussed above, Ig has superior effectiveness to no treatment. Similarly, Hahn et al. (1996a) and Dyck et al. (1986) both found that plasma exchange was a more effective treatment for CIDP than sham exchange (Dyck et al. 1986; Hahn et al. 1996a).

### Ig vs immunosuppressants

No RCTs were identified providing either a direct or indirect comparison of Ig and immunosuppressants. Two studies were identified that investigated the use of immunosuppressants as Ig- and steroid-sparing agents (Hughes et al. 2018; R. M. C. Trial Group 2009).

Hughes et al. (2018) switched Ig and steroid responders to either fingolimod or placebo (Ig was stopped immediately before the first dose of immunosuppressant; steroids were tapered down over 8 weeks). The trial was stopped for futility. A total of 44 patients experienced worsening (defined as ≥ 1-point change in INCAT). There was no difference between immunosuppressant and placebo groups (58% vs 57%, p = 0.91).

Mahdi-Rogers et al. (2009) investigated whether the addition of an immunosuppressant (methotrexate) or placebo to patients currently responding to either steroids or Ig would decrease treatment requirements by 20%. No difference in response was found (OR for response 1.21 955 CI 0.4, 3.7). Similarly, no difference in MRC (MD 0.4 95% CI -2.34, 3.17, p = 0.76), ALDS (MD -0.47 95% CI -3.62, 1.87, p = 0.73) or ONLS (MD not reported, p = 0.93) was reported.

Based on these results, immunosuppressants at the doses investigated do not appear to be an effective adjunct to Ig or steroids in patients with CIDP.

### Ig in paediatric patients

No evidence from RCTs was identified.

A systematic review investigating the use of Ig to treat paediatric neurological conditions was identified (Gadian et al. 2017). The review included ten series of 114 paediatric patients with CIDP. The response rate in those initially treated with IVIg was 79% compared to a response rate of 74% following treatment with steroids and 14% following plasma exchange. The review found that first-line treatment with IVIg or steroids appears to be similarly efficacious.

### Other comparisons

Effectiveness data on comparisons outside the defined PICO for this review are presented in Table 98 (Appendix B) and summarised briefly below.

#### Ig vs Ig

Advice from the Reference Group was that a comparison between different forms of Ig is not relevant to this Assessment. Two studies investigating different forms of Ig were identified as being potentially relevant for inclusion in the network meta-analysis:

* Markvardsen et al. (2017) found no difference between patients initially treated with either SCIg or IVIg (Markvardsen et al. 2017).
* Kuitwaard et al. (2010) found no difference between IVIg-responding patients randomised to either continued IVIg or SCIg.

#### Ig vs immunoadsorption

Advice from the Reference Group is that immunoadsorption is not a relevant comparator for this review as these capture columns are not used in Australia. One study comparing Ig to immunoadsorption was identified:

* Zinman et al. (2005) found no difference between immunoadsorption and Ig, although the study was low quality and had unacceptably high losses to follow-up.

#### Evidence on comparators (Ig not investigated)

Six studies on treatments for CIDP other than Ig were identified as being potentially relevant for a network meta-analysis:

* Dyck et al. (1982) found that steroids were significantly better than placebo for CIP treatment, although these results are limited by high numbers of patients lost to follow-up/withdrawn (Dyck et al. 1982).
* Van Shaik et al. (2010) found no difference between pulsed dexamethasone and daily prednisolone over six months follow-up (van Schaik et al. 2010).
* Dyck et al. (1985) reported that the addition of immunosuppressant (azathioprine) to prednisone did not impact treatment effectiveness (Dyck et al. 1985).
* Hahn et al. (1996a) and Dyck et al. (1986) both found that plasma exchange was a more effective treatment for CIDP than sham exchange (Dyck et al. 1986; Hahn et al. 1996a).
* Lieker et al. (2017) found no difference in response rate following plasma exchange and immunoadsorption in patient’s refractory to Ig and/or steroids.

Table 29 Summary of effectiveness data on Ig compared to no treatment, steroids or plasma exchange as a treatment for CIDP

| Study ID | Follow-up  N | INCAT | MRC | NDS | Grip strength | Clinically meaningful response | Other outcomes |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ig vs NT** | | | | | | | |
| Hahn et al. (1996b) | 4 weeks  I: 25  C: 25 |  |  | I: -24.4 ± 7.57  C: 4.8 ± 8.35  P < 0.002 | I: 6.3 kg ± 2.41  C: -0.8 kg ± 2.69  P < 0.005 | I: 19/30  C: 5/30  P = NR | Clinical grade  I: -1 ± 0.42, C: 0.4 ± 0.425, P < 0.002 |
| Hughes et al. (2008) | Up to 24 weeks  I: 59  C: 58 | I: -1.1 ± 1.8  C: -0.3 ± 1.3  P = 0.01 | I: 3.3 ± 5.6  C: 0.2 ± 4.5  P = 0.001 |  | I: 13.2 kPa ± 19.3  C: 1.5 kPa ± 15.6  P < 0.001 | I: 32/59  C: 12/58  P = 0.0002 | ISS:  I: -1.2 ± 3.4, C: 0.2 ± 3.9, P = 0.021 |
| Mendell et al. (2001) | 6 weeks  I: 29  C: 21 |  |  |  |  | I: 11/29  C: 2/21  P = 0.019 | AMS  I: 0.63 ± 0.86  C: -0.1 ± 0.46  P = 0.006 |
| Vermeulen et al. (1993) | 3 weeks  I: 15  C: 13 |  | I: 1.6 ± 3.04  C: 1.31 ± 3.4  P = NR |  |  | I: 2/15  C: 3/13  P = NR |  |
| **Ig vs St** | | | | | | | |
| Hughes et al. (2001) | 6 weeks  I: 21  C: 21 | I: -0.71 ± 1.19  C: -0.62 ± 1.52  P = 0.59 |  |  |  |  | 10MWS (m/s)  I: 0.01 ± 0.01, C: 0.01 ± 0.02, P = 0.75  9HPB (s)Clinically meaning  -1.64 ± 3.87, C: -2.4 ± 6.45, P = 0.75 |
| Nobile-Orazio et al. (2012) | 26 weeks  I: 24  C: 21 |  | I: 4.7 ± 7.69  C: 1.8 ± 11.64  P = 0.0929 |  | I: 19.4 kPa ± 35.15  C: 5.4 kPa ± 39.69  P = 0.2653 | I: 21/24  C: 10/21  P = 0.0085 | ONLS  I: -1 ± 9.11, C: -1 ± 3.33, p = 0.1322  SF36  I: 14.2 ± 25.31, C: 16.7 ± 29.49, p = 0.610  ISS  I: -0.67 ± 5.57, C: 0 ± 11.24, p = 0.0686  10MWT (s)  I: -3.2 ± 6.45, C: -0.5 ± 15.1, p = 0.2300  Discontinue treatment  I: n = 3/24, C: 11/21, p = 0.0085 |
| **Ig vs PE** | | | | | | | |
| Dyck et al. (1994) | 6 weeks  I: 19  C: 19 |  |  | I: -36.1 ± 32  C: -38.3 ± 34.6  P = NS (NR) |  |  |  |

Notes: Clinically meaningful response was defined as: NDS >20 (Hahn et al; (1996b)); INCAT >1 (Hughes et al. (2008)); functional grade >1 (Mendell et al. (2001)); and Rankin score >1 (Vermeulen et al. (1993). In Nobile-Orazio et al. (2012) clinically meaningful response was defined as patients continuing treatment. Discontinuation was due to side effects, intolerance or inefficacy.

Abbreviations: Ig = immunoglobulin; St = steroids; PE = plasma exchange; NT = no treatment; I = intervention; C = comparator; 9PHT = nine peg hole test; AMS = average muscle score; SF36 = Short-Form-36; MRC = Medical Research Council Sum Score; INCAT = Inflammatory Neuropathy Cause and Treatment; NDS = Neurological Disability Score; 10MWT = 10 metre walk time; 10MWS = 10 metre walk speed; ISS = INCAT sensory sum score; ONLS = Overall Neuropathy Limitation Scale; MD = mean difference; CI = confidence interval.

Table 30 Summary of effectiveness data for CIDP maintenance.

| Study ID | Follow-up time  n | INCAT | MRC | Grip strength | Other outcomes |
| --- | --- | --- | --- | --- | --- |
| Van Schaik et al. (2018) | Ig (high-dose) vs Ig (low dose) vs Pl  Up to 24 weeks | MD (95% CI)  I1 vs C: 0.0 (-1.0, 0.0) p = 0.0046  I2 vs C -1.0 (-1.0, 0.0), < 0.001  I1 vs I2: 0.0 (0.0, 0.0) p = 0.10 | MD (95% CI)  I1 vs C: 2.0 (1.0, 4.0) p = 0.003  I2 vs C 2.0 (1.0 4.0), = 0.002  I1 vs I2: 0.0 (-1.0, 1.0) p = 0.47 | MD (95% CI)  I1 vs C: 7.6 (2.0, 14.0) p = 0.004  I2 vs C 5.7 (0.7 11.7) = 0.01  I1 vs I2: -1.7 (-5.4, 2.3) p = 0.20 | I-RODS  MD (95% CI)  I1 vs C: 3.0 (0.0, 9.0) p = 0.03  I2 vs C 5.0 (2.0 9.0) = 0.002  I1 vs I2: -1.7 (-5.4, 2.) p = 0.20 |
| Markvardsen et al. (2013) | Ig vs Pl  12 weeks |  | 5.7% improvement with Ig  P = 0.04 | 28% improvement with Ig  P = 0.01 | ODSS  I: -04 ± 0.7, C: 0.7 ± 1.5, p = 0.04  40MWT: 17% improvement with Ig, p = 0.04  9HPT: 21% improvement with Ig, p = NS |
| Mahdi-Rogers et al. (2009) | Is vs Pl as Ig- and St-sparing agent  39-42 weeks |  | MD (95% CI)  2.05 (-0.21, 4.32)  P = NS |  | ALDS  MD -0.47 (95% CI -3.67, 1.87)  ONLS median change (IQR)  I: 0 (0.75, 0); C: 0 (-1, 0); p = 0.93 |
| Hughes et al. (2018) | Switch to Is or Pl  Mean 9 months |  |  | MD (95% CI) 1.2 (-5.9, 8.2) | R-ODS (MD (95% CI))  -0.8 (-5.0, 3.54) |

Abbreviations: Ig = immunoglobulin; St = steroids; Pl = placebo; I = intervention; C = comparator; MRC = Medical Research Council Sum Score; INCAT = Inflammatory Neuropathy Cause and Treatment; NDS = Neurological Disability Score; MD = mean difference; CI = confidence interval; RODS = Rasch-built Overall Disability Scale; ODSS: INCAT overall disability sum score; ALDS = Academic Medical Centre Linear Disability Score.

## Extended Assessment of Harms

Owing to a paucity of comparative safety data, the extended assessment of harms considers the broader experience of patients with CIDP receiving a range of interventions in level IV and III-3 comparative studies. These studies lack contemporaneous control groups, they suffer from the confounding effects of multiple concurrent interventions, and they contain limited detail regarding the nature of adverse events. However, these observational case series make up a substantial proportion of publications on patients with CIDP and they typically followed patients for longer than did those enrolled in the RCT evidence. These studies can therefore provide important information about rarer adverse events and/or the longer-term safety profile of particular interventions. With respect to interpretation, the following key limitations of the evidence base should be noted:

* Level IV and III-3 studies do not exclude patients receiving multiple interventions, therefore the attribution of a particular adverse event to the intervention under study may be questionable.
* Studies were overwhelmingly retrospective in nature; therefore, adverse event reporting was typically limited to the availability and accuracy of case notes or records.
* The risk of any particular outcome cannot be estimated from these series as the sample sizes were typically small and the reported rates of adverse events exhibit significant heterogeneity across studies.
* Whether there was consecutive enrolment in studies was typically unclear, and the inclusion and exclusion criteria were poorly defined overall. Consequently, selection bias may be significant within this evidence base.
* Adverse events were under-reported, as revealed by statements from authors such as, “the most frequent minor side effect was headache, which was easily controlled with symptomatic medications”, wherein the actual number of patients or events was not reported (Jann et al. 2005).

The extended assessment of harms should be read in light of the above comments and it should be noted that interpretation of comparative safety is informed by the understanding that the mainstay of treatment for CIDP comprises IVIg, steroids and plasma exchange (Dyck and Tracy 2018). Each of these treatments is associated with potential adverse effects and has unique limitations (Dyck and Tracy 2018). Other immunosuppressant medications including methotrexate, azathioprine and others are typically employed when first-line treatments provide insufficient disease control and/or with a view to reduce dependence on first-line treatments (Dyck and Tracy 2018). Most patients with CIDP will require long-term treatment and may require multiple therapies over the course of their disease. Individual patient factors need to be considered when comparing the safety profile of various therapies for CIDP. Furthermore, most patients will receive treatment for durations longer than those represented in the literature and will likely have periods off treatment and/or changes between treatments.

This review has identified that the safety of IVIg is the most thoroughly examined in the literature, perhaps because it is a favoured treatment option for CIDP. Steroids have also frequently been examined. Other treatments, including plasma exchange and immunosuppressant drugs, have not been widely studied in the context of CIDP (although there is significant experience with all treatments in the broader literature). This extended assessment of harms is presented as follows: a commentary on the comparative safety of the investigated interventions in terms of the nature of frequent and serious adverse events, followed by a summary of each adverse event profile as represented by the total evidence for each separate intervention. Table 39 and Table 40 at the end of Section B.7, and Table 99 (Appendix C) at the end of the safety section provide the following:

* Table 39 summarises adverse events reported in the included studies for IVIg, including SCIg, steroids and plasma exchange. The events are presented as the number of patients experiencing the event (n), the number of studies reporting that event (including explicitly reported 0 rates, k), and the total number of patients in the reporting studies (N).
* Table 40 provides the same information for immunosuppressant drugs and immunoadsorption. These are reported separately due to the paucity of available literature, and with the understanding that, in practice, these interventions would typically be considered second-line and/or adjunct therapies
* Table 99 (Appendix C) summarises the characteristics of the included studies, the rate of adverse events, and the nature of serious events on a per study basis.

### Adverse events in patients receiving IVIg or SCIg

Evidence considered for the safety of IVIg or SCIg consisted of:

* 17 level IV case series reporting on adverse events associated with IVIg. The oldest of these publications was from 1997 and the most recent 2018.
* 5 level III-3 studies including a cohort of patients receiving IVIg published between 1995 and 2018. These studies were not considered relevant for comparative safety because there was no a priori decision to enrol patients in different cohorts. Thus, groups differed in sample size and baseline characteristics, rendering them essentially level IV evidence. Furthermore, these studies reported no comparisons between groups for safety.
* The IVIg arm of six level II studies was previously reported in the section on comparative safety and included in the extended assessment of harms to provide a comprehensive overview of the nature of adverse events associated with IVIg.[[16]](#footnote-17)

Sample sizes across the included studies or arms range from 10 to 281. Table 99 (Appendix C) shows that the studies were heterogenous in terms of the completeness of adverse event reporting, the observation period and the duration of maintenance treatment with IVIg. Only three studies considered SCIg (Christiansen et al. 2018; Cocito et al. 2014; Markvardsen et al. 2014b).

**Any adverse event and serious adverse events**

A total of 1,108 patients were included in studies where the overall rate of adverse events was reported. Among these patients, a total of 410 (37%) experienced an adverse event, bearing in mind that a single patient could have experienced multiple events. The proportion of patients experiencing any adverse event ranged from 0% (Christiansen et al. 2018) to 94% (Kuwabara et al. 2017), highlighting the differences in the quality of reporting across studies.

A total of 1,169 patients were included in 20 studies reporting an overall rate of serious adverse events. (Some studies only reported serious events and therefore the total denominator is higher for SAEs). Across these studies, 38 patients (3%) were reported to experience serious adverse events. The proportion in any study experiencing an adverse event ranged from 0 (six studies) to 14% (Hughes et al. 2018). It is important to note that not all studies reported the nature of the serious adverse events, and the designation of serious was ‘as per study classification’ so may be inconsistent across publications. For example, one study may classify deep vein thrombosis as serious while another may not. Reported[[17]](#footnote-18) serious adverse events included: cerebral infarction (n = 2), deep vein thrombosis (n = 1), haemolysis (n = 4), inguinal hernia (n = 1), Steven Johnson syndrome (n = 1), pneumonia (n = 1), anxiety (n = 1), worsening of CIDP (n = 3), worsening of chronic diverticulitis (n = 1), cholesteatoma (n = 1), skin reaction (n = 3), hypersensitivity (n = 1), pulmonary embolism (n = 1), hypertension (n = 1), respiratory failure (n = 2), migraine (n = 1), epilepsy (n = 1), polypharmacy (n = 1), heart failure (n = 1), and cardiac arrest (n = 1). For serious adverse events according to study see Table 99 (Appendix C).

**Nature of the adverse events**

Table 99 (Appendix C)describes the number and type of each adverse event reported in any of the included studies in patients receiving IVIg. This table also shows the total number of studies (or study arms) reporting the event and the total number of patients across reporting studies. It should be noted that a single patient may have experienced multiple events and be counted more than once within the table.

The most frequently reported adverse event in patients receiving IVIg was headache, which was reported in 155 patients. Several studies reported that many patients in their series experienced headache, however, the studies did not report actual numbers. Consequently, this outcome is likely to be under-reported in the included studies. Headache was followed by general disorders and administration site conditions (n = 80) that included fever, chills and flu-like reaction etc. Gastrointestinal disorders (n = 55), skin disorders (n = 31, predominantly rash) and infections (n = 46) were also common. Less frequent, but possibly severe or serious events, were vascular disorders and blood and lymphatic system disorders namely: deep vein thrombosis (n = 3), cerebrovascular event (n = 2), and haemolysis (n = 11). Deaths included one case of cardiac arrest and a second of heart failure, the details of which are reported in the section on comparative safety.

### Adverse events in patients receiving steroids

**Any adverse event and serious adverse events**

Steroid regimens used in the included studies were varied including both IV and oral regimens with prednisolone, dexamethasone and methyl prednisone (IV). This is summarised in Table 39.

A total of 12 arms of studies reported safety outcomes in 358 patients treated with steroids. Overall adverse events were reported in 94 patients, occurring in 12% (Cocito et al. 2010) to 94% (Lopate et al. 2005) of patients across the included studies.

Serious events were infrequently reported (total of 13 patients), however, the nature of these events was unclear. Included studies reported that 0 to 44% of patients experienced serious adverse events with steroids, including gastritis (n = 1), psychosis (n = 1), Cushingoid appearance (n = 3), gastrointestinal bleeding (n = 2), infectious complications (n = 3), and one death in a patient with urinary sepsis (Wertman et al. 1988).

**Nature of the adverse events**

Overall, the type of adverse events reported in patients receiving steroids was consistent with the known adverse event profile for steroid therapy. Steroid treatment, particularly at doses greater than 7.5 mg/day prednisone or equivalent, is known to be associated with a range of adverse events (Huscher et al. 2009) of which those reported in the included studies are typical. Steroids are also associated with loss of bone mineral density over the longer term, which was reported in one patient who experienced a decrease in bone mineral density while on dexamethasone (Van Schaik et al, 2010). The adverse effect profile of steroids is dose-related and varies according to the length of time a patient remains on therapy. Therefore, the adverse event profile of steroids in a clinical trial may not represent the variability in dose and duration in practice.

The most commonly reported adverse events included insomnia (n = 35), unspecified conditions (n = 41), weight gain (n = 46), Cushingoid appearance (n = 23) and indigestion (n = 23). Table 99 (Appendix C) reports the adverse events associated with any steroid regimen in the included studies.

### Adverse events in patients receiving plasma exchange

Adverse events associated with plasma exchange were poorly reported by the included studies. Four studies including 104 patients reported any adverse event in patients undergoing plasma exchange. Only three studies (Table 31) reported the overall proportion of patients experiencing an adverse event (19 – 41%) and the study reporting the highest rate (Vucic and Davies 1998) provided no further details. Described events included difficulty accessing veins (n = 3) and deficiency of coagulation factors (n = 1) in a study of 21 patients (Cocito et al. 2010), myocardial infarction (n = 1) and a cerebrovascular event (n = 1) in a study of 18 patients (Hahn et al. 1996a), and septicaemia associated with a tunnelled venous catheter (n = 1) (Choudhary and Hughes 1995). This was the only event described in this study of 33 patients, even though the authors reported a total of seven patients with adverse events.

This study reported that in patients experiencing two to five complications, the mean number of procedures was 18. The authors report a linear relationship between the frequency of adverse reactions and the number of treatment episodes per patient. No fatalities occurred and the authors conclude that complications rated as severe occurred in 0.7% of procedures, with the most frequent being infection of the venous access site (0.5% of procedures) and sepsis (0.2% of procedures) (Choudhary and Hughes 1995).

Two further studies reported only isolated events with plasma exchange and these are not formally considered included studies. Hahn, Bolton et al. 1996a randomised patient to plasma exchange or sham exchange and reported that one patient experienced a stroke one day after an uncomplicated plasma exchange and a second patient experienced a myocardial infarction with symptoms starting during a plasma exchange session[[18]](#footnote-19). Dyck, Litchy et al. 1994 who compared plasma exchange to IVIg, did not provide a breakdown of safety events, but did state that no patients experienced major complications. The authors reported that one patient (of 9) in the plasma exchange arm had an infection of the indwelling catheter.

Table 31 Studies reporting outcomes with plasma exchange

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Patients** | **Plasma exchange details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Choudry 1995 (Choudhary and Hughes 1995)  III-3 (IVIg v PE)  R  22 | CIDP considered by the consultant neurophysiologist to have demyelinating neuropathy | Frequency NR however, initial treatment was 5 exchanges over 8-14 days. | NR  Nature of AEs only partially reported. | 7/33 (21%)  NR  SAE: septicaemia arising from a tunnelled central venous catheter. |
| Vucic 1998 (Vucic and Davies 1998)  IV  R  32 | CIDP patients (criteria NR) undergoing plasmapheresis | The duration of each procedure was 1.5-2 hours. 5% human serum albumin alone or with normal saline was the usual replacement fluid. | NR  Nature of AEs incompletely reported. | 13/32 (41%)  NR |
| Cocito 2010 (Cocito et al. 2010)  III-3  R  IVIg: 153  Steroids: 155  PE: 21 | CIDP (EFNS/PNS criteria) | Details of the interventions were not reported. | Highly varied according to patient and treatment.  AEs with each treatment are reported but SAEs are not. | 4/21 (19%)  NR  SAE: NR |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; PE: plasma exchange; NR: not reported

### Adverse events in patients receiving azathioprine

Two studies (Table 32) with a total of 95 patients reported on azathioprine (Cocito et al. 2011; Lopate et al. 2005). Cocito et al. (2011) reported that 16 of 77 patients (21%) treated with azathioprine experienced an adverse event, but the nature of the events was not reported. Serious adverse events occurred in 10 patients in this study (13%). Lopate et al. (2005) reported that 10 of 18 patients (55%) experienced adverse events including increased liver function test (LFT) results (n = 1), anaemia/cytopenia (n = 4), and nausea/emesis (n = 5).

Table 32 Studies reporting outcomes with azathioprine

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Azathioprine details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Lopate et al. 2005 (Lopate et al. 2005)  III-3  R  18 | CIDP (EFNS/PNS criteria) | Oral immunosuppressive agents – further details NR | Oral agents: 4.7 years  Nature of AEs reported. | 10/18 (55%)  NR |
| Cocito 2011 (Cocito et al. 2011)  IV  R  110 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | 100–200 mg/day | Median 5.4 years  Nature of AEs NR | 16/77 (21%)  10/77 (13%) |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR: not reported

### Adverse events in patients receiving cyclosporin

Three studies with a total of 44 patients reported on cyclosporin (Barnett et al. 1998; Cocito et al. 2011; Lopate et al. 2005). Barnett et al. (1998) reported adverse events in 13 patients (68%) with events including nephrotoxicity requiring dose reduction (n = 2), nephrotoxicity requiring cessation (n = 2), hypertension (n = 4), nausea (n = 3), oedema (n = 3) and hirsutism (n = 4). Lopate et al. (2005) did not report numbers of patients experiencing adverse events but events reported included anaemia/cytopenia (n = 1), hypertension (n = 3) and renal insufficiency (n = 3). Cocito et al. (2011) reported that 6 of 12 (50%) and five of 12 (42%) of patients experienced any adverse event and a serious adverse event, respectively.

Table 33 Studies reporting outcomes with cyclosporin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Cyclosporin details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Lopate et al. 2005 (Lopate et al. 2005)  III-3  R  13 | CIDP (EFNS/PNS criteria) | Oral immunosuppressive agents – further details NR. | Oral agents: 4.7 years  Nature of AEs reported. | NR  NR  Nature of adverse events but not overall n/N |
| Barnett 1998 (Barnett et al. 1998)  IV  R  19 | Patients with CIDP diagnosed by an accepted combination of neurophysiological, and biopsy criteria. MGUS (n = 5), polyclonal gammopathy (n = 1) | 8-11 mg/kg per day in n = 8, 3-7 mg/kg per day in n = 10. A stepwise reduction in dose was made at 1 month, 3 months, and 6 months, generally to 2–3 mg/kg. | 4-7 years (progressive – relapsing disease)  Nature of AEs reported. | 13/19 (68%)  NR |
| Cocito 2011 (Cocito et al. 2011)  IV  R  44 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | Cyclosporin 100–300 mg/day. | Median 5.4 years  Nature of AEs NR. | 6/12 (50%)  5/12 (42%) |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR: not reported

### Adverse events in patients receiving cyclophosphamide

Good et al. (1998) reported the following events from 15 patients treated with cyclophosphamide: nausea (n = 4), headache and light headedness (n = 1), rash (n = 1) and moderate alopecia (n = 2). Drug-induced leukopenia developed in all patients, but leukocyte count returned to normal 2 to 3 weeks after the last treatment. No patients developed haematuria, prolonged bone marrow depression or malignancy. Cocito et al. (2011) reported that two of 13 treated patients experienced adverse events, of which one was serious (Table 34).

Table 34 Studies reporting outcomes with cyclophosphamide

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Cyclophosphamide details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Cocito 2011 (Cocito et al. 2011)  IV  R  110 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | 1 g/m2 IV/monthly, or 2 mg/kg/daily | Median 5.4 years  Nature of AEs NR | 2/13 (15%)  1/13 (8%) |
| Good 1998 (Good et al. 1998)  IV  P  15 | CIDP according to established criteria | IV Cyclophosphamide: 1 g/m2 over 1.5-2 hours as initial treatment and as monthly pulse treatments unless they showed sustained improvement over three courses of pulse. In patients failing to show a significant leukocyte count drop the dose was increased by 25% on subsequent pulses. | Mean 36.6 months  Nature of AEs reported | Overall AEs NR |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR: not reported

### Adverse events in patients receiving immunoadsorption

Two studies with a total of 31 patients reported on immunoadsorption (Table 35), but the proportion of patients experiencing adverse events went unreported (Dorst et al. 2018; Galldiks et al. 2011). Dorst et al. (2018) included 17 patients and reported the following events: pneumothorax (n = 1), thrombosis of the jugular vein (n = 2), febrile infection (n = 1), mild oedema (n = 2), dislocation of catheter (n = 1), bradycardia (n = 1), tachycardia (n = 1), hypotonia (n = 2), urinary tract infection (n = 1), gastrointestinal infection (n = 1) and exanthema of the face (n = 1). The authors reported that hypotonia, bradycardia and tachycardia are frequent and that common subclinical laboratory changes included mild anaemia, thrombocytopenia, hypokalaemia, hypocalcaemia, hypoproteinemia and increase of C-reactive protein. Galldiks et al. (2011) reported that no serious adverse events were observed in their series (n = 14).

Table 35 Studies reporting outcomes with immunoadsorption

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Immunoadsorption details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Dorst 2018 (Dorst et al. 2018)  IV  P  17 | CIDP (EFNS/PNS criteria) who had not responded to steroids, IVIg or both treatments. | Shaldon catheter (jugular vein). One cycle of IA consisted of 5 treatments on 5 consecutive days. Range of cycles was 1-9 per patient. | NR  Nature of AEs reported | 2/17 (12%)  NR |
| Galldik 2011 (Galldiks et al. 2011)  IV  R  14 | CIDP patients (according to current diagnostic guidelines) who had an unsatisfactory response to at least two of steroids, IVIg or plasma exchange. | Double-lumen central venous catheter in the jugular or subclavian vein: frequency adjusted according to clinical signs and fibrinogen levels. If necessary, treatment intervals were extended depending on the degree of fibrinogen depletion. Ten patients were treated in-hospital. Four of these 14 patients were treated in outpatient clinics using long-term maintenance IA with 1–2 treatments per week. | NR  Authors report in all patients, Immunoadsorption was safe and well tolerated, and no severe side effects occurred. | NR  0/14 (0%) |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR: not reported

### Adverse events in patients receiving methotrexate

Three single-arm studies with a total of 30 patients reported on methotrexate (Table 36). One RCT, Mahdi-Rogers et al. (2009), reported the addition of methotrexate or placebo to patients currently responding to either steroids or Ig in a cohort of 60 patients. The RCT reported individual adverse events but not the overall burden of adverse events. Adverse events for the addition of methotrexate versus placebo included cough or shortness of breath (9/28; 32% vs 7/32; 22%), infections (4/28; 14% vs 11/32; 34%), bruises and bleeding (2/28; 7% vs 2/32; 6%), mouth ulcers (0/28; 0% vs 5/32; 16%), rash (1/28; 4% vs 1/32; 3%), and nausea or vomiting (2/28; 7% vs 2/32; 6%). Serious adverse events in the methotrexate group included myocardial infarction, inspiratory stridor of unknown cause, and severe limb and respiratory muscle weakness. One patient died of respiratory failure after the end of the trial. In the placebo arm, one patient had a rib fracture requiring hospital admission. Both arms of the trial demonstrated similar numbers of abnormal laboratory test results (neutropenia, increased bilirubin, increased alkaline phosphatase, increased alanine transaminase, increased aspartate transaminase), except lymphopenia (10/27; 37% in the methotrexate arm vs 5/28; 18% in the placebo). The authors do not believe that any of the serious adverse events were related to the study drug.

In the case series evidence, Fialho et al. (2006) reported on ten patients who received methotrexate and noted that in general it was well tolerated. Adverse events included one patient who experienced mild hair loss (resolved on a lower-dose), another who developed a severe chest infection after eight months of treatment without neurological improvement, and a third who deteriorated despite the addition of first mycophenolate and then cyclosporin to the methotrexate regimen. This patient died suddenly with hypotension and fever of undiagnosed cause (Fialho et al. 2006). Lopate et al. (2005) reported that five of eight patients experienced an adverse event including increased LFT results (n = 2) and nausea/emesis (n = 3) (Lopate et al. 2005). Cocito et al. (2011) reported one patient with an adverse event (8%) but further details were unavailable.

Table 36 Studies reporting outcomes with methotrexate

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Methotrexate details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Mahdi-Rogers 2009  II  P  60 (28 with methotrexate and 32 with placebo) | CIDP diagnosed by a neurologist, present for at least 6 months, receiving IVIg | Intervention: 7.5mg once a week for 4 weeks followed by 10 mg once a week for 4 weeks, and 15 mg once a week for 32 weeks.  V Placebo | 39-42 weeks  Nature of AEs reported | Methotrexate v placebo  NR  3/28 (11%) v 1/30 (3%)  SAE (methotrexate): myocardial infarction (1), inspiratory stridor (1), severe limb and respiratory muscle weakness (1)\*  SAE (placebo): fractured rib (1) |
| Fialho 2006 (Fialho et al. 2006)  IV  R  10 | CIDP fulfilling recognised clinical criteria and neurophysiological evidence of demyelination | According to patient needs from 10-15 mg weekly for as long as clinically appropriate | NR  Nature of AEs reported | 3/10 (30%)  1/10 (10%)  SAE: death (1) due hypotension and fever of unknown origin. |
| Lopate et al. 2005 (Lopate et al. 2005)  III-3  R  8 | CIDP (EFNS/PNS criteria) | Oral immunosuppressive agents – further details NR | Oral agents: 4.7 years  Nature of AEs reported | NR  NR  Nature of adverse events but not overall n/N |
| Cocito 2011 (Cocito et al. 2011)  IV  R  12 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | Methotrexate 7.5–15 mg/weekly | Median 5.4 years  Nature of AEs NR | 1/12 (8%)  NR |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR = not reported

\*this patient died of respiratory distress after the end of the trial.

### Adverse events in patients receiving mycophenolate mofetil

Gorson et al. (2004) reported on 21 patients treated with mycophenolate mofetil of whom five experienced adverse events. Events included nausea (n = 3), malaise (n = 2), headache (n = 2) and diarrhoea (n = 1). One patient discontinued due to nausea. Cocito et al. (2011) reported on 12 patients treated with mycophenolate mofetil of whom two (16%) experienced an adverse event (Table 37).

Table 37 Studies reporting outcomes with mycophenolate mofetil

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Mycophenolate mofetil details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Cocito 2011 (Cocito et al. 2011)  IV  R  110 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | 1–2 g/day | Median 5.4 years  Nature of AEs NR | 2/12 (16%)  NR |
| Gorson 2004 (Gorson et al. 2004)  IV  R  21 | Patients with demyelinating polyneuropathy fulfilling criteria for CIDP | Mycophenolate Mofetil: Mean dose 2.1 g/day, and the average duration of therapy was 13 months (range, 9-18 months) | NR Nature of AEs reported. | 5/21 (24%)  NR |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; NR = not reported

### Adverse events in patients receiving rituximab

Two studies with a total of 41 patients reported on rituximab (Benedetti et al. 2011; Roux et al. 2018). Benetti et al. (2011) reported flu-like symptoms (n = 1) and a skin rash (n = 2) within 13 patients (15%). Roux et al. (2018) reported three adverse events in 28 patients (11%) including skin rash (n = 1), vomiting (n = 1) and lymphoma (n = 1). The lymphoma patient developed a primary CNS lymphoma seven months after rituximab infusion and died four months later (Table 38).

Table 38 Studies reporting outcomes with rituximab

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | **Rituximab details** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| Benedetti 2011 (Benedetti et al. 2011)  IV  R  13 | Patients with CIDP (EFNS/PNS criteria), four patients had comorbid haematological disease | 375 mg/m2 IV weekly for 4 consecutive weeks. One patient with severe Waldenstrom macroglobulinemia received 1000 mg IV every 6 months for four years | 1-5 years  Nature of AEs reported. | 2/13 (15%)  0/13 (0%) |
| Roux 2018 (Roux et al. 2018)  IV  R  28 | CIDP patients (EFNS/PNS criteria) | Varied. The most frequent was a first injection (1 g) followed by a second one (1 g) 2 weeks later (for 13 patients). Two patients received weekly infusions of 375 mg/m2 for 4 weeks; and nine patients received 375 mg/m2/month for 4 or 6 months, five of whom received rituximab with another chemotherapy because of a haematological indication. One patient (with lupus) received one infusion of 375 mg/m2 every 3 months for 3 years. | Median 2 years  Nature of AEs reported. | 3/28 (11%)  1/28 (4%)  SAE: CNS lymphoma (1) 7 months after rituximab infusion. |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society

### Summary of extended safety data

Generally speaking, IVIg is reported to be associated with an adverse event rate of 5-15% of all IVIg infusions and 20-50% of patients. Many adverse events are understood to be mild and reversible, with the majority of patients continuing to receive subsequent infusions. Risks of adverse events increase with high-dose, high rate of infusion, first infusion and product switching. Patient factors such as underlying organ deficiency will also influence the likelihood of experiencing a particular adverse event. In patients with CIDP, the most frequently reported adverse event was headache (reported in 155 patients)[[19]](#footnote-20), followed by general disorders and administration site conditions (n = 80) that included fever, chills and flu-like reaction etc. Gastrointestinal disorders (n = 55), skin disorders (n = 31, predominantly rash) and infections (n = 46) were also common. Less frequent but serious events were vascular disorders and blood and lymphatic system disorders namely deep vein thrombosis (n = 3), cerebrovascular event (n = 2), and haemolysis (n = 11). Deaths included one case of cardiac arrest and a second of heart failure, the details of which are reported in the section on comparative safety.

In comparison, steroids were associated with psychiatric disorders, metabolic complications, infections and gastrointestinal disorders. There was no association with vascular disorders and blood and lymphatic system disorders or nervous system disorders. The most common adverse events reported were insomnia (n = 35), mood changes (n = 23), Cushing appearance (n = 20), indigestions (n = 23), hypertension (n = 14) and infections (n = 15). Of these, serious events (as determined by study authors) included gastritis (n = 11), psychosis (n = 1), Cushingoid appearance (n = 3), gastrointestinal bleeding (n = 2) and infectious complications (n = 3). There was one death in a patient with urinary sepsis.

The broader literature indicates that long term corticosteroid use is associated with hypertension; bone fracture; cataract; nausea, vomiting, and other gastrointestinal conditions; metabolic issues such as weight gain, hyperglycaemia, and type 2 diabetes; and cardiovascular adverse events. Safety measured at or after 12 months of treatment in the reviewed evidence on steroids is discussed here.

Within the population of CIDP patients, the steroids study with the longest follow-up is a level IV study in which 15 patients received IV methylprednisolone at 1000 mg/day for 10 days followed by the same dose once every four weeks for five years (Boru et al. 2014). This cohort was followed for 10 years. Long-term adverse events were weight gain (n = 6), glucose intolerance (n = 3) and osteopenia (n = 1). One other patient was not included in long-term follow-up because of early discontinuation due to hypertension and nausea. Another study (Wertman et al. 1988), reported several serious adverse events in 16 patients receiving high-dose steroids for 5.2 years. One RCT (van Schaik et al. 2010) in which patients received pulsed high-dose dexamethasone or standard oral prednisolone (both tapered to 0 over 32 weeks), reported comprehensively on safety up to 12 months, including ocular assessments, bone mineral density and blood pressure monitoring. These authors report that most adverse events were minor and transient with persistent events being weight gain (>3kg n = 7/40, 16%), moderate hypertension (3/40, 7.5%), and diabetes mellitus (2/40, 5%).[[20]](#footnote-21) One patient (with a history of glaucoma) stopped treatment due to an attack of glaucoma, Five patients developed new hypertension or worsening of existing hypertension (n = 20 at baseline had mild or moderate hypertension of which the majority remained stable or improved over the study period). With respect to bone density, no new cases of osteopenia or osteoporosis were identified. However, T score worsened in one patient on dexamethasone.

As discussed in B.6, RCTs that followed patients for 4.5 years did not identify new serious adverse events beyond those in the 52-week analysis.

Adverse events with plasma exchange were poorly reported but included difficulty accessing veins (n = 3) and deficiency of coagulation factors (n = 1), myocardial infarction (n = 1), cerebrovascular event (n = 1), and septicaemia associated with a tunnelled venous catheter (n = 1). However, the total number of patients in studies reporting safety with plasma exchange was small (n = 104) relative to studies of steroids and IVIg. Studies reporting on the experience of CIDP patients receiving azathioprine, cyclosporin, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab and immunoadsorption were also reviewed. However, the quantity and quality of evidence was poor, with total patient numbers typically less than 100. All of these interventions were associated with adverse events with notable or severe complications including the development of lymphoma in a patient receiving rituximab[[21]](#footnote-22), thrombotic events with immunoadsorption, and significant nephrotoxicity in patients receiving cyclosporin. Azathioprine, methotrexate and mycophenolate mofetil were associated with adverse events such as nausea.

The overall rate of any adverse event with steroids was 12%-94%, and for IVIG was 0-95%. The rate of any adverse event with plasma exchange was 19%-41% of patients, with one study reporting that complications rated as severe occurred in 0.7% of procedures, the most frequent being infection of the venous access site (0.5% of procedures) and sepsis at 0.2% of procedures (34). Other interventions were limited to studies with small cohorts and do not lend themselves to a comparison of the rate of adverse events. Taken together, the extended assessment of harms indicates that IVIg can be considered a relatively safe intervention, with serious adverse events being infrequent and common adverse events being typically transient and mild. Steroids, the main comparator, result in a similar number of patients experiencing adverse events, however, the number of adverse events and the impact of them on a patient’s quality of life is dependent on dose and duration of therapy. Clinical feedback indicates that longer-term harms of steroids in this population may not be adequately represented in the evidence base. It would be anticipated that the long-term adverse event profile of extended high-dose steroids is unfavourable relative to IVIg. Whether patients can be effectively titrated to low-dose steroids would affect the anticipated adverse event profile.

Plasma exchange appeared relatively safe, however, infectious and vascular complications of catheters are a recognised concern with plasma exchange and the evidence available in patients with CIDP is too limited to provide robust conclusions about comparative safety.

### Tables summarising the characteristics of included studies and adverse events

Table 39 summarises adverse events reported in the included studies for IVIg (including SCIg), steroids and plasma exchange. Events are presented as the number of patients experiencing the event (n), the number of studies reporting that event (including explicitly reported 0 rates, k), and the total number of patients in the reporting studies (N). Events are ordered according to frequency, except for of bolded and underlined adverse events, which are those known to be associated with the intervention in broader (non-CIDP) literature. Table 40 provides the equivalent information for immunosuppressant drugs and immunoadsorption, which are reported separately due to a paucity of available literature, and in the understanding that, in practice, these interventions would typically be considered second-line and/or adjunct therapies. Immunoadsorption is a more recent intervention and is included in this table because of the limited data regarding its safety. Table 99 (Appendix C) summarises the characteristics of the included studies and the rate of all adverse events, serious adverse events, and the nature of serious events on a per study basis.

Table 39 Adverse events reported in patients receiving IVIg (includes SCIg), steroids or plasma exchange

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event category** | **Observed complications with IVIG**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies  **Represents recognised complications with IVIG** | **Observed complications of steroid therapy**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies  **Represents recognised complications with steroids** | **Observed complications of plasma exchange**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies  **Represents recognised complications with plasma exchange** |
| **Any adverse event** | **410/1108 (37%)** | **94/358 (26%)** | **Not estimable** |
| **Blood and lymphatic system disorders** | **Haemolysis:** n = 11, k=5, N = 371  **Neutropenia:** (NR) | Increased white blood cell count (NR) | **Immunoglobulin depletion** (NR)  **Coagulation factor depletion:** n = 1, k=1, N = 21 |
| **Cardiac disorders** | Cardiac arresta: n = 2, k=2, N = 177  Heart failurea: n = 1, k=2, N = 54  Fluid retention (limbs/peripheral): n = 6, k=3, N = 257 | **Fluid retention:** n = 3, k=1, N = 10  **Premature atherosclerotic disease:** (NR)  **Arrhythmias**: (NR) | Myocardial infarction n = 1, k=1, N = 18 |
| **Endocrine disorders** | Not applicable/NR | Adrenal insufficiency (NR) | Not applicable |
| **Eye disorders** | Not applicable/NR | **Cataracts** (NR)  **Glaucoma** (NR, n = 1 ↑ intraocular pressure) | Not applicable |
| **Gastrointestinal disorders** | Nausea: n = 32, k=7, N = 422  Vomiting: n = 8, k=3, N = 257  Indigestion: n = 6, k=1, N = 30  Diarrhoea: n = 3, k=1, K=49  Abdominal/gastric pain: n = 3, k=1, N = 30  Inguinal hernia: n = 2, k=1, N = 49  Colitis: n = 1, k=1, N = 24 | **Gastritis**: n = 4, k=3, N = 61  **Ulcer formation**: n = 3, k=1, N = 155  **Gastrointestinal bleeding** n = 2, k=1, N = 16  Indigestion: n = 23, k=3, N = 77  Abdominal/gastric pain: n = 2, k=1, N = 21  Diarrhoea: n = 2, k=1, N = 21  Vomiting: n = 1, k=2, N = 31 | Not applicable |
| **General disorders and administration site conditions** | **Reactions resembling anaphylaxis:** n = 1, k=1, N = 26  **Anaphylaxis in IgA-deficient patients:** (NR)  Fever: n = 30, k=3, N = 167  Chills: n = 18, k=2, N = 143  Fatigue: n = 10, k=3, K=300  Flu-like syndrome: n = 8, k=2, N = 50  Dose administration syndrome: n = 6, k=1, N = 27  Thoracic pain or pressure: n = 2, k=1, N = 44  Rigors: n = 1, k=1, N = 44  Hyperthermia: n = 1, k=1, N = 207 | Dose administration syndrome (IV methylprednisone): n = 6, k=1, N = 16  Fatigue: n = 5, k=1, N = 10  Malaise: n = 3, k=2, N = 31  Thoracic pain or pressure: m=1, k=1, N = 21 | **Anaphylaxis** (NR) |
| **Infections and infestations** | **Concurrent infections/phlogistic reactions** (NR)  Infections: n = 46 across a number of studies with pharyngitis being the most common and sepsis occurring in 1 patient. Catheter infection was described in 1 patient. | **Dose-dependent increase in the risk of infection especially with common bacterial, viral, and fungal pathogens**  Total infections n = 15 across a number of studies | **Infectious catheter complications:** n = 1, k=1, N = 33  One study reported infection of the venous access site in 0.5% of procedures with sepsis in 0.2% of procedures. |
| **Metabolism and nutrition disorders** | Hyperglycaemia: n = 1, k=1, N = 24 | **Hyperglycaemia:** n = 5, k=2, N = 36  **Diabetes:** n = 9, k=2, N = 195  **Cushingoid appearance** n = 20, K=3, N = 66  **Weight gain:** n = 46, K=7, N = 281  Impaired glucose tolerance: n = 1, k=1, N = 16 | **Hypocalcaemia** (NR)  **Hypokalaemia** (NR) |
| **Musculoskeletal and connective tissue disorders** | Weakness (Asthenia): n = 9, k=1, N = 113  Back pain: n = 6, k=2, N = 217  Muscle pain: n = 2, k=1, N = 44 | **Osteopenia**=1, k=1, N = 15  **Osteoporosis:** n = 3, k=1, N = 155  **Osteonecrosis** (NR)  Weakness (Asthenia): n = 1, k=1, N = 10  Limb pain: n = 1, k=1, N = 21 | Not applicable |
| **Nervous system disorders** | **Headache:** n = 155, k=14, N = 587  Dizziness/light headedness: n = 8, k=3, N = 163  Paraesthesia: n = 2, k=2, N = 50  Syncope: n = 1, k=2, N = 50  CIDP worsening: n = 4, k=2, N = 77 | Headache: n = 7, k=2, N = 48  Dizziness/light headedness: n = 2, k=1, N = 21  Tremor: n = 1, k=1, N = 21  Neuralgia: n = 1, k=1, N = 21 | Not applicable |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | Uterine leiomyoma: n = 1, k=1, N = 24  Carcinoma of the bronchus: n = 1, k=1, N = 30 | Lymphoma: n = 3, k=3, N = 50  Rectum polyp: n = 1, k=1, N = 21 | Not applicable |
| **Psychiatric disorders** | Insomnia: n = 1, k=2, N = 50  Anxiety: n = 1, k=2, n = 73 | **Emotional lability** (NR)  **Hypomania** (NR)  **Mania** (NR)  **Depression:** n = 1, k=1, N = 21  **Psychosis:** n = 3, k=2, N = 50  **Delirium:** n = 1, k=1, N = 21  **Confusion:** (NR)  **Disorientation:** (NR)  **Insomnia:** n = 35, k=4, N = 241  Mood changes: n = 23, k=2, N = 50  Agitation: n = 5, k=2, N = 31  Visual hallucinations: n = 1, k=1, N = 21  Anxiety: n = 1, k=1, N = 21 | Not applicable |
| **Renal and urinary disorders** | **Acute kidney injury** (NR)  **Hyponatremia** (NR)  Reversible decrease in renal function: n = 3, k=1, N = 26 | Acute kidney injury/renal insufficiency: n = 1, k=1, N = 16 | Not applicable |
| **Respiratory, thoracic and mediastinal disorders** | **Transfusion-related acute lung injury (TRALI)** (NR)  Upper respiratory tract inflammation: n = 4, k=1, N = 49  Dyspnoea: n = 2, k=2, N = 50  Respiratory failure: n = 2, k=2, N = 231  Cough: n = 1, k=1, N = 24  Pneumothorax: n = 1, k=1, N = 207 | Dyspnoea: n = 1, k=1, N = 21 | **Shortness of breath** (NR)  **TRALI** (NR) |
| **Skin and subcutaneous tissue disorders** | **Rash:** n = 26, k=6, N = 517  Erythema: n = 4, k=2, N = 115  Dermatitis: n = 1, k=1, N = 24 | **Skin thinning:** n = 8, k=2, N = 50  **Ecchymoses** (NR)  **Acne:** n = 7, k=1, N = 40  **Hirsutism** (NR)  Erythema: n = 5, k=1, N = 15  Delayed wound healing: n = 4, k=1, N = 40  Rash: n = 1, k=2, N = 37  Dermatitis: n = 0, k=1, N = 21 | Hives (NR) |
| **Unclassified** | Not applicable/NR | Increased appetite: n = 17, k=1, N = 40 | Not applicable/NR |
| **Vascular disorders** | **Thromboembolic events (see below)**  **Deep vein thrombosis**: n = 3, k=2, N = 219  **Cerebrovascular event**: n = 2, k=1, N = 49  Hypertension: n = 14, k=5, N = 371  Hypotension: n = 1, k=1, N = 30  Flushing/blushing: n = 1, k=2, n = 68 | Hypertension: n = 14, k=5, N = 242  Flushing/blushing: n = 1, k=1, N = 21 | **Hypotension** (NR)  **Vascular catheter complications** (NR)  Cerebrovascular event n = 2, k=2, N = 37 |

a. cardiac disorders: Includes one myocardial infarction with no further detail and one cardiac arrest in a patient who later died of respiratory failure (details in comparative safety). Heart failure requiring hospitalisation occurred four weeks after the first IVIg treatment (details in comparative safety). NR: not reported

Table 40 Adverse events reported in patients receiving immunosuppressants or immunoadsorption

|  |  |  |  |
| --- | --- | --- | --- |
| **Adverse event category** | **Observed complications with azathioprine (AZA), methotrexate (MTX), cyclophosphamide (CYP) and mycophenolate mofetil (MMF)**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies | **Observed complications of immunoadsorption**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies | **Observed complications of Rituximab**  n = number reported in the included studies, k = number of studies reporting that outcome, N = total patient numbers in those studies |
| **Blood and lymphatic system disorders** | Anaemia or cytopenia  AZA: n = 4, k=1, N = 18  CSA: n = 1, k=1, N = 13  Leukopenia (intended effect)  CYP: n = 15, k=1, N = 15 | None reported | None reported |
| **Cardiac disorders** | Oedema  CyP: n = 3, k=1, N = 13 | Mild oedema  n = 2, k=1, N = 17  Bradycardia or Tachycardia n = 2, k=1, N = 17 | None reported |
| **Gastrointestinal disorders** | Nausea  AZA: n = 5, k=1, N = 18  CSA: n = 3 k=1, N = 13  CYP: n = 4, k=1, N = 15  MTX: n = 5, k=2, N = 36  MMF: n = 3, k=1, N = 21  Diarrhoea  MMF: n = 1, k=1, N = 21 | None reported | Vomiting  n = 1, k=1, N = 28 |
| **General disorders and administration site conditions** | Malaise  MMF: n = 2, k=1, N = 21 | Febrile infect  n = 1, k=1, N = 17 | Flu-like symptoms  n = 1, k=1, N = 13 |
| **Infections and infestations** | Severe chest infection  MTX: n = 1, k=1, N = 10  Infection  MTX: n = 4, k=1, N = 28 | Infections  n = 2, k=1, N = 17 | None reported |
| **Investigations** | Increased liver function test results  AZA: n = 1, k=1, N = 18  MTX: n = 2, k=1, N = 8  Lymphopenia  MTX: n = 10, k=1, N = 28  Neutropenia  MTX: n = 1, k=1, N = 28  Increased bilirubin  MTX: n = 1, k=1, N = 28  Increased alkaline phosphatase  MTX: n = 2, k=1, N = 28  Increased alanine transaminase  MTX: n = 1, k=1, N = 28 | None reported | None reported |
| **Musculoskeletal and connective tissue disorders** | None reported | Hypotonia  n = 2, k=1, N = 17 | None reported |
| **Nervous system disorders** | Headache  CYP: n = 1, k=1, N = 15  MMF: n = 1, k=1, N = 21 | None reported | None reported |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | None reported | None reported | Lymphoma  n = 1, k=1, N = 28 |
| **Renal and urinary disorders** | Nephrotoxicity requiring dose reduction or cessation  CSA: n = 7, k=2, N = 26 | None reported | None reported |
| **Respiratory, thoracic and mediastinal disorders** | Cough or shortness of breath  MTX: n = 9, k=1, N = 28 | Pneumothorax  n = 1, k=1, N = 17 | None reported |
| **Skin and subcutaneous tissue disorders** | Hirsutism  CSA: n = 4, k=1, N = 13  Rash  CYP: n = 1, k=1, N = 15  MTX: n = 1, k=1, N = 28  Alopecia  CYP: n = 1, k=1, N = 15  MTX: n = 1, k=1, N = 10 | Exanthema of the face  n = 1, k=1, N = 17 | Rash  n = 2, k=2, N = 41 |
| **Vascular disorders** | Hypertension  CSA: n = 7, k=2, N = 26 | Thrombosis of jugular vein n = 2, k=1, N = 17 | None reported |

## Interpretation of the Clinical Evidence

**Safety**

Treatments for CIDP including IVIg, steroids, plasma exchange and immunosuppressant and/or immunomodulatory drugs differ in their mode of action, speed of control, degree of invasiveness, side effect profile and cost. The evidence reviewed in this Assessment indicates that the overall rate of serious adverse events with any treatment over the short to intermediate term is low. However, a formal test of non-inferiority or superiority could not be applied, owing to the paucity of studies reporting safety outcomes and limitations in trial design. As most patients with CIDP will require long-term treatment and may require multiple therapies over the course of their disease, comparison of the safety profiles of various therapies for CIDP should be considered in light of the heterogenous clinical presentation and respective needs of CIDP patients.

Side effects of IVIg frequently involve headache, fever, rash and infusion-like reactions that tend to be transient and non-severe. Rare but serious events include haemolysis. The data review of CIDP patients shows an adverse event profile consistent with the broad literature on the safety of IVIg. Steroids result in a similar number of patients experiencing adverse events, however, the number of events and their impact on patient quality of life is dependent on dose and duration of therapy. Based on the rheumatoid arthritis experience (Huscher et al. 2009) it is anticipated that the long-term adverse event profile of extended high-dose steroids is unfavourable relative to IVIg. Whether patients can be effectively titrated to low-dose steroids (< 7.5 mg/day of prednisone or equivalent) will impact the anticipated adverse event profile. The safety of plasma exchange and immunosuppressant and/or immunomodulatory drugs was poorly reported in the included studies, and/or was reported in too few studies to allow comment.

No evidence to inform on the safety of combinations of treatment strategies was available.

The Reference Group identified that a limitation of the evidence base is that it failed to adequately capture the adverse events associated with steroid use. The Reference Group suggested the adverse event profile reported in the publication by Wilson et al. (2007) provides an overview of the risks of steroid use and is applicable to the Australian CIDP population. Results from this publication are included in Section B6. Steroid use increased the risk of diabetes, osteoporosis, fractures, glaucoma and serious infection in patients with giant cell arteritis.

**Effectiveness**

The evidence reviewed in this Assessment indicates that, relative to no treatment, Ig likely has superior effectiveness (moderate-quality evidence). There is moderate evidence indicating that Ig has at least non-inferior effectiveness relative to steroids. Advice from the Reference Group is that the evidence may support a finding of superior effectiveness based on the relative number of patients discontinuing treatment. There was insufficient evidence on the comparison of Ig and plasma exchange to support a finding of non-inferiority. Overall, there was limited, mixed-quality evidence investigating treatments for CIDP. Generally, trials were small and follow-up duration was short. Risk of bias was “high” in eleven of the 20 identified RCTs and “of concern” in a further three. The relative long-term effectiveness of any of the active treatments for CIDP is thus uncertain. Ig was found to elicit a clinically meaningful response in the approximately 50% of patients receiving the treatment, and thus is likely to be beneficial for CIDP patients.

Available evidence indicates that there is little short-term (≤ 6 months) benefit from the addition of immunosuppressants to other treatments (using drug and dosage studies in the RCTs). No long-term data was available.

On the basis of the benefits and harms reported in the evidence base (summarised in Table 41), it is suggested that; relative to:

* No treatment, Ig has inferior safety and superior effectiveness; noting that Ig is rarely associated with serious adverse events.
* Steroids, Ig has superior safety and at least non-inferior effectiveness. Advice from the Reference Group is that the evidence may support a finding of superior effectiveness based on the relative number of patients discontinuing treatment.
* Plasma exchange, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.
* Immunosuppressants, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.
* Combination therapy, there is insufficient evidence to comment on the relative safety and effectiveness of Ig.

Note the Reference Group agreed that it was not appropriate to perform a GRADE summary for safety outcomes due to the different safety profiles of the intervention and comparators.

Table 41 Balance of clinical benefits and harms of Ig, relative to no treatment, as measured by the critical patient-relevant outcomes in the key studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcomes  Follow-up | Participants (studies) | Quality of evidence (GRADE) a | Risk with no treatment | Risk difference with Ig |
| Relative to no treatment | | | | |
| INCAT follow-up: median 6 months | 117 (1 RCT) | ⨁⨁⨁◯ MODERATE a | The mean change in INCAT was -0.3 | mean change 0.7 lower (1.3 lower to 0.2 lower) |
| MRC follow-up: range 3 weeks to 24 weeks | 145 (2 RCTs) | ⨁⨁⨁◯ MODERATE b | Change in MRC favoured Ig in both RCTs with different magnitude (study 1: n = 117, mean change 3.1, p = 0.001 and study 2: n = 18, mean change = 0.29, p = NR) | |
| Clinically meaningful response follow-up: range 3 weeks to 24 weeks | 255 (4 RCTs) | ⨁⨁⨁◯ MODERATE a | Clinically meaningful response as higher in the Ig group in ¾ studies. Rates of response ranged from 13% to 63% in the Ig group and 10% to 23% in the no treatment group. | |
| **Relative to steroids** | | | | |
| INCAT  follow-up: 6 weeks | 42  (1 RCT) | ⨁⨁⨁◯ MODERATE a | The mean INCAT was **0** | MD **0.22 lower** (0.62 lower to 1.06 higher) |
| Discontinue treatment  follow up: 6 months | 45  (1 RCT) | ⨁⨁⨁◯ MODERATE a | 524 per 1,000 | 241 fewer per 1,000 (from 346 to 68 fewer, RR = 0.54) |
| MRC  follow-up: 6 months | 45  (1 RCT) | ⨁⨁⨁◯ MODERATE a | Mean change in MRC was 1.8 ± 11.64 | Mean change in MRC was 4.7 ± 7.69 (p = 0.0929) |

Source: GRADE Working Group grades of evidence (Guyatt et al., 2013)  
⨁⨁⨁⨁ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.   
⨁⨁⨁⨀ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.   
⨁⨁⨀⨀ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.  
⨁⨀⨀⨀ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

INCAT = Inflammatory Neuropathy Cause and Treatment; MD = mean difference; MRC = Medical Research Council Sum Score; RCT = randomised controlled trial.

a. Assessed using the Cochran Risk of Bias tool, b. Inconsistent findings in the two trials

# Section C Translation Issues

## C.1. Overview

Three key issues arise in translating the evidence provided in Section B to an economic model presented in Section D: firstly, the applicability of the populations in key trials to clinical practice in Australia; secondly, the selection of utilities; and thirdly, the extrapolation of trial evidence beyond the maximum follow-up of key trials. Each of these issues is addressed in separate pre-modelling studies in Sections C2, C3 and C4. The sections provide an overview of the issue to be addressed, the pre-modelling methodology to translate trial data into assumptions for economic modelling, and how results are used in Section D.

Table 42 Outline of Section C issues being addressed

| **Section** | **Issue** |
| --- | --- |
| C2 | Applicability of the trial-based evidence to the NBA-listing population |
| C3 | Selection of utilities |
| C4 | Extrapolation of trial-based evidence. |

Abbreviations: MBS = Medicare Benefits Schedule

## C.2. Applicability translation issues

### C.2.1. Applicability of the trial-based evidence to the CIDP population

#### C.2.1.1 Identification of issue that needs to be addressed

Applicability describes the manner in which the participants and circumstances of use in key trials and studies presented in Section B, differ from the Australian population indicated for treatment. This pre-modelling study addresses whether characteristics of patients are representative of Australian CIDP patients currently using Ig; and whether the circumstances of use of Ig and steroids in trials are representative of how these products are being used in Australian clinical practice.

### C.2.1.2 Focused analytical plan

Patient demographic characteristics, along with inclusion and exclusion criteria of included clinical trials, are reviewed and compared with the current criteria for Ig use in Australia. Inclusion covers age, gender and disease characteristics.

### C.2.1.3 Results of pre-modelling study

CIDP patients currently eligible for Ig treatment in Australia are specified in Version 3 of ‘*the Criteria’* for the clinical use of Ig in Australia. The criteria specify that confirmed CIDP patients with significant disability or compromised walking (ONLS score of at least two points, and the MRC sum score), or CIDP patients who relapse within six months of commencing a trial off Ig therapy, are eligible for Ig. Review by a neurologist should be undertaken after four months of Ig therapy to determine response or lack thereof. Reviews should be conducted annually to support continuation of Ig therapy. Patients who relapse within six months of the last Ig dose are also eligible for Ig therapy. Patient characteristics in key trials, along with dose regimen and frequency, and setting are summarised in Table 43.

Table 43 Features of Immunoglobulin trial patient populations

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Inclusion** | Intervention and Comparator | Baseline | |
| Patient Characteristic | Disease Characteristic |
| Ig (I) vs Pl  ICE Study  (Hughes et al. (2008))  I: n = 59  C: n = 58 | Adult patients with diagnosed CIDP (motor and sensory dysfunction) with significant disability (INCAT 2-9)  Patients treated for CIDP in last 3 months excluded. | IVIg, Cutter Biological Product, Miles Inc. 5% human protein in 9-11% mannose, 0.4 g/kg daily for 5 days  Placebo, 10% dextrose daily for 5 days | Age: 52 (range 9-79), % male: 37  NDS  I: 78.3 ± 27.5, C: 76.6 ± 27.7  Clinical grade  I: 4.6 ± 1.9, C: 4.2 ± 1.9 | Whole group  Status: definite: 21, probable: 9  Type: progressive: 16, relapsing: 14  Time since diagnosis: NR |
| Ig (I) vs St (C)  Hughes et al. (2001)(Hughes et al. 2001)  I: 17  C: 15 | Diagnosis of CIDP by neurologist, progressive or relapsing motor and sensory dysfunction of more than one limb, reduced or absent tendon reflexes, CSF less than 10 white cells, INCAT criteria[[22]](#footnote-23) | IVIg (Sandoglobulin)  1 g/kg/day for 2 days  + placebo St  Oral prednisolone  60 mg daily tapering to 10 mg daily over 6 weeks + placebo Ig | Age. I: 55.8, C: 52.1  % male, I: 71, C: 60 | Type: progressive  n = 12,  relapsing  n = 20  INCAT  I: 4.11 ± 2  C: 3.47 ± 1.3 |
| Ig vs St  Nobile-Orazio et al. (2012)(Nobile-Orazio et al. 2012a)  I: n = 24  C: n = 21 | Typical CIDP according to EFNS/PNS criteria. Active or stationary phase but not in remission | IVIg (IgVena, Kedrion, Italy). 0.5 g/kg/day for 4 consecutive days each month for 6 months  IV methylprednisolone 0.5g for 4 consecutive days each month for 6 months | Age  I: med 54, C: med 66  % male  I: 63%, C: 71% | Progressive 17/45  Relapsing 18/45  Rankin score.  I: median 2  C: median 3  ONLS  I: median 3  C: median 4 |
| Ig (I) vs Pl (C)  Hahn et al. (1996b)(Hahn et al. 1996b)  I: n = 16  C: n = 14 | Definite or probable CIDP (1991 AAN criteria). Continually progressive disease (>8 weeks) OR static or recently progressed disease. Muscle weakness interferes with ambulation (NDS ≥ 40). Ig naïve patients. | IVIg  Cutter Biological Product, Miles Inc. 5% human protein in 9-11% mannose  0.4 g/kg daily for 5 days  Placebo  10% dextrose daily for 5 days | Age: 52 (range 9-79)  % male: 37 | Definite: 21, Probable: 9  Type: progressive: 16, relapsing: 14  NDS  I: 78.3 ± 27.5  C: 76.6 =- 27.7  Clinical grade  I: 4.6 ± 1.9  C: 4.2 ± 1.9 |

**Abbreviations**: AAN = American Academy of Neurology, CIDP = Chronic inflammatory demyelinating polyneuropathy, Ig = Immunoglobulin, IV = Intravenous, P = placebo, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, ONLS = Overall Neuropathy Limitations Scale, NDS = neurologic disability score, INCAT = Inflammatory Neuropathy Cause and Treatment, St = steroid. I = intervention, C = comparator.

#### Patient characteristics in trials compared to listing

The characteristics of the patient populations in major trials such as Hughes et al. (2001, 2008) appear to be aligned with the patient population currently eligible for IVIg according to Version 3 of *‘the Criteria’*. Patients in the Hughes et al. (2001) trial were drawn from nine European centres (located in the UK, Belgium, Italy, Spain, the Netherlands, Greece and the Czech Republic) between July 1998 and November 1999. Characteristics are outlined in Table 44 taken from McCrone et al. (2003) who used trial data from Hughes et al. (2001) for economic analysis (McCrone et al. 2003).

Table 44 McCrone et al. (2003) patient characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | All patients in study | | Patients with cost data for first treatment period | |
| **P–I**  **(n = 15)** | **I–P**  **(n = 17)** | **Prednisolone**  **(n = 13)** | **IVIg**  **(n = 12)** |
| Male, n (%) | 9 (60) | 12 (71) | 9 (69) | 7 (58) |
| Female, n (%) | 6 (40) | 5 (29) | 4 (31) | 5 (42) |
| Age | 52.1 (18.3) | 55.8 (16.2) | 53.9 (17.3) | 52.0 (13.6) |
| Illness duration | 5.2 (6.5) | 5.3 (7.8) | 5.6 (6.9) | 5.5 (8.3) |
| Worst arm disability grade in any attack | 2.2 (1.1) | 2.6 (1.4) | 2.0 (1.1) | 2.3 (1.3) |
| Worst leg disability grade in any attack | 1.6 (0.8) | 2.5 (1.8) | 1.5 (0.5) | 2.1 (1.7) |
| Physical disability grade at randomisation | 3.5 (1.3) | 4.1 (2.0) | 3.5 (1.4) | 3.3 (1.5) |

**Abbreviations**: P–I = prednisolone followed by IVIg; I–P = IVIg followed by prednisolone

**Source**: McCrone et al. (2003)

Hughes et al. (2001, p. 196) noted that patients had neurological examination along with biochemical testing including serum protein electrophoresis (Hughes et al. 2001). Clinical diagnosis of CIDP included progressive or relapsing motor and sensory dysfunction of more than one limb over more than two months caused by neuropathy, reduced or absent tendon reflexes, less than 10 white cells/ll in the cerebrospinal fluid, and neurophysiological criteria. The criteria incorporated significant physical disability in upper or lower limb function, and stable or worsening clinical condition.

Hughes et al. (2001) included 32 randomised patients from nine European centres. Average patient age was 54.1 years, with a ratio of 21 males to 11 females and average disability grade at randomisation of 3.81. The Hughes et al. (2001, p. 196) study excluded those with systemic diseases that could be associated with neuropathy; those pregnant or planning to be; those with concurrent medical conditions that could affect treatment; those with significant respiratory impairment; those who had received IVIg, corticosteroids or plasma exchange in the six weeks before treatment; those under the age of 18; and those who met the criteria for multifocal motor neuropathy and had previously failed to respond to IVIg or corticosteroids (Hughes et al. 2001). Most of the trials in Section B exclude children, therefore applicability is limited when age is considered. Children only comprise a small proportion of CIDP patients in Australia. The McLeod et al. (1999) CIDP prevalence study using AAN criteria in Newcastle, NSW, found the average patient age to be 47.6 years, with 51% of patients having relapsing‐remitting CIDP over 7.1 years (McLeod et al. 1999a).

The Hughes et al. (2008, p. 137) study included patients 18 years of age or older from 33 centres in Europe, North America, South America and Israel. Eligible patients had a diagnosis of CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb resulting from neuropathy over the two months before study entry, and significant disability as defined by an overall INCAT disability score of 2–9. Mean ages on each arm of the study were 50 and 53 years. Males accounted for 53% and 79%, and the periods since first CIDP symptoms were 5·8 and 4·8 years. Baseline INCAT disability scores of 4·2 and 4·1 were reported.

Hughes et al. (2008) used exclusion criteria, such as patients who had been treated with steroids (>10 mg/day prednisolone or equivalent), IVIg, or plasma exchange in the three months prior (Hughes et al. 2008). Patients who had been treated with other immunomodulatory or immunosuppressive agents such as interferon or azathioprine in the previous six months were also excluded, along with those who had evidence of central demyelination; those with persistent neurological deficits from stroke, CNS trauma or peripheral neuropathy from other causes (eg, diabetes mellitus, IgM paraproteinemia, or uraemic, toxic or familial neuropathy); and those with a motor syndrome that fulfilled criteria for multifocal motor neuropathy with conduction block and evidence of systemic disease that might cause neuropathy.

Some of these exclusions would apply in Australia. However, those who had received IVIg, corticosteroids or plasma exchange in the six weeks before treatment and had previously failed to respond to corticosteroids, would not be excluded from treatment in Australia. It is likely that the Ig-using CIDP patient population in Australia would have a high proportion of patients who had previously failed to respond to corticosteroids. In the Australian scenario, where a high proportion of steroid-resistant patients is possible, patient response to steroids versus Ig in the trial patient population would favour the comparator. Steroid resistance is defined as patients contraindicated to steroids, and patients for whom steroids did not elicit a therapeutic response.

Another major RCT from which data is sourced in the economic model is that by Nobile-Orazio et al. (2012). The study included 45 patients (24 IVIg, 21 IV methylprednisolone) from 14 Italian neurological centres. Patients were eligible if they were at least 18 years of age, had definite typical CIDP according to the EFNS/ PNS criteria, had some disability (scoring 2 or more on either the ONLS or the modified Rankin scale), were in an active or stationary phase but not in remission compared with the last available assessment, and were without improvement in the ONLS and modified Rankin scale scores between the screening and inclusion visits.” (ibid, p. 494). Average patient age was 66 and 54 years, and 15 of 21 and 15 of 24 patients were men on each arm.

The PICO noted that there is no specific diagnostic test for CIDP. Clinical signs and symptoms, evidence of demyelination on electrophysiological or pathological studies, and the exclusion of other causes are typically employed for diagnosis. The EFNS/PNS diagnosis guidelines suggest nerve conduction studies, cerebrospinal fluid cells and protein, MRI spinal roots, brachial plexus and lumbosacral plexus, nerve biopsy studies, clinical improvement following immunomodulatory treatment (such as IVIg), and tests to detect concomitant disease and/or hereditary neuropathy be used in diagnosis. Patients are then classified as definite, probable or possible CIDP. In Australia, to be eligible for Ig, patients must be diagnosed as having CIDP plus suffering significant disability or compromised walking as objectively measured by an ONLS score of at least two points, and the MRC sum score. This diagnosis is similar to that for entry into key trials.

While the average age and diagnosis of CIDP is reasonably well aligned between trials and Australian Ig use criteria, the types of CIDP evident in trial participants varied (see Table 43) and there is limited data about the characteristics of CIDP patients in Australia. The NBA records the age and weight of CIDP patients using Ig. In 2017-18 the average patient was 64 years, weighing 82.5kg. McLeod et al. (1999) studied the prevalence of CIDP in NSW in 1996 (McLeod et al. 1999a). A crude prevalence of CIDP was 1.9 per 100,000 population using AAN criteria and 51% of patients had a relapsing-remitting course. Clinical feedback provided during the evaluation indicated that 60% of patients have the chronic progressive form and require lifelong treatment, 30% have the relapsing-remitting form and require recurrent treatment for relapses (often treated lifelong after the second relapse), and 10% are monophasic and can be phased off treatment.

Expert opinion sought during the PICO confirmed that treatment for CIDP would not differ, whether it be for relapsing and remitting or progressive CIDP. Further, it was suggested that improvements in the recognition of CIDP may fend off the relapsing and remitting course of this disease. Whether CIDP is progressive, relapsing or monophasic has an impact on the type of economic model used to undertake the evaluation. Ig treatment needs to be costed in the longer-term for chronic forms of the disease, whereas treatment is short-term for the monophasic form. Given that 60% of patients have the chronic progressive form of CIDP, a 10-year economic model is presented in Section D. As patients in key trials had chronic and relapsing-remitting forms of the disease, there is some uncertainty about the magnitude of relapse assumptions and average dosing for a typical patient. Sensitivity analysis is presented at the end of Section D to examine the impact on economic results of changing these assumptions.

#### Circumstances of use

Steroids or IVIg are recommended in Australia as first-line treatment options for patients with moderate to severe disability (except for pure motor CIDP, where only IVIg is recommended). Participating patients in key trials had varying degrees of steroid resistance. Optimal treatment varies for resistant and non-resistant sub-groups, whereas trial results have been typically presented for comparator groups as a whole. This issue, and its impact on economic model results, is discussed in Section D sensitivity analyses.

The allowable IVIg dose ranges are outlined in Version 3 of *‘the Criteria’* Ig use in Australia for both patients commencing initial Ig treatment and those who have relapsed within six months of a trial off therapy. This includes an induction dose of 2g/kg in 2 to 5 divided doses and a maintenance dose of up to 0.4-1g/kg once every 2 to 6 weeks. A maximum dose of 2g/kg may be given in any 4-week period. The NBA report on the issue and use of Ig (Annual Report 2015-16) outlines the number of CIDP patients receiving IVIg therapy in Australia. The total number of patients has increased from 1,551 in 2011-12 to 2,250 in 2015-16 and 2,595 in 2017-18.

Average Ig use per Australian CIDP patient has increased from 437g to 497g over this period. This dose is lower than that of the economic study of Blackhouse et al. 2010 in Canada (around 1,447 g[[23]](#footnote-24) in the first year) and those of the Italian SCIg versus IVIg comparisons of Cocito (2012) (annual Ig dose of 840g per year), and Lazzaro et al. (2014) (960g per year). These economic models were developed for chronic CIDP patients assumed to receive Ig over the entire year. The lower average Ig use per patient in Australia is partly a result of total Ig use being averaged across chronic, monophasic and relapse-remission patients that would not all utilise Ig for the entire year. Other factors such as more appropriate care as a consequence of the national Ig criteria could also contribute to lower use per CIDP patient per year. Using a trial maintenance dose (based on Hughes et al. 2008) of 17.33g/kg per year (1g/kg every 3 weeks) equates to 1,430g Ig usage per patient per year based on the average patient weight of 82.5kg reported for Australian CIDP patients by the NBA. This usage estimate was included in the trial and extrapolated analyses to examine the sensitivity of estimated ICER to the dosing assumption. The higher volume of Ig per year is in line with the trial of Hughes et al. 2008, where patients received 18.33g/kg/year in the first year (loading 2g/kg over 2-4 days, 1 g/kg over 1-2 days every 3 weeks) and 17.33g/year in following years.

The Hughes et al. (2008) ICE study was a response-conditional crossover trial that used IV Ig or placebo every three weeks for up to 24 weeks in an initial treatment period. Patients received a baseline loading dose of 2g/kg over 2–4 days followed by a maintenance infusion of 1g/kg over 1–2 days every 3 weeks for up to 24 weeks. Patients who showed no improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. (ibid, p. 137) (Hughes et al. 2008). Nobile-Orazio et al. (2012) provided IVIg at a daily dose of 0·5g/kg for four consecutive days and IV steroid placebo or daily IV methylprednisolone (0·5g in 250 mL of sodium chloride solution) for four consecutive days (Nobile-Orazio et al. 2012a). Each patient was treated every 28 days (within 3 days) for six months, after which, therapy was discontinued and patients followed-up for a further six months for deterioration (ibid, p. 494).

Australian Ig guidelines provide recommendations for usage, and trials fall within these dosage allowances. Average use in Australia varies by CIDP type, and it is difficult to ascertain dosage per year for chronic, relapse and monophasic patients. Trials have included these patient subtypes; however, longer-term dosage is not specified as most trials cease before one year of follow-up.

#### Setting and comparator

Hughes et al. (2001, 2008) sourced patients from European treatment centres (UK, Belgium, Italy, Spain, the Netherlands, Greece and Czech Republic) between July 1998 and November 1999 (Hughes et al. 2001; Hughes et al. 2008). In Australia, the infusion of IVIg is undertaken at hospitals for inpatients, at outpatient clinics and at private same-day infusion facilities. Expert opinion in the PICO indicated that the most common setting for IVIg delivery is the public outpatient setting, although it was noted that patients are commonly admitted as a ‘same-day’ patient (i.e. inpatient). Care of a CIDP patient is primarily managed by a neurologist.

Corticosteroids are a first-line treatment for CIDP and the PICO noted that 50% of Australian patients not receiving Ig therapy will receive corticosteroids. Four PBS-listed glucocorticoids are used in Australia (prednisone, prednisolone, dexamethasone and methylprednisolone) but there is no consensus on the optimum dosing regimen. Key trials use higher initial dosing that tapers (see Table 45). This pattern is included in the economic model, following the Canadian economic modelling study of Blackhouse et al. (2010).

Table 45 Features of Corticosteroid trial or observational study patient populations

| **Study** | **Inclusion** | Intervention and Comparator | Baseline | |
| --- | --- | --- | --- | --- |
| Patient Characteristic | Disease Characteristic |
| St (I) vs St (C)  van Schaik et al. (2010)(van Schaik et al. 2010)  I: 24  C: 17 | Patients aged 18 years and over with newly diagnosed definite or probable CIDP (ENC diagnostic criteria). Required to have signs and symptoms severe enough to warrant treatment. Treatment naïve. | Oral dexamethasone 40mg/day for four days then placebo for 24 days. 6 cycles  Oral prednisolone  60mg per day for 5 weeks then tapering to 0mg over 27 weeks | Age, I: med 59.9, C: med 60.8 | INCAT  I: med 8.5 IQR 1-15  C :med 9 IQR 0-17  ALDS  I: 69.9 ± 16.1  C: 63.2 ± 21.2  MRC  I: med 50 IQR 24-57 |
| St + Is vs St  Dyck et al. (1985)(Dyck et al. 1985)  I: n = 15  C: n = 14 | Symptoms for at least 6 months, all static or worsening, no associated disease that would cause neuropathy, a neurologic disability score greater than 50 points, no treatment with prednisone or immunotherapy for at least 3 months | Prednisone 120mg alternate days tapering over 13 weeks + azathioprine 2mg/kg/day  Prednisone 120mg alternate days tapering over 13 weeks | Age  I: median 41  (range 18-63)  C: median 46  (range 19-70)  % male  I: 46%  C: 70% | NDS  I median 119 range 70-203  C: median 110 (range 53-164) |
| Dyck et al. (1982)(Dyck et al. 1982)  USA  I: n = 14  C: n = 14 | Patients with CIDP for >6 months and previously untreated with immunosuppressive therapy | Prednisone 120mg alternate days; 5mg alternate days tapering to 0mg over 13 weeks | Age  I: med 46.5 range 22-76  C: med 50 (range 9-83)  % male  I: 71%  C: 64% | Status: NR  Type: chronic progressive: 14, recurrent: 14  Time since diagnosis  I: median 25 mo (range 6-84)  C: median 32 mo (range 8-168) |
| Boru et al. (2014)(Boru et al. 2014)  20 CIDP patients (14 male, 6 female). | Diagnosed as CIDP according to clinical, electrophysiologic and nerve biopsy findings | 1,000mg/day methylprednisolone for 10 days. Then 1000mg/day IV pulse prednisolone once every 4 weeks.  Patients treated for 5 years and followed-up for 10 years. | Mean age of patients 48.1 ± 14.6 years. Mean duration of disease 6.8 ± 3.1 years. | Patients with Modified Rankin score of 2.7 ± 0.5 at the start of treatment |
| van Lieverloo et al. 2018(van Lieverloo et al. 2018)  67 daily prednisone or prednisolone,  37 pulsed dexamethasone,  21 pulsed intravenous methylprednisolone  Serbia, Italy and Netherlands | EFNS/PNS criteria for CIDP | Daily prednisone or prednisolone, 1–1.5mg/kg body weight during the first 6 weeks, tapering to zero during a period of at least 8 months.  Oral pulsed dexamethasone 40mg per day for 4 days consecutively each month, for 6 months  IV pulsed methylprednisolone, starting with 500mg daily for 4 days | Average age = 53.4  Walking unassisted, 80%  CIDP type  Typical: 98 (78%)  Atypical: 27 (22%)  Median MRC sum score (range)  53 (34–60) | Primary outcome was assessed 6 months after start of treatment. The secondary outcome was the remission rate in treatment responders.  60% responded to corticosteroids, Of the 75 responders, 61% remained in remission, during a median follow-up of 55 months. |

**Abbreviations**: AAN = American Academy of Neurology, CIDP= Chronic inflammatory demyelinating polyneuropathy, Ig= Immunoglobulin, IV= Intravenous, P = placebo, EFNS/PNS= Neurological Societies/Peripheral Nerve Society, ONLS= Overall Neuropathy Limitations Scale, NDS = neurologic disability score, INCAT = inflammatory Neuropathy Cause and Treatment.

To estimate comparator patient costs on the steroid arm, Blackhouse et al. (2010) assumed average patient weight and dosing from the Hughes et al. (2001) study. Long-term use of corticosteroids is associated with a number of potentially serious side effects including diabetes, increased risk of fracture, glaucoma, cataracts and increased susceptibility to infection. Treatment costs and probabilities of these events occurring are included in the model based on Wilson et al. (2017). Corticosteroids are used in conjunction with steroid-sparing therapy in the form of immunosuppressants for steroid non-responders and those suffering adverse events. The cost of a typical immunosuppressant regimen is included in the economic model for patients in these health states.

### C.2.1.4 Relationship of pre-modelling study to the economic evaluation

The key trials presented in Section B have similarities with Australian Ig use and NSW data. Patient age of around 50-60 years, gender, setting for Ig delivery and disability eligibility criteria are similar. Average ages and weights from the trials are used for costing Ig and steroids. All Ig responders are assumed to be compliant. Ig product costs account for more than 80% of the estimated resource use in the 10-year model and are the key driver of the calculated ICER. Differences in costs between Ig and steroid use are captured in the incremental cost per QALY calculation that summarised cost-effectiveness results

Participating patients in key trials had varying degrees of steroid resistance. Optimal treatment varies for steroid-resistant and non-resistant sub-groups, whereas trial results have been typically presented for comparator groups as a whole. It is likely that, in Australia, the CIDP patient population using Ig would have a high proportion of patients who had previously failed to respond to corticosteroids. Response to steroids versus Ig in the trial patient population would favour the comparator, in the Australian scenario of a high proportion of steroid-resistant patients.

The types of CIDP evident in trial participants is varied and there is limited data about the characteristics of CIDP-eligible patients in Australia. Clinical feedback provided during the evaluation indicated that 60% of patients have the chronic progressive form requiring lifelong treatment. The base case of the economic model assumes longer-term administration of Ig for CIDP. Average Australian dosing is included in the base calculation as trial populations include progressive and relapse patients. This assumption favours the intervention and is subject to sensitivity analysis.

## C.3. Selection of Utility Value issues

### C.3.1 Identification of issue that needs to be addressed

CIDP impacts patient quality of life (QoL). QoL is typically measured for cost-utility models using instruments such as EQ-5D surveys and converted to a Quality-Adjusted Life Year (QALY) utility index of between 0 and 1, with 1 being the highest quality of life. Many of the trials and observational studies reported in Section B outline patient disability (INCAT, ONLS score, Six-Minute Walk Test [6MWT] and muscle strength e.g. MRC Sum, MRS) along with adverse events. EQ-5D has not been reported across many studies, as many are not powered to measure treatment effect on quality of life parameters. Cost-utility analysis requires the derivation of quality of life outcomes, as measured by instruments such as EQ-5D, or other generic questionnaires.

### C.3.2 Focused analytical plan

The literature was reviewed to determine EQ-5D values for CIDP patients. QoL data is derived from these sources for inclusion as utility values in the economic model.

### C.3.3 Results of pre-modelling study

#### Literature search for CIDP State Utilities

Published data on CIDP survival and QoL is limited given the rare nature of the disease. To identify published QoL analyses for CIDP patients a literature search was conducted in 20 April 2019 in Embase, Cochrane Library and HTA agency websites including Canadian Agency for Drugs and Technologies in Health (CADTH) and National Institute for Health and Care Excellence (NICE). A limited number of publications assessing the impact of CIDP on patient’s QoL were found, with most relevant studies covered already in the recent review by Rajabally and Cavanna (2015). The review is summarised, and cited studies used for CIDP utility.

##### Utilities for CIDP

###### Rajabally and Cavanna (2015)

The authors undertook a systematic review of the scientific literature on the effects of health-related QoL (HRQoL) in CIDP patients. The review comprised a Medline search of all English language articles published between 1966–October 2014 on HRQoL in all forms of chronic inflammatory neuropathies. The search yielded 23 articles, with the key studies summarised in Table 47. The authors concluded that available data is limited because few studies have systematically considered HRQoL in patients with inflammatory neuropathies. Moreover, in treatment trials HRQoL measures have exclusively been used as secondary outcome measures.

Table 46 Studies on health-related quality of life in CIDP

| **Publication & study type** | **HRQoL scale or index (SD)** | **Participants and setting** | **Comments** |
| --- | --- | --- | --- |
| Hughes et al. 2001(Hughes et al. 2001)  Therapeutic | **Speed of walking over 10 m after 2 weeks (m/second)**  Steroid 0.01 (0.02)  Ig 0.01 (0.01)  Difference 0.00 (0)  **Disability grade after 6 weeks**  Steroid -0.62 (1.52)  Ig -0.71 (1.19)  Difference 0.22 (0.4) | 25  Nine European centres | Authors reported the results of a multicentre double-blind crossover RCT comparing IVIg against oral corticosteroids over 6 weeks in 25 CIDP patients. Both arms resulted in non-significant improvements at 2 weeks in the 11-point INCAT scale. Participants were also provided with the SF-36 questionnaire. |
| McCrone et al. 2003(McCrone et al. 2003)  Therapeutic | **EQ-5D**  **Baseline**  Steroid 0.64  Ig 0.57  **6-weeks**  Steroid 0.63  Ig 0.69  Difference 0.12.  (P = 0.164) | 25  Nine European centres (from Hughes et al. 2001) | Study detailed EuroQoL (EQ)-5D for patient included in Hughes et al. (2001). EQ-5D remained stable for the prednisolone group, however, 0.12 non-significant improvement in QoL was reported for IVIg patients. This improvement was used in the Blackhouse et al. (2010) comparison of Ig vs steroids economic model in Canada. |
| Merkies et al. 2002 (Merkies et al. 2002)  Cross-sectional | **MRC sensory sum score**  Entry 47.6  12 weeks 53.9  26 weeks 56.4  52 weeks 57.4  **INCAT**  Entry 8.8  12 weeks 5.4  26 weeks 3.7  52 weeks 4.0 | 114 Dutch patients  (83 with GBS, 23 with CIDP, 8 with MGUSP) | Study measured SF-36, MRC sum score, sensory sum score, INCAT score and Hughes functional scale in 23 stable CIDP patients, 83 GBS and 8 PDN against a nationwide sample of 1742 healthy individuals in the Netherlands The authors concluded except for the domains “physical functioning” and “role functioning–physical,” and PCS score, reached within normal values at 6 and 12 months of follow-up (p.87). |
| Padua et al. 2004 and 2005 (Padua et al. 2004; Padua et al. 2005)  Prospective cohort treated with (IVIg), Italy | **PCS SF-36**  Base 32.5  8-day follow-up 37  Wilcoxon (0.0014)  **MCS SF-36**  Base 43.6  8-day follow-up 44 | 25  (8 CIDP) | SF-36 improved with IVIg in a heterogeneous population consisting of 8 CIDP patients, 3 MMN, 3 GBS and 10 myasthenia gravis. Signiﬁcant improvements in vitality, physical role, and physical function sub-scores were associated with IVIg therapy. Mental scores did not improve. |
| Garssen et al. 2004 (Garssen et al. 2004)  Interventional: Physical Training | **SF-36 (PCS)**  Entry 44.0  6 weeks 45.6  12 weeks 50.1  **SF-36 (MCS)**  Entry 51.6  6 weeks 52.7  12 weeks 55.9 | 18  (4 CIDP) | Authors examined improvement in CIDP with a 12-week bicycle exercise program which included 16 GBS and 4 CIDP patients. Reported outcomes included Fatigue Severity Score (FSS), Fatigue Impact Scale (FIS), GBS disability score, Hospital Anxiety and Depression Scale (HAD), Rotterdam Handicap Scale (RHS) and SF-36. Signiﬁcant improvements from baseline were obtained for FSS, FIS, HAD and RHS. |
| Hughes et al. 2008 (Hughes et al. 2008) Therapeutic | **INCAT score**  IGIV-C  Base 4·2 (1·4)  Extension 0.1 (0.7)  Placebo  Base 4·1 (1·5)  Extension 0.4 (1.7)  **MRC sum score**  IGIV-C  Base 49·3 (6·9)  Extension 0·8 (4·1)  Placebo  Base 50·0 (7·2)  Extension –1·0 (4·4) | 117  IGIV-C (n = 59) Placebo (n = 58) | The ICE trial was a randomised, double blind, response-conditional crossover study which examined IVIg vs placebo. It included 117 patients recruited across 33 centres. In the first treatment phase, 32/59 (54%) IGIV-C and 12/58 (21%) placebo patients had an improvement in adjusted INCAT disability score through to week 24 (p = 0.0002). Improvements from baseline to endpoint were also reported for grip strength in both dominant and non-dominant hands. |
| Merkies et al. 2009(Merkies et al. 2009b) Therapeutic | **LSM difference**,  (p-value)  Physical 12.7 (0.06)  Role 10.5 (0.3)  Bodily pain 11.1 (0.6)  General 6.8 (0.16)  Vitality 6.5 (0.16)  Social 7.7 (0.25)  Emotional 23.1 (0.03)  Mental health 2.5 (0.54) | 117  IGIV-C (n = 59) Placebo (n = 58) | SF-36 was administered at screening/baseline and at endpoints of each phase. During the first period, the endpoint was defined as week 24. The authors reported: “greater improvements in both SF-36 physical and mental component scores were observed with IGIV-C vs placebo” (ibid, 1337). |
| Merkies et al. 2010(Merkies et al. 2010) | “Grip strength, Medical Research Council (MRC) sum score, and INCAT sensory sum score were the [and changes from baseline] was explained by impairment and activity and participation measures” (p. 208) | 117  IGIV-C (n = 59) Placebo (n = 58) | Study examined correlations between strength, grip and disability in the ICE study. The authors concluded that baseline PCS was correlated with MRC sum score, grip strength, INCAT disability score and Rotterdam handicap scale. Baseline MCS did not correlate with strength or functional parameter. Changes in MCS and PCS were associated with INCAT sensory and disability scores, along with MRC sum score. |
| Harbo et al. 2008(Harbo et al. 2008) Cross-sectional, Denmark | **Isokinetic strength** of all measured muscles was reduced by 19.4% (p 0.01) in CIDP patients. It was closely related to manual muscle strength, ODSS, NIS, walking performance, and physical SF-36. | 14  8.7 years (3.3–11.5) of CIDP Aarhus University Hospital | Cross-sectional study investigated isokinetic strength in 14 CIDP patients using isokinetic strength, muscle strength, neurological symptom score, Overall Disability Sum Score, 10-metre walk and 40-metre walk, as well as the physical components of the validated Danish version of the SF-36. |
| Harbo et al. 2009(Harbo et al. 2009b) | SF-36 Responders  Day 1 and Day 15  Physical function  70. and 80.0  Physical function  46.7 and 75.0  Bodily pain  90.3 and 94.7  General health  80.7 and 80.2  Vitality  67.5 and 70.8  Social functioning  91.7 and 97.9  Role emotional  94.4 and 100.0  Mental health  87.7 and 87.3 | 8  responders | One-armed study of improvement in acute motor response with IVIg in 11 patients following withdrawal and re-establishment of therapy. Outcomes included isokinetic strength, neuropathy impairment score (NIS)-strength score, nine-hole peg test, 40-metre walk test and SF-36. “On days 5 and 10 after re-initiation of IVIG therapy isokinetic muscle strength increased by 5.5% (1.6 –9.6) and 11.9% (7.5–16.5), respectively, but there was no further increase at day 15” (ibid, p.439). |
| Harbo et al. 2009(Harbo et al. 2009a) SC versus IV comparison | Equally effective, the mean change in muscle strength after SCIG being 3.6% (95% CI ) 3.6% to 10.9%) vs. 4.3% (1.3% to 10.0%) after IVIG (P = 0.86). 1 patient had 3-week erythema and oedema at the injection sites. All other adverse effects were transient | 9  Denmark | Study examined SCIg and IVIg in a single-blind randomised crossover trial that included 9 patients with MMN on IVIg treatment. The primary outcome was dynamometric strength score. HRQoL was also assessed using SF-36. Both arms were equally effective. |
| Cocito et al. 2012(Cocito et al. 2012) | Therapeutic | 5 | Prospective longitudinal study from Italy examined whether SCIg was equivalent to IVIg in 5 CIDP patients previously on IVIg. MRC scores, ONLS, grip strength and sensory sum score, plus SF-36 PCS, MCS and Modiﬁed LQI for secondary outcomes were equivalent. |
| Cocito et al. 2013(Cocito et al. 2013) | Therapeutic | 10 | Authors reported signiﬁcant QoL improvements in 10 patients with CIDP, as measured by the LQI with use of 20% SCIg versus 16% SCIg. |
| Nobile-Orazio et al. 2012(Nobile-Orazio et al. 2012a) 6-month therapy with IVIg vs that with IV methylprednisolone in Italy. | **Short-form-36 Methylprednisolone**  **Immunoglobulin**  **(p-value)**  Enrolment  38·7 (17·0)  56·3 (17·9)  6 months  55·4 (24·1)  70·5 (17·9)  0·0610  Δ (p-value)  16·7 (0·0008)  14·2 (0·0011)  0·3634 | 45 patients  (24 IVIg, 21 IV methyl prednisolone) | IVIg compared to IV pulsed corticosteroids, across 6 months. More patients stopped methyl- prednisolone (11/21) than IVIg (3/24). Discontinuation was due to lack of efﬁcacy. SF-36 increased by 16.7 points at 6 months with steroids (p = 0.0008) and by 14.2 points with IVIg (p = 0.011), however, there was no signiﬁcant difference between arms (p = 0.3634). |
| Mahdi-Rogers et al. 2014(Mahdi‐Rogers et al. 2014) | **Economic, HRQoL**  0.62 for CIDP, which is lower than UK average of 0.86, but higher than 0.55 for 737 patients with multiple sclerosis or 0.54 for 97 patients with Parkinson's disease in UK surveys. No difference observed between Ig treatment, or not. | 106 | EQ-5D survey undertaken in the UK across CIDP, MMN and PDB patients, completed by 43 CIDP patients of 50 who were sent the survey. Utility scores were not signiﬁcantly related to gender, age, disease duration or IVIg treatment. HRQoL was signiﬁcantly higher in patients who were independently mobile or had no upper limb disability. The mean (SD) utility scores were 0.62 (0.23) for CIDP, 0.63 (0.22) for PDN and 0.72 (0.14) for MMN (P = 0.52). |
| Maxwell et al. 2013(Maxwell et al. 2013) Canada | **Polyneuropathy and general population SF-36**  Physical functioning  54.3 and 85.8  Role physical  51.8 and 82.1  Bodily pain  54.9 and 75.6  General health  49.8 and 77.0  Energy/vitality  47.6 and 65.8  Social functioning  64.2 and 86.2  Role emotional  69.1 and 84.0  Mental health  65.4 and 77.5 | 154  (39, CIDP) | Cross-sectional Canadian study used the Peripheral Neuropathy QoL Instrument-97, in a population of 154 patients with neuropathy, among whom 31.9% had diabetic polyneuropathy, 16% CIDP and 9% PDN, against a normative sample. “Comparison of QoL between the Canadian normative sample and patients with neuropathy showed lower scores for all eight of the SF-36 domains in the neuropathy patients (p<0.001) “(p. 39). |
| dos Santos et al. 2014(Santos et al. 2014) SF-36 scores in a cohort of CIDP patients | **HRQoL, cognitive**. Results were unfortunately not adequately detailed for meaningful conclusions. | 41  Brazil | Impaired patients were compared to non-matched normal subjects in a cross-sectional study from Brazil. Normative values for the relevant Brazilian population were not available for analysis. |

**Abbreviations**: AAN = American Academy of Neurology, CIDP = Chronic inflammatory demyelinating polyneuropathy, Ig = Immunoglobulin, IV = Intravenous, P = placebo, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, ONLS = Overall Neuropathy Limitations Scale, NDS = neurologic disability score, INCAT = inflammatory Neuropathy Cause and Treatment.

The authors (p. 22) concluded that SF-36 appears to be a useful generic instrument to evaluate HRQoL in CIDP and paraproteinemic demyelinating neuropathy (PDN), as shown by its performance across the studies analysed in this review. Correlations of HRQoL measures were otherwise consistently found at baseline with strength scores, isokinetic strength and functional scores in CIDP. “The degree of impairment may be lesser than in other neurological disorders – particularly in regard to pain and general health perception, social functioning and mental health.” (ibid, p. 22) This was possibly attributed to most studies being conducted in countries with high standards of healthcare. The authors noted that improved quality of life with IVIg over steroids was not conﬁrmed with the 6-month data from the latest comparative study (Nobile et al. 2012) and cross-sectional UK study found Ig use did not inﬂuence patient-reported HRQoL.

#### Literature search for Adverse Event State Utilities

The Blackhouse et al. (2010) Canadian economic model that compared Ig with steroids in CIDP patients quantified disutilities for steroid AEs including fracture, diabetes, glaucoma and serious infection. The disutility due to fracture was estimated using a Canadian model evaluating corticosteroid-induced osteoporosis (Goeree et al. 2006), the disutility for diabetes from the Ontario Diabetes Economic Model (O'Reilly et al. 2007) and for cataract surgery (Hopkins et al. 2008). The disutility for glaucoma was assumed to be 0.061 (Jampel et al. 2002) and 1.0 for two weeks during a serious infection (Bae et al. 2003). Most of these studies are North American.

A search was conducted 20 April 2019 to identify Australian studies of QoL analyses of AEs in CIDP patients. Embase, Cochrane Library, and HTA agency websites (CADTH and NICE) were searched using the terms shown in Table 47. Titles and abstracts were reviewed, and a manual search was performed.

Table 47 Search strategy for Australian CIDP adverse events utility literature review

|  |  |
| --- | --- |
| Search | Terms |
| 1 | Diabetes mellitus OR type 2 diabetes |
| Fracture OR Osteoporosis |
| Cataract |
| Glaucoma |
| Infection |
| Steroids OR Corticosteroids |
| 2 | [AQoL] OR [Australian quality of life] OR QALY |
| 3 | [EQ-5D] OR [SGRQ] or [HRQL] |
| 4 | [SF-6D] OR [short-form 6D] |
| 5 | [Time trade off] OR [TTO] OR [Standard gamble] |
| 6 | [Health utilities] OR [utility values] OR [utility scores] |
| 7 | Australia or Australian |
| 8 | [2] OR [3] OR [4] OR [5] OR [6] |
| 9 | [1] AND [8] AND [7] |

Table 48 Results of Australian adverse events utility literature review

|  | **Diabetes** | **Fracture** | **Cataract** | **Glaucoma** | **Infection** | **Steroids** |
| --- | --- | --- | --- | --- | --- | --- |
| Number of titles and abstracts reviewed after search | 96 | 46 | 4 | 2 | 9 | 374 |
| TOTAL number of exclusions | 90 | 41 | 3 | 2 | 9 | 374 |
| Other HTA websites a |  |  |  |  |  |  |
| Other |  |  |  |  |  | 1 |
| Number of utility studies included | 6 | 4 | 1 | 0 | 0 | 1 |

a HTA agencies included: NICE, CADTH

Abbreviations*:* CADTH = Canadian Agency for Drugs and Technologies in Health; HTA = Health Technology Assessment, NICE = National Institute for Clinical Excellence

Titles of key studies are outlined in Table 49 and described in the following text.

Table 49 Studies identified outlining utilities for Adverse Event states

|  |  |
| --- | --- |
| **Study** | **Reference** |
| **Australian Utilities for Diabetes** | |
| Glasziou et al. 2007 | Glasziou et al. (2007) Which health-related quality of life score? A comparison of alternative utility measures in patients with Type 2 diabetes in the ADVANCE trial. Health and Quality of Life Outcomes |
| Clarke et al. 2009 | Clarke et al. 2009 Using the EQ-5D index score as a predictor of outcomes in patients with type 2 diabetes, Medical Care, 61-68 |
| Gordon et al. 2014 | Gordon et al. 2014 A cost-effectiveness analysis of a telephone-linked care intervention for individuals with Type 2 diabetes, Diabetes research and clinical practice, 103-111 |
| Kortt, and Clarke 2005 | Kortt, and Clarke 2005. Estimating utility values for health states of overweight and obese individuals using the SF-36, Quality of Life Research, 14, 2177-2185 |
| Keating et al. 2012 | Keating et al. 2012. Utility-Based Quality of Life Associated With Overweight and Obesity: The Australian Diabetes, Obesity, and Lifestyle Study, Obesity |
| Afzali et al. 2013 | Afzali et al. 2013 A model-based economic evaluation of improved primary care management of patients with type 2 diabetes in Australia, Applied Health Economics and Health Policy, 11, 661-670 |
| **Australian Utilities for Corticosteroids** | |
| Tilden et al. 2015 | Tilden et al. 2015. Quantifying The Cost and Quality of Life Implications Of Adverse Events Associated With Long-Term Oral Corticosteroid Use, Value in Health, November 2015 Volume 18, Issue 7, Page A688 |
| **Australian Utilities for Fractures** | |
| Abimanyi-Ochom et al. 2015 | Abimanyi-Ochom et al. 2015. Changes in quality of life associated with fragility fractures: Australian arm of the International Cost and Utility Related to Osteoporotic Fractures Study (AusICUROS). Osteoporosis International, 1781-1790 |
| Karnon et al. 2016 | Karnon et al. 2016. What are we paying for? A cost-effectiveness analysis of patented denosumab and generic alendronate for postmenopausal osteoporotic women in Australia, Cost Eff Resour Alloc (2016) 14:11 |
| Liew et al. 2010 | Liew et al. 2010 Cost-effectiveness of risedronate for corticosteroid-induced osteoporosis in Australia, 13 (7), A558-A559 |
| Milte et al. 2018 | Quality of life in older adults following a hip fracture: an empirical comparison of the ICECAP-O and the EQ-5D-3 L instruments. Health and Quality of Life Outcomes (2018) 16:173 |
| **Australian Utilities for Cataract** | |
| Abell and Vote 2014 | Abell and Vote 2014 Cost-effectiveness of femtosecond laser-assisted cataract surgery versus phacoemulsification cataract surgery. Ophthalmology, 10-16 |

##### Australian utilities for corticosteroids

###### Tilden et al. (2015)

The aim of the paper was to investigate the excess risk of complications associated with long-term maintenance oral corticosteroid use and to quantify the cost and QALY burden of these events. The systematic review identified 72 studies focused on type 2 diabetes, myocardial infarction, glaucoma, cataract, ulcer, osteoporosis, infection and stroke. A risk estimate for each adverse event was established and applied to the Australian annual cost and QALY burden of each event. Based on this calculation, the expected annual cost was $598.32 per patient per year with a QALY loss of 0.0367 per year of treatment. Adverse event burden of disease was considered reversible once oral corticosteroids ceased.

##### Australian utilities for diabetes

###### Glasziou et al. (2007)

The ADVANCE[[24]](#footnote-25) study included 978 Australian patients with type 2 diabetes. During the study patients completed EQ-5D and SF-36 questionnaires at baseline. Estimated utilities for diabetes conditions ranged from 0.68 to 0.85, with lower values associated with serious complications such as stroke or myocardial infarction.

###### Clarke et al. 2009

This cohort study involved 7,348 patients with type 2 diabetes over five years. Patients were age 50 to 75 years and had been recruited to the Australian FIELD[[25]](#footnote-26) study. The average index score was 0.82 with no prior complication but was lower for patients with prior vascular events (0.76) and other major complications (0.65).

###### Gordon et al. 2014

The authors developed a Markov model using data from the TLC diabetes trial and other published evidence. The 5-year model consisted of three health states related to glycaemic control. The study used average utility values at 12-month follow-up (0.726) for the ‘sub-optimal control’ category, an increment of 0.029 was included for ‘average control’ and 0.058 for ‘optimal control’.

###### Kortt, and Clarke 2005

The study used HRQoL data from the Australian 1995 National Health Survey, which included SF-36 responses from 12,661 individuals in the general population. They were transformed into utility values using the SF-6D algorithm developed by Brazier. Regression analyses quantified impacts of body mass index (BMI) and five obesity-related medical conditions (diabetes, coronary heart disease, depression, musculoskeletal disorders and cancer) on utility. The mean value for the SF-6D utility index was 0.803. Type 2 diabetes reduced this value by -0.0188, coronary heart disease by -0.0538, depression by -0.1665, musculoskeletal disorders by -0.0647 and cancer by -0.0870.

###### Keating et al. 2012

This study was a cross-sectional analysis of 10,959 adults participating in baseline data collection for the nationally representative Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. QoL was evaluated using the SF-6D. Relative to the healthy weight group (mean UQoL score 0.77), mean adjusted UQoL differences were 0.001 for the overweight group, -0.012 for Class-I obese, -0.020 for Class-II obese, and -0.069 for Class-III obese.

###### Afzali et al. 2013

This study estimated the lifetime costs and QALYs associated with two models of management of type 2 diabetes in primary care. A model was developed with data sourced from Australian and UK observational studies. The mean value for patients without a history of diabetes was 0.785, taken from a UK study. Disutilities for heart attack, amputation, stroke, blindness and heart failure ranged from -0.05 to -0.280. These consequences are associated with longer term diabetes, rather than a year of elevated haemoglobin A1c [HbA1c], which returns to normal following the discontinuation of steroids in the economic model for CIDP.

##### Australian utilities for fractures

###### Abimanyi-Ochom et al. 2015

The authors examined changes in HRQoL due to fracture in Australian adults aged over 50 years using the EQ-5D-3 L questionnaire. Participants recruited within two weeks of a fracture (hip, wrist, humerus, vertebral and ankle) were followed-up at baseline and 4, 12 and 18 months. The average HRQoL for all participants prior to fracture was 0.86, which declined to 0.42 in the immediate post-fracture period. Those with wrist, humerus or ankle fracture returned to their pre-fracture HRQoL after 18 months.

###### Karnon et al. (2016)

The study aimed to identify age-specific general population utility weights (Clemens et al. 2014) and found no Australian utility weights for the fracture states, so utility multipliers reported in a recent meta-analysis (Peasgood et al. 2009, Chau et al. 2015), and those from the FREEDOM trial (Cummings et al. 2009) were used. The multiplier for hip fracture in the first year was 0.70, which increased to 0.8 in the second year. Non-hip fracture was assigned a first-year weight of 0.84, which increased to 0.96 in the second year.

###### Liew et al. (2010)

The authors undertook an economic study comparing bisphosphonate risedronate with placebo to prevent vertebral fractures in patients with corticosteroid-induced osteoporosis in Australia. A utility of 0.71 was taken from the literature and included in the study for vertebral fracture.

###### Milte et al. (2018)

This study used EQ-5D-3 L (health and physical function focus) and ICECAP-O (well-being and capability focus) questionnaires to measure QoL in older Australians following hip fracture. A total of 87 participants completed the ICECAP-O and EQ-5D-3 L instruments 1 to 3 weeks after surgery. The mean ICECAP-O score was 0.639 and the mean EQ-5D-3 L utility score was 0.545.

##### Australian utilities for cataract

###### Abell and Vote 2014

The authors prepared an economic analysis of femtosecond laser-assisted cataract surgery and conventional phacoemulsification cataract surgery using QALYs. Pre-cataract surgery QoL was estimated at 0.85215 and post-cataract surgery utility 0.978.

### C.3. 4 Relationship of pre-modelling study to the economic evaluation

#### Utilities for health states

Utility values used in the economic model for each of the health states are outlined in Table 50. An event-free utility of 0.85 for males and female adults aged 45-64 was recorded as population norms for the EQ-5D-3L by age and gender based on a representative adult sample in Queensland (Clemens et al. 2014). Disutilities are applied to this value for each of the model’s CIDP health states.

Mahdi-Rogers et al. (2014) compared the utility of CIDP patients with a normative sample using cross-sectional analysis from England. Utility scores were not signiﬁcantly related to gender, age, disease duration or IVIg treatment. A value of 0.62 was reported for CIDP, which was 0.24 lower than the UK average of 0.86. This utility reduction is included as a disutility for CIDP patients using corticosteroids with no AEs.

The Hughes et al. (2001) trial reported clinical outcomes for Ig use compared to corticosteroids over six weeks. The key outcome was level of physical disability measured using an 11-point scale. McCrone et al. (2003) reported these changes using the EQ-5D instrument. They reported that EQ-5D was largely unchanged (0.64–0.63) for the prednisolone group (P = 0.956), however increased from 0.57 to 0.69 for the IVIg group (P = 0.072). IVIg resulted in a mean relative gain in QoL compared with prednisolone of 0.12. This was noted by the authors as not statistically significant at conventional levels but the trend favoured IVIg (P = 0.164). This gain in Ig over steroids is applied to generate a disutility for Ig responders of -0.12. The utility assumption for Ig, as for other health states are summarised in Table 50. Utility values are converted to a weekly value by dividing by 52. As the Mahdi-Rogers et al. (2014) study found no significant differences in utility between those treated, or not with Ig, the utility benefit is subject to sensitivity analysis.

The Blackhouse et al. (2010) Canadian economic model included disutilities for steroid AEs including fracture, diabetes, glaucoma and serious infection. A disutility for diabetes of -0.000160 for those age 50-54 years in the first year of the AE was sourced from the Ontario Diabetes Economic Model. Australian studies identified in the literature review generally included diabetes patients with serious complications, therefore far higher utility reductions were evident. For example, Kortt and Clarke 2005 used SF-36 responses from the Australian 1995 National Health Survey. Regression analyses found type 2 diabetes reduced patient utility by -0.0188. The economic model assumes steroids cease with elevated HbA1c and patients transition to immunosuppressants. Correspondingly, the lower value of -0.000160 from the Canadian study is combined with steroid CIDP patient disutility to generate a disutility of -0.240160.

As no utilities were found for health states that sub-grouped CIDP patients with diabetes (or any other steroid AE) the calculation of a combined disutility is uncertain. The disutility is at the lower end of disutilities for diabetes cited in the literature and also subject to sensitivity analysis in Section D. As already noted, Mahdi-Rogers et al. (2014) found no signiﬁcant differences in CIDP utilities related to gender, age, disease duration or IVIg treatment in a cross-sectional survey of British patients.

Table 50 Summary of utility inputs for the Section D cost-effectiveness model

| Health state | Utility/ Disutility | Nature of estimate | Source | Alternative estimates of utility value |
| --- | --- | --- | --- | --- |
| Ig Initial Treatment | -0.120 | McCrone et al. (2004) reported these changes using changes in quality of life using the EuroQol EQ-5D instrument from the 6-week Hughes trial. | McCrone et al. (2003) | 0/+10% |
| Ig Responder | -0.120 | McCrone et al. (2003) | 0/+10% |
| Corticosteroids  (no adverse events) | -0.240 | Cross-sectional analysis from the southeast of England. | Mahdi-Rogers et al. 2014 | 0/+10% |
| Corticosteroids non-responder + azathioprine | -0.240 | Assumed to be the same as steroid responders | Study Assumption | 0/+10% |
| Fracture | -0.377 | The non-hip fracture multiplier of 0.84 was applied to a general population utility of 0.85 and added to steroid disutility. | Karnon et al. (2016) | 0/+10% |
| Diabetes | -0.240 | The disutility in the Canadian model is added too steroid CIDP patient disutility. The lower value -0.000160 from the Canadian study is combined with steroid disutility to generate a disutility of -0.240160 | Blackhouse et al. (2010) disutilities for steroid AEs | 0/+10% |
| Glaucoma | -0.301 | Blackhouse et al. (2010) disutilities for steroid AEs of 0.061. It is added to steroid disutility | Blackhouse et al. (2010) | 0/+10% |
| Cataract | -0.330 | The disutility in Abell and Vote 2014 is added to steroid disutility | Abell and Vote (2014) | 0/+10% |
| Infection | -0.279 | A disutility of -0.04 is added to steroid patient disutility | Blackhouse et al. (2010) | 0/+10% |
| Azathioprine non-responder | -0.240 | In the absence of utility data for this state, it is assumed to be the same as steroid non-responder + azathioprine. | Study Assumption | 0/+10% |
| Disabled | -0.360 | CIDP disabled utility is estimated to be 0.49, or a disutility of -0.36 for a general population 50-year-old utility of 0.85 | Assumption based on Ahmad et al. (2017). utility weights for Australian Multiple Sclerosis patients. | 0/+10% |

Abbreviations: AE= adverse event. CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

The Blackhouse et al. (2010) study included cataract disutility values by assuming 0.38 prior to cataract surgery and 0.10 after surgery. Australian studies were identified, including Abell and Vote 2014. Pre-cataract surgery QoL was estimated at 0.85215 and post-cataract surgery utility 0.978. An average disutility of -0.085 is added to the CIDP steroid disutility.

Abimanyi-Ochom et al. (2015) and Karnon et al. (2016) examined fracture disutilities in Australia. In Abimanyi-Ochom et al. (2015) the average HRQoL for all participants prior to fracture was 0.86, which declined to 0.42 in the immediate post-fracture period. Those with wrist, humerus or ankle fracture returned to their pre-fracture HRQoL after 18 months. Karnon et al. (2016) applied a multiplier for hip fracture in the first year of 0.70, which increased to 0.8 in the second year. The non-hip fracture multiplier of 0.84 was applied to 0.85 and added to CIDP disutility. The remaining steroid AE disutilities are taken from Blackhouse et al. (2010).

The Thai study by Bamrungsawad et al. (2016) examined the costs and outcomes for IVIG plus corticosteroids in comparison with immunosuppressants plus corticosteroids in steroid-resistant CIDP patients. The study included the probability of becoming disabled in patients non-responding to therapy of 0.098 and an associated disabled utility of -0.178. Being disabled was defined as patients with an MRC scale for one muscle group of three or less. The review of patient records associated with study found 24/29 (82.76 %) of steroid-resistant CIDP patients to be disabled. Utility estimates were based on the Thai EuroQol 5D (EQ-5D-3L) but included only four disabled patients.

No utility estimates were found in the Australian literature for disabled CIDP patients. In the absence of CIDP-specific utility data, multiple sclerosis health state utility values are derived from the study of Ahmad et al. (2017). The authors used data from the Australian Multiple Sclerosis Longitudinal Study undertaken in 2008. They transformed responses to the World Health Organisation (WHOQOL-100 quality of life measurement instrument) to EQ-5D values for mild, moderate and severe Multiple Sclerosis states. Mild severity was defined using Expanded Disability Status Scale (EDSS) levels of 0–3.5, moderate 4–6 and severe levels 6.5–9.5. Utility values of 0.614, 0.506 and 0.404 were calculated for each state, respectively.

Multiple Sclerosis patients with an EDSS score of less than 4 are able to walk without impairment, therefore moderate and severe patients broadly correspond with the disabled CIDP state in the economic model. Clinical feedback during preparation of the Assessment indicated 15% of disabled CIDP patients would be severe and the remainder moderate. Based on this proportion, the CIDP disabled utility is estimated to be 0.49, or a disutility of -0.36 for an Australian general population 50-year-old utility of 0.85 (Clemens et al. 2014). This disutility is included in the economic model for disabled CIDP patients. It is less than that for other disability states reported in the literature. For example, disabling stroke was estimated to have a utility of 0.39 in studies such as Wu et al. (2014) and Shah and Gage (2011) This represents a disutility of around -0.46 for a general population utility of 0.85. The disabled utility estimate is subject to sensitivity analysis.

## C.4. Extrapolation translation issues

### C.4.1 Identification of issue that needs to be addressed

Randomised trials included in Section B have a maximum follow-up of less than one year. The benefits of reduced corticosteroids adverse events are likely to be realised across a longer-term horizon and not captured within this period of time. This pre-modelling study outlines the assumptions for extrapolating data from a trial period of six months into a 10-year economic evaluation.

### C.4.2 Focused analytical plan

Results of the economic model are separated into two analyses. The first step is a trial analysis in which all costs and health outcomes are quantified within six months. This corresponds with the time frame of major trials such as the Hughes et al. (2008) ICE study. A longer-term projection of 10 years is also undertaken, and results of the model presented as an extrapolated analysis. Rates are converted to weekly equivalents and projected over the longer time frame. The sources of this data and sensitivity analyses undertaken where assumptions are uncertain are detailed.

### C.4.3 Results of pre-modelling study

Assumptions included in the trial and 10-year models and their sources are outlined in Table 51. The IVIg response rate for initial treatment is a pooled response rate of 0.61 from the Zinman et al. (2005), Hughes et al. (2008) and Nobile-Orazio et al. (2012) studies. It is higher than the pooled estimate in Blackhouse et al. 2010 of 0.473. This lower pooled estimate included response rates from the IVIg treatment arms of Zinman et al. (2005), Thompson et al. (1996), Mendell et al. (2001), Hughes et al. (2008), Vermuelen et al. (1993) and Hahn et al. (1996) which had limited months of follow-up.

The Ig relapse rate was taken from the Hughes et al. (2008) ICE study. Blackhouse et al. (2010) noted that this was the only study to report relapse rates over a 6-month period. The 25-week relapse rate for Ig in this study was estimated to be 13%, converted to a weekly probability using -(LN(1-0.13))/25. The ICE study does not extrapolate beyond 1-year; therefore, the proportion of responding patients is assumed to be stable beyond 12 months. Based on this assumption, around half of Ig patients are retained on this therapy after 10-years.

Steroid therapy response rates have been reported in a number of studies. A 77% response was reported by Lopate et al. (2005) who treated CIDP patients with IVMP pulse therapy over six months. Nobile-Orazio et al. (2015) administrated IV methylprednisolone, with a response rate of 48%. Muley et al. (2008) provided once-weekly oral steroids for three months, with remission reported in 60% of patients. Eftimov et al. (2012) followed patients for five years, reporting that 33% of patients had cure or remission, 33% had stable active disease and 10% had unstable active disease. After five years, 12.5% of dexamethasone patients had hypertension, 12.4% Cushing appearance and 8.3% fractures.

Boru et al. (2014) also presented longer-term data. The authors retrospectively evaluated 20 CIDP patients treated with monthly high-dose IV methylprednisolone for five years, then followed-up for 10 years. Patients who dropped out of the study included two patients who moved cities, and others who ceased treatment due to side effects like hypertension and intractable nausea (1 patient), pregnancy (1 patient) and no response to treatment (1 patient). Osteopenia was found in 6.7% of patients, increased body weight in 40% of patients and impaired glucose tolerance in 20% of patients after 10 years. Diabetes and hypertension did not occur in any patients. Van Lieverloo et al. (2018) administered either prednisolone, pulsed dexamethasone, or pulsed IV methylprednisolone and found that 60% of patients responded to corticosteroids. Of the 75 responders, 61% remained in remission during a median follow-up of 55 months.

Patient baseline population characteristics vary among the above steroid studies. Some precluded those contraindicated to steroids and others do not. A weekly non-response probability is included so 40% of the steroid arm is responsive after 5-years. Non-responsive patients and those with AEs transition to immunosuppressants. It is assumed the proportion of responsive patients is stable after 5-years.

Bamrungsawad et al. (2016) included a zero probability of response to immunosuppressant plus corticosteroids. A 99.99% non-response rate at 1-year is converted to weekly rate of 0.66422 for steroid-resistant patients. It is assumed that 75% of patients in steroid adverse event states would be non-respondent to immunosuppressants after one year. Bamrungsawad et al. (2016) also estimated the proportion of non-responding immunosuppressant plus corticosteroids patients who would become disabled. They defined a disabled patient as someone with an MRC scale for one muscle group of three or less. Using these criteria 24/29 (82.76 %) of non-responding immunosuppressant CIDP patients were found to be disabled when medical records were reviewed. The probability of becoming disabled in patients not responding to therapy was 0.098 over 12 weeks, or 0.0086 per week.

Table 51 Summary of response and relapse assumptions for extrapolation

| Parameter | Study | Weekly rates | | |
| --- | --- | --- | --- | --- |
| 0-1 years | 1 to 5 years | 5+ years |
| Ig response probability | The IVIg response rate for initial treatment is a pooled response rate from the Zinman et al. (2005), Hughes et al. (2008) and Nobile-Orazio et al. (2012) studies. It is higher than the pooled estimate in Blackhouse et al. 2010 of 0.473. This calculation included response rates from the Ig treatment arms of Zinman (2005), Thompson (1996), Mendell (2001), Hughes (2008), Vermuelen (1993) and Hahn (1996) which had limited months of follow-up. The response rate is included at 4 months in line with Australia Ig criteria timing. | 0.61000  At 4 months | NA | NA |
| Ig relapse probability | The Ig relapse rate was based upon data from the ICE study. The 25-week relapse rate for Ig in this study was estimated to be 13%. It is converted to a weekly probability using -(LN(1-0.13))/25. The ICE study does not extrapolate beyond 1-year; therefore, the proportion of patients who are responsive is assumed to be stable after 1 year. | 0.00557 | 0.00000 | 0.00000 |
| Corticosteroids (non-responder) probability | van Lieverloo et al. (2018) indicated 60% of patients responded to corticosteroids and of the 75 responders, 61% remained in remission, during a median follow-up of 55 months Eftimov et al. (2012) reported long-term results of PREDICT study for 5 years. 33% of patients had cure or remission, 33% had stable active disease and 10% had unstable active disease. Patient baseline population characteristics vary among trials, with some precluding those who were contraindicated to steroids, and others not. Correspondingly, there is uncertainty about steroid response rates among trials for the Australian patient population. Weekly non-response probably is included so 40% of the steroid arm is responsive after 5-years. Non-responsive patients and those with AEs transition to immunosuppressants | 0.00246 | 0.00246 | 0.00000 |
| Azathioprine non-responder probability | Bamrungsawad et al. (2016) included a zero probability of response to immunosuppressant plus corticosteroids. A 99.99% non-response at 1-year is converted to weekly rate of 0.66422 for steroid-resistant patients. It is assumed that 75% of patients in steroid adverse event states would be non-respondent to immunosuppressants after one year | 0.66422 | 0.66422 | 0.66422 |
| Disability among Immunotherapy Non-responder probability | Bamrungsawad et al. (2016) defined a disabled patient as someone with an MRC scale for one muscle group of three or less. Using this criterion 24/29 (82.76 %) of immunosuppressants non-responder CIDP patients were disabled when medical records were reviewed. The probability of becoming disabled for patients not responding to therapy was 0.098 over 12 weeks, or 0.0086 per week. | 0.00860 | 0.00860 | 0.00860 |

Abbreviations: AE= adverse event. CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

Adverse event rates for patients availing steroids are reported separately for fracture, glaucoma, diabetes, infection and cataracts. They are mostly derived from Blackhouse et al. (2010), along with mortality odds ratios. They are outlined in Table 52. Rates from Wilson et al. (2017) have been used in a sensitivity analysis.

Table 52 Summary of steroid adverse event and mortality assumptions for extrapolation

| Parameter | Study | Weekly rates | | |
| --- | --- | --- | --- | --- |
| 0-1 year | 1 to 5 years | 5+ years |
| Fracture probability | A fracture annual probability of 0.0098, or 0.00019 per week for Corticosteroids patients, was taken from Bae et al. 2003 in the Blackhouse et al. (2010) study. Fractures were not reported in the Van Schaik et al. 2010 description of PREDICT, however they were reported in Eftimov et al. 2012. A total of 2 of the 39 (Table 3. p. 1083) (5.13%) were reported to have fractures, equating to 8.3% of the dexamethasone group and none of the prednisolone group. This value is converted to a weekly probability. | 0.00023 | 0.00023 | 0.00023 |
| Diabetes probability | A diabetes annual probability of 0.0043, or 0.00008 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). Impaired glucose tolerance was found in 3 (20%) patients after 10 years of follow-up in the Boru et al. 2014 study. The dexamethasone arm of PREDICT had adverse event prevalence of 8.3% for hypertension, 54.1% increased body weight, 8.3% diabetes, 33.3% Cushing appearance and 4.2% impaired glucose tolerance. A higher 5-year value of around 10% is included in this study, which corresponds to a weekly probability of 0.00045. | 0.00045 | 0.00045 | 0.00045 |
| Glaucoma probability | A glaucoma annual probability of 0.0008, or 0.00002 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). | 0.00002 | 0.00002 | 0.00002 |
| Cataract probability | A cataract annual probability of 0.0114, or 0.00022 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). | 0.00022 | 0.00022 | 0.00022 |
| Infection probability | An infection annual probability of 0.0035, or 0.00007 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). The 5-year probability of fracture probability associated with this estimate is less than 2%. | 0.00007 | 0.00007 | 0.00007 |
| Ig mortality odds ratio | CIDP was not assumed to results in increased mortality. The ABS annual mortality rate for 55-year old’s in Australia in 2017 was 0.0045 for men and 0.0027 for women. These are converted to weekly values using a gender balance of 0.49. | 1.0000 | 1.0000 | 1.0000 |
| Corticosteroids mortality odds ratio | CIDP was not assumed to result in increased mortality. | 1.0000 | 1.0000 | 1.0000 |
| Fracture mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.0127 for first-year fractures. This is included as an odds ratio of 1.0142 for 55-59-year old’s and applied to weekly base mortality. | 1.01420 | 1.01420 | 1.01420 |
| Diabetes mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.001160 for first year diabetes for 55-59-year-olds. This is included as an odds ratio of 1.001160 and applied to weekly base mortality. | 1.00116 | 1.00116 | 1.00116 |
| Glaucoma mortality odds ratio | Not assumed to result in increased mortality | 1.0000 | 1.0000 | 1.0000 |
| Cataract mortality odds ratio | Not assumed to result in increased mortality | 1.0000 | 1.0000 | 1.0000 |
| Infection mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.018 for 25-64-year old’s in hospital. This is included as an odds ratio of 1.018 and applied to weekly base mortality. | 1.01800 | 1.01800 | 1.01800 |

Abbreviations: AE= adverse event. CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

Background mortality rates by age were taken from the 2017 ABS life table and assumed a gender balance of 49% male. CIDP is not assumed to increase the risk of mortality. For example, a recent population study in Iceland determined the incidence, clinical characteristics and prognosis of idiopathic CIDP during a 21-year period. In total, 19 individuals participated, with 14 being men (74%). The mean age at diagnosis was 57 years. A standardised mortality ratio for the 21-year study period was estimated at 0.9, which was not considered to differ from general population mortality (Hafsteinsdottir and Olafsson 2016). Annual ABS mortality age rates are converted to weekly probabilities using -(LN(1-annual rate))/52. The increased risk of death from steroid adverse events was estimated in Blackhouse et al. (2010). The risks were applied as odds ratios for diabetes, fracture and infection, and applied to Australian age-specific mortality from the ABS Australian 2017 life table. Weekly mortality rates are presented in Table 52. No other adverse events are assumed to have increased mortality

### C.4. 4 Relationship of pre-modelling study to the economic evaluation

As noted, the economic modelling is split into two analyses. The first step is the trial analysis in which all costs and health outcomes are quantified within six months. The extrapolated analysis covers 10 years. Assumptions sourced from 6-month trials are supplemented with longer-term one arm observational studies. Rates are converted to weekly equivalents. Given the uncertainties about this assumption, rates and odds ratios are subject to sensitivity analysis in Section D.

## C.5 Relationship of each Pre-Modelling Study to the Economic Evaluation

Section C included three pre-modelling studies addressing issues related to applicability and extrapolation that have implications for the economic model presented in Section D. A summary of the results and implications is provided in Table 53.

Table 53 Summary of results of pre-modelling studies and their uses in the economic evaluation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Section | Pre-modelling study | Results used in Section D | Cross-reference | Results used in sensitivity analyses | Cross-reference |
| Applicability of the trial-based evidence to the NBA population | Study C.2 | The population described in Section B is similar to that used in the economic model | Section D.2. | Differing assumptions about steroid and Ig response rates are included given differences between trial and Australian Ig patient characteristics | NA |
| Selection of utilities | Study C.3 | Utilities used in Blackhouse et al. (2010) are applied to the Australian model. | Section D.4.1. | All utilities are subject to univariate sensitivity analysis | NA |
| Extrapolation of trial-based evidence | Study C.4 | Weekly probabilities are used in the 6 month and 10-year models. | Section D.4.1. | Response and relapse rates are subject to univariate sensitivity analysis. A multivariate analysis of steroid adverse event rates is included using the assumptions in Wilson et al. | NA |

*Abbreviations:* NBA = National Blood Authority; NA = not applicable

# Section D Economic Evaluation

## Overview

Immunomodulation therapy is claimed to have superior safety and non-inferior effectiveness, based on two small, short-term clinical trials comparing Ig to prednisolone and plasma exchange. This Assessment has undertaken an economic evaluation using a cost-utility approach.

The model estimates cost per year of life and cost per QALY as an incremental cost-effectiveness ratio (ICER). The model compares Ig with corticosteroids. Results of the economic model are presented in two steps: the first outlines cost-effectiveness results for six months, which corresponds to the length of follow-up of the largest RCT (Hughes et al, 2008); the second step involves extrapolating data over a 10-year period.

An average hypothetical cohort of 1,000 CIDP patients progresses between treatments based on IV Ig and steroid response rates and adverse event rates within a cohort-based Markov model. Resource use is attached to each state using Ig product costs and MBS Item costs for Ig therapy against corticosteroids. Plasma exchange, immunosuppressants and combinations of two or more therapies are also used to treat CIDP in Australia. The costs of immunosuppressants are included as costs for patients in the steroid non-responder state and for those who have experienced steroid AEs. Plasma exchange is included in a sensitivity analysis substituting for immunosuppressants to treat patients in the steroid non-responder state.

## Populations and settings

### D.2.1. Population

The modelled patient population is based on those of Hughes et al. (2001, 2008). CIDP patients currently eligible for Ig treatment in Australia should be confirmed with CIDP and have significant disability or compromised walking objectively measured by an ONLS score of at least two points and the MRC sum score, in addition to CIDP patients who have relapsed within six months of commencing a trial off Ig therapy. Many of the exclusion criteria would apply in Australian clinical practice (see Table 54).

Table 54 Comparison between eligibility criteria in study and circumstances of use

| **Characteristic** | **Study** | Australian eligibility criteria |
| --- | --- | --- |
| **Inclusion criteria** | Patients in Hughes et al. (2001) trial drawn from 9 European centers (the UK, Belgium, Italy, Spain, the Netherlands, Greece and Czech Republic) July 1998-November 1999. Patients had neurological examination and hematological and biochemical testing, including serum protein electrophoresis. Clinical diagnosis of CIDP included progressive or relapsing motor and sensory dysfunction of more than one limb over more than 2 months caused by neuropathy, reduced or absent tendon reflexes, along with neurophysiological criteria. The criteria incorporated significant physical disability in upper or lower limb function, and stable or worsening clinical condition. Similar criteria evident in Hughes et al. (2008), with patients recruited from North America, South America, Israel and Europe. Eligible patients had a diagnosis of CIDP, progressive or relapsing motor and sensory dysfunction of at least one limb resulting from neuropathy over the 2 months before study entry, and significant disability as defined by an overall INCAT disability score18 of 2–9. An INCAT disability score of 2 had to be exclusively from leg disability to be eligible. These criteria are similar to that for eligibility in Australia. | Criteria for CIDP patients 10 years or older includes significant disability or compromised walking objectively measured by an ONLS score of at least two points, and MRC sum score. In children younger than 10 years’ significant disability or compromised walking measured by the 6MWT, and/or an MRS score of at least 2 points is required.  For patients over 10 years who relapse within 6 months of commencing a trial off Ig therapy, deterioration in disability as measured by an increase of at least 1 point in the Adjusted ONLS, or a reduction in the MRC sum score of at least 3 points, when compared to the review score before stopping previous treatment is required to access treatment. In a previously stable child less than 10 years of age, deterioration in disability as measured by a reduction in the 6MWT or an increase of at least 1 point in the MRS compared to the review score before stopping previous treatment is required. |

| **Characteristic** | **Study** | | **Australian eligibility criteria** |
| --- | --- | --- | --- |
| **Exclusion criteria** | Hughes et al. (2001) excluded those who had associated systematic diseases that could be associated with neuropathy, were or planned to be pregnant, had concurrent medical conditions which could affect treatment, had significant respiratory impairment, had received IVIg, corticosteroids or plasma exchange in the 6 weeks before treatment, were under the age of 18, met the criteria for multifocal motor neuropathy and had previously failed to respond to IVIg or corticosteroids.  Hughes et al. (2008) had similar exclusion criteria such as treatment with steroids (>10mg/day prednisolone or equivalent), IVIg, or plasma exchange in the 3 months before study entry; use of supplements in the previous month (omega-3 fatty acids have been reported to have anti-inflammatory properties); treatment with other immunomodulatory or immunosuppressive agents (interferon or azathioprine) in the previous 6 months; myelopathy or evidence of central demyelination; persistent neurological deficits from stroke, CNS trauma, or peripheral neuropathy from other causes (eg, diabetes mellitus, IgM paraproteinemia, or uremic, toxic, or familial neuropathy); a motor syndrome that fulfilled criteria for multifocal motor neuropathy with conduction block (ie, upper limb motor weakness without sensory deficit and with a 50% decrease in action potential amplitude or area on proximal compared with distal stimulation in motor nerves); and evidence of systemic disease that might cause neuropathy.  Many of these exclusions would apply in Australia, except those who had received IVIg, corticosteroids or plasma exchange in the 6 weeks before treatment and had previously failed to respond to IVIg or corticosteroids would not be excluded. | | |
| **Dose regimen and frequency** | Hughes et al. (2001) trial included a first treatment period of 6 weeks, followed by a 4-week washout period, after which the second 6-week treatment period with the other intervention commenced. IVIg infusions were given as 1.0g/kg on 2 consecutive days or 2.0g/kg in 24 hours. The induction period is 4 months in Australia.  Hughes et al. (2008) ICE trial patients received a baseline loading dose of 2g/kg over 2–4 days and then a maintenance infusion of 1g/kg over 1–2 days every 3 weeks for up to 24 weeks. The dosage is similar; however, the 24-week initial phase is longer than the 4-month Australian induction phase. | Australian recommendations include an induction dose of 2g/kg in 2 to 5 divided doses (access to a second initial dose should be a rare occurrence) followed by maintenance dosing of up to 0.4-1g/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. | |
| **Setting** | Hughes et al. (2001, 2008) sourced patients from neurologists across European centres (the UK, Belgium, Italy, Spain, the Netherlands, Greece and Czech Republic) July 1998-November 1999. | Infusion of IVIg in Australia is undertaken as an inpatient in private hospitals, inpatient public hospital (as a private patient), inpatient public hospital (as a public patient), outpatient clinic and private same-day infusion facilities unattached to a hospital. Most patients (approximately 75%), have IVIg delivered in a hospital setting as a day procedure. | |

Patient age, exclusion criteria and disability score are reasonably well aligned in key trials and in Australian practice. As noted in Section C, the types of CIDP evident in trial participants is varied and there is limited data about the characteristics of eligible CIDP patients in Australia. Whether CIDP is progressive and relapsing has an impact on the type of economic model used to undertake the evaluation. Ig treatment needs to be costed over a longer term for chronic forms of the disease, whereas monophasic treatment is short-term. 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), although expert opinion sought during the drafting of this PICO Confirmation confirmed that IVIg is often a preferred first-choice treatment option for patients with moderate to severe CIDP in Australia. Participating patients in key trials had varying degrees of steroid resistance. Optimal treatment varies for resistant and non-resistant sub-groups, whereas trial results have been typically presented for comparator groups as a whole. This issue, and its impact on economic model results, is discussed in Section D sensitivity analyses

#### Dose regimen and frequency

The IVIg dose range permissible under governance arrangements is specified in Version 3 of *The* *Criteria* both for patients commencing initial Ig treatment and those who have relapsed within six months of a trial off therapy. The criteria specify an induction dose of 2g/kg in 2 to 5 divided doses (access to a second initial dose should be a rare occurrence) and maintenance dose of up to 0.4 to 1g/kg, once every 2 to 6 weeks. Average Ig use per Australian CIDP patient was 497g in 2017-18. A maximum dose of 2g/kg may be given in any 4-week period. Based on an average Australian patient weight of 83kg, the maximum Ig per patient per year could be 1,992g.

The Hughes et al. (2008) ICE study was a response-conditional crossover trial providing IVIg or placebo. Patients received a baseline loading dose of 2g/kg over 2–4 days and then a maintenance infusion of 1g/kg over 1–2 days every 3 weeks for up to 24 weeks. This regimen was used as the basis for costing in the economic study in Canada of Blackhouse et al. 2010 (around 1,447g[[26]](#footnote-27) in the first year). The model was developed for chronic CIDP patients assumed to receive Ig over the entire year. As noted earlier, the lower average Ig use per patient in Australia is partly a result of total Ig use being averaged across chronic, monophasic and relapse-remission patients. All of these patient sub-groups would not use Ig for the entire year.

Other factors such as more appropriate care as a consequence of the national Ig criteria could also contribute to lower use per CIDP patient per year. Annual Ig use estimates of 497g and 1,430g per patient per year are included in the trial and extrapolated analyses to examine the sensitivity of estimated ICER to the dosing assumption. The lower estimate is based on average annual Ig use per patient in Australia and the higher, a trial-based dosing assumption.

**D.2.2. Settings**

Infusion of IVIg for CIDP management in Australia is undertaken in inpatient private hospitals, inpatient public hospitals (as either a private or public patient), outpatient clinics and 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 in the PICO noted that the most common setting for IVIg delivery is the public outpatient facility but patients are commonly admitted as a ‘same-day’ patient i.e. inpatient. Care of a CIDP patient is primarily managed by a neurologist.

The economic model assumes an Australian health care setting, with the modelled population representing adults with CIDP and significant disability or compromised walking objectively measured by an ONLS score of at least two points, and the MRC sum score. Dosing follows the above Australian recommendations administered in an inpatient ‘same-day’ setting. IVIg infusion is generally initiated by a registered nurse and a patient must be monitored throughout the infusion by a registered or enrolled nurse. Analgesia or antihistamines may be required to manage reactions such as headaches, flushes or rashes. It is noted that patients could possibly be trained to self-infuse at home, which would reduce administration costs. This possibility is included as a sensitivity analysis at the conclusion of Section D. It does not have a significant impact on the estimated ICER but would potentially help with convenience and overall patient adherence.

Corticosteroids are a first-line treatment for CIDP. The PICO noted that 50% of Australian patients not receiving Ig therapy will receive corticosteroids. Four glucocorticoids—prednisone, prednisolone, dexamethasone and methylprednisolone—are used and listed on the PBS but there is a lack of consensus on the optimum dosing regimen. Following the Canadian economic modelling, an initial high dose (e.g. prednisone at 40mg per day for two months) is included with a gradual reduction in dose. To estimate product costs, current average Australian CIDP patient weight of 82.5kg is used. This weight is heavier than the figure of 75kg included in the Hughes et al. (2001) study used by Backhouse et al. (2001).

Ig product costs account for more than 80% of the estimated resource use in the 10-year model and are the key driver of the calculated ICER. Differences in costs are captured in the incremental cost per QALY calculation that summarised cost-effectiveness results. Long-term corticosteroid use is associated with a number of potentially serious side effects (metabolic changes, increased susceptibility to infection, hypertension and impaired wound healing) making them poorly suited to long-term continuous therapy, hence the requirement for dose tapering and the development of pulse regimens. Corticosteroids are used in conjunction with steroid-sparing therapy in the form of immunosuppressants.

## Structure and rationale of the economic evaluation

A cost-utility analysis was undertaken to determine the value of Ig against steroids. A summary of the key characteristics of the economic evaluation is given in Table 55.

Table 55 Summary of the economic evaluation

|  |  |
| --- | --- |
| **Perspective** | This economic evaluation was conducted from the perspective of the Australian health system. It includes resource use supported by government and patients. |
| **Intervention** | * Intravenous Ig (IVIg) |
| **Comparator** | * Corticosteroids |
| **Type of economic evaluation** | Cost-utility analysis |
| **Sources of evidence** | * Blackhouse et al. (2010) Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of CIDP in Canada. * Trials outlined in Section B. * Clinical feedback during preparation of Contracted Assessment. |
| **Time horizon** | 6-month trial and 10-year extrapolated time horizon  Sensitivity analyses include a time horizon of 5 years |
| **Outcomes** | Quality-adjusted life-years (QALY) / life-years (LY) |
| **Methods used to generate results** | Cohort expected value analysis |
| **Health states** | * Ig (Initial treatment and responder) * Corticosteroids (no adverse events) * Fracture * Diabetes * Glaucoma * Cataract * Infection * Corticosteroid Non-Responder + Azathioprine * Azathioprine Non-Responder * Disabled * Death |
| **Cycle length** | 1 week |
| **Discount rate** | 5% used for base and 0% and 7% sensitivity analyses |
| **Software packages used** | Microsoft Excel 2010 |

Abbreviations: CIDP = Chronic Inflammatory Demyelinating Polyneuropathy, Ig = Immunoglobulin, LY= Life Years, QALY = Quality-adjusted life-years

As noted, a stepped evaluation was undertaken. The first step captures costs and health outcomes over 6 months, which aligns with the large Hughes et al. (2008) ICE trial involving 117 patients. An extrapolated analysis is undertaken over 10-years for scenarios where patients can transition too steroid and associated adverse event states (similar to the Canadian Blackhouse et al. 2010 study), then to second-line treatment and disability. Sensitivity analyses were conducted for key cost, transition and utility assumptions.

### D.3.1. Literature review

#### CIDP economic models

A literature review was conducted in April 2019 using the search terms provided in Table 56 to identify cost-effectiveness studies for CIDP interventions. The search included Embase (1947-), other HTA websites (CADTH, National Institute for Health and Care Excellence (NICE)) and the Cochrane Library.

Table 56 Search terms used

| **Element of clinical question** | **Search terms** |
| --- | --- |
| Population | [CIDP] OR [Chronic Inflammatory Demyelinating Polyneuropathy] OR [paraproteinemic demyelinating neuropathies] OR [PDN] OR [a sensorimotor neuropathy] |
| Intervention | Not applicable |
| Comparator (if applicable) | Not applicable |
| Outcomes (if applicable) | Not applicable |
| Other | Health economics OR economic aspect OR economics OR biomedical technology assessment OR economic evaluation OR health care cost OR technology assessment OR cost-effectiveness analysis OR cost minimisation analysis OR cost-minimisation analysis OR cost-utility analysis |
| Limits | English language  Remove duplicates  1990-2019 |

Table 57 Summary of the process used to identify and select studies for the economic evaluation

|  | **Embase**  **Global Health, MEDLINE, PyscInfo** | **Other HTA websitesa** | **Cochrane Library** |
| --- | --- | --- | --- |
| Number of titles and abstracts reviewed after search | 357 | 2 | - |
| Total number of exclusions | 345 | 1 | - |
| Number of HTA reports/ cost-effectiveness outcomes reported | 12 | 1 | - |
| Consolidated number of studies excluding duplicates | 12 | | |

a HTA agencies included: NICE, CADTH. 20 April 2019

Of 359 studies screened, only 12 published economic studies focusing on CIDP treatment interventions were identified (listed in Table 58). Six additional studies were identified that covered CIDP management costs and utility, and these were also included as ‘other economic’ publications.

Table 58 Economic models assessing CIDP treatment

| **Study** | **Reference** |
| --- | --- |
| **Published economic models assessing CIDP treatment** | |
| Blackhouse et al. (2010) | Cost-utility of Intravenous Immunoglobulin (IVIG) compared with corticosteroids for the treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Canada. Cost-Effectiveness and Resource Allocation 2010, 8:14 |
| McCrone et al. (2003) | Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol, 10:687-694 |
| Bamrungsawad et al. (2016) | Economic Evaluation of Intravenous Immunoglobulin plus Corticosteroids for the Treatment of Steroid-Resistant Chronic Inflammatory Demyelinating Polyradiculoneuropathy in Thailand. Clin Drug Investig, 36:557–566 |
| Cocito (2012) | Economic and quality of life evaluation of different modalities of immunoglobulin therapy in chronic dysimmune neuropathies. Journal of the Peripheral Nervous System 17:426–428 |
| Cats et al. (2011) | Home-based IVIg treatment is convenient and time-saving in patients with multifocal motor neuropathy. J Peripher Nerv Syst 16:147–149 |
| Membe et al. (2008) | Economic assessment of different modalities of immunoglobulin replacement therapy. Immunol Allergy Clin North Am 28:861–874 |
| Lazzaro et al. (2014) | Subcutaneous vs intravenous administration of immunoglobulin in chronic inflammatory demyelinating polyneuropathy: An Italian cost-minimisation analysis. Neurol Sci 35:1023–1034 |
| Markvardsen and Harbo (2017) | Subcutaneous immunoglobulin treatment in CIDP and MMN. Efficacy, treatment satisfaction and costs Journal of the Neurological Sciences 378, 19–25 |
| Hadden and Marreno (2015) | Switch from intravenous to subcutaneous immunoglobulin in CIDP and MNN: improved tolerability and patient satisfaction. Ther Adv Neurol Disord. 8(1):14-19 |
| Le Masson et al. (2018) | Home versus hospital immunoglobulin treatment for autoimmune neuropathies: a cost-minimisation analysis. Brain Behav. 8(2): e00923 |
| Rajabally and Afzal (2019) | Clinical and economic comparison of an individualised immunoglobulin protocol vs. standard dosing for chronic inflammatory demyelinating polyneuropathy. Journal of Neurology, 266:461–467 |
| Högy et al. (2005) | Pharmacoeconomic evaluation of immunoglobulin treatment in patients with antibody deficiencies from the perspective of the German statutory health insurance. Eur J Health Econ. Mar;6(1):24-9. |

|  |  |
| --- | --- |
| **Other economic studies** | |
| Divino et al. (2018) | The economic burden of CIDP in the United States: A case-control study. PLoS ONE 13(10): e0206205. https://doi.org/10.1371/journal.pone.0206205 |
| Mahdi-Rogers et al. (2014) | Economic costs and quality of life in chronic inflammatory neuropathies in southeast England. European Journal of Neurology, 21: 34–39 |
| Mengel et al. (2018) | Costs of illness in chronic inflammatory demyelinating polyneuropathy in Germany, Muscle Nerve. Nov; 58(5):681-687. |
| Owens (2018) | The economic burden and managed care implications of chronic inflammatory demyelinating polyneuropathy. Am J Manag Care. 24: S380-S384 |
| Suryavanshi and Khanna (2016) | Hospitalisation burden associated with chronic inflammatory demyelinating polyneuropathy in the United States. Value Health. 19(3): A60-A61 |
| Guptill et al. (2014) | Patient demographics and health plan-paid costs in chronic inflammatory demyelinating polyneuropathy. Muscle Nerve. 50(1): 47-51. |

##### Description of the studies

###### Blackhouse et al. (2010)

The objective of the Blackhouse et al. (2010) study was to estimate the cost-effectiveness of IVIg compared to corticosteroid treatment of CIDP in Canada. A Markov model was developed to calculate costs and QALYs over five years of treatment. The analysis assumed a patient starting age of 54 years and weight of 75kg. The model included 12-week cycles. Patients on the Ig arm entered the model for Ig induction treatment, with those responding either continuing to respond or relapsing in each 12-week cycle.

Non-responding Ig patients were assumed to utilise corticosteroids, where they were at risk of AEs in each cycle including fracture, diabetes, glaucoma, cataract and serious infection. Patients were assumed to have AEs for one year prior to discovery, at which point corticosteroids were stopped and HbA1c (diabetes) or elevated intraocular pressure (glaucoma) normalised. Diabetes and fracture had increased mortality risks, while the other steroid AEs were not assumed to impact patient mortality risk.

The key health benefit was the inclusion of the 0.12 (p = 0.07) utility gain from Ig over corticosteroids reported by McCrone et al. (2003), which was measured over a 6-week treatment period. Incremental costs and QALYs of Ig treatment compared to corticosteroids were $124,065 and 0.177, resulting in an ICER of $687,287. The frequency and dosing of Ig had a large impact on model results. The annual Ig maintenance cost was over $70,000, which is higher than that in Australia and reflects greater per patient dosing. The NBA 2016 reported average Ig use per patient in Australia of 437g to 476g between 2012-2016. Based on a cost of $60.41 per gram Ig costs are less than $30,000 per year.

###### McCrone et al. (2003)

This economic study estimated the incremental cost-effectiveness analysis of IVIg over prednisolone for CIDP treatment using data in Hughes et al. (2001). The regimen for prednisolone was 60mg per day during the first 2 weeks, 40mg per day in week three, 30mg per day in week four, 20mg per day in week five and 10mg per day in week six. A similar prednisolone regimen could be expected in Australia, although there is no standard regimen. The costs of treatment on each arm are outlined in Table 59. Prednisolone patient costs were largely inpatient care (71%), while Ig accounted for most of the cost (91%) for the IVIg group. The cost difference between the two treatments was estimated to be $3,754 over the 6-week period.

Table 59 Six-week cost (€, 2000-01 prices) of services at baseline and during first treatment period

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cost component | Baseline | | First treatment period | |
| **Prednisolone**  **(*n* = 13)** | **IVIg**  **(*n* = 12)** | **Prednisolone**  **(*n* = 13)** | **IVIg**  **(*n* = 12)** |
| Inpatient | 826 | 608 | 929 | 0 |
| Day patient | 166 | 102 | 0 | 0 |
| Outpatient | 120 | 98 | 62 | 129 |
| Other workers | 462 | 30 | 173 | 0.3 |
| Informal care | 429 | 662 | 140 | 301 |
| Non-drug costs | 2,000 | 1,500 | 1,304 | 430 |
| IVIg/prednisolone | N/A | N/A | 8 | 4,321 |
| Total | 4,003 | 3,000 | 1,312 | 4751 |

**Source**: McCrone et al. (2003), Table 2, p. 691.

Differences in the level of physical disability was the key difference between patients on each arm of the 6-week treatment. The EuroQol EQ-5D score improved to a greater extent for Ig patients, although not statistically significant. The average relative gain was 0.12 for Ig compared to prednisolone. Ig adverse events were not included in the economic model.

###### Bamrungsawad et al. (2016)

This economic study examined the use of Ig and corticosteroids with immunosuppressants plus corticosteroids in steroid-resistant Thai CIDP patients using Markov modelling. Steroid-resistant CIDP patients were characterised as those who gained no benefit or no remission within three months of starting corticosteroid therapy. A cycle length of 12 weeks was included in the model, which consisted of health states of initial treatment, no response, relapse, remission, disability and death.[[27]](#footnote-28)

Model parameters were sourced from clinical literature, meta-analyses, medical record reviews and electronic hospital databases. The authors noted that there were no previous studies reporting CIDP-specific utility data or any HRQoL data suitable for conversion into utility values. They applied the Thai EuroQol 5D (EQ-5D-3L) questionnaire to 11 patients using purposive sampling. The utility scores of pre-disabled and disabled patients were 0.546 and -0.178 for 7 and 4 patients, respectively, in each of these states. A disabled patient was defined as someone with MRC scale of three or less for one muscle group. An ICER of US$1,672 per QALY gained was estimated. Model results were most sensitive to the utility score of disabled patients.

###### Cocito (2012)

This economic study was undertaken in Italy to compare home-delivered SCIg with hospital-based IV Ig. The study included 10 patients (5 CIDP, 5 MMN) who had previously been treated with IV Ig in hospital for six months. Self-administered questionnaires were completed within 15 days of the last IVIg infusion and after six months of SCIg treatment. Costs of immunoglobulin, infusion pumps, infusion materials, medical staff, monitoring, and side effects (SE) were included in the analysis.

Similar monthly dosing was included for IVIg and SCIg. IVIg was administered as a daily dose for two consecutive days every month, while SCIg involved five weekly infusions of a 3.2g dose. Cost of Ig was €48/g for IVIg and ¤ €49.2/g for SCIg outlined in Table 60 for a base-case analysis. Estimates were based on an adult weight of 70kg and monthly Ig dose of 1g/kg body weight. SCIg had lower costs for medical-nursing staff and treatment of serious events. The cost of Ig accounted for 97% of direct costs for SCIg and 93% for IVIg. The yearly dose was calculated at 840g/patient, which is around double the average dose in Australia.

Table 60 Costs of IVIg and SCIg (€)

|  |  |  |  |
| --- | --- | --- | --- |
| **Component** | **Cost in Euros** | | |
| **SCIg** | **IVIg** | **Difference** |
| Immunoglobulin | 41,328 | 40,320 | 1008 |
| Infusion pump | 266 | 0 | 266 |
| Infusion materials | 1,072 | 384 | 688 |
| Medical and nursing staff | 106 | 1, 332 | −1,227 |
| Pre-medication | 0 | 25 | -25 |
| Monitoring SEs | 0 | 1,322 | -1,322 |
| Medicines for SEs |  | 63 | -63 |
| **Total** | **42,772** | **43,456** | **-685** |

IVIg = intravenous immunoglobulin, SCIg = subcutaneous immunoglobulin. SE = Side effects

Patients also completed a Quality of Life Index questionnaire (presented in Table 61). There was a significant improvement for all three Quality of Life Index Scales. The SF 36 domains relating to physical and emotional roles and social functioning all showed significant improvement.

Table 61 Quality of life evaluation of different modalities of immunoglobulin therapy

| **Evaluation approach** | **Index** | **Baseline** | | **Final visit** | | **p-value** |
| --- | --- | --- | --- | --- | --- | --- |
| **Mean** | **SD** | **Mean** | **SD** |
| SF-36 | PF | 60.5 | 34.59 | 59.5 | 37.52 | n.s. |
| RP | 52.5 | 47.79 | 77.5 | 38.09 | 0.042 |
| BP | 60 | 36.14 | 64.6 | 30.17 | n.s. |
| GH | 50.9 | 12.31 | 52.7 | 16.14 | n.s. |
| VT | 54.5 | 17.86 | 57.5 | 15.50 | n.s. |
| SF | 47.5 | 31.62 | 82.5 | 25.13 | 0.042 |
| RE | 40 | 51.63 | 83.3 | 32.39 | 0.033 |
| MH | 67.2 | 18.64 | 67.6 | 13.78 | n.s. |
| PCS | 41.2 | 11.49 | 41.8 | 9.95 | n.s. |
| MCS | 41.7 | 13.63 | 51.1 | 7.51 | n.s. |
| EQ-5D | EQ-5D Index | 0.680 | 0.20 | 0.722 | 0.24 | n.s. |
| EQ-5D VAS | 71 | 15.05 | 72 | 16.53 | n.s. |
| LQI | I | 30.5 | 6.07 | 38.9 | 4.25 | 0.002 |
| II | 19.8 | 4.84 | 24.3 | 3.05 | 0.021 |
| III | 15.4 | 3.43 | 20.6 | 0.84 | 0.001 |

IVIg = intravenous immunoglobulin, n.s. = not significant, SCIg = subcutaneous immunoglobulin, SF-36, = Short-Form 36 Health Survey Questionnaire. Scales: BP = bodily pain, EQ-5D = EuroQoL 5 Dimensions Questionnaire, EQ-5D Index, = EuroQoL summary index, EQ-5D VAS = EuroQoL visual analogue scale, GH, = general health, LQI = Life Quality Index, MCS, = mental component summary, MH = mental health;, PCS = physical component summary, PF = physical functioning, RE = role emotional, RP = role-physical, SF = social functioning, VT = vitality, I = treatment interference, II = therapy-related problems, III = therapy setting

Cats et al. (2011)

Home-administered Ig treatment for MMN was compared to treatment in hospital among 59 Dutch patients. Questionnaires were completed for time, dose, adverse events, perceived advantages, and disadvantages. Non-serious adverse events were reported by 13% of all patients, while 4% had serious adverse events. Convenience (92%) and time gain (63%) were reported as advantages of home administration, while absence of a physician in case of an adverse event (27%) and problems with IV access or the infusion system (10%) were disadvantages.

Membe et al. (2008)

This study reviewed economic assessments of CIDP treatment modalities of treatment and included some of the previously noted studies (listed in Table 62). The authors concluded that economic studies “appear similar in terms of clinical end points, cost items, results of the cost-effectiveness analysis, assumption about treatment settings and assumptions about the comparative effectiveness of SCIg and IVIg. The key difference was the degree to which SCIg was cost-effective.” They attributed differences in study perspectives and costs of Ig as key drivers of economic results.

Table 62 Ig economic studies included in Membe et al. (2008)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Design and population | Clinical outcomes | Costs included | Results |
| Gardulf et al, Sweden. Home SCIg versus hospital SCIg and hospital IVIg | 165 patients age 13-76 years | Frequency of adverse systemic reactions, occurrence and intensity of tissue reactions and serum IgG changes | Ig preparation, materials, personnel, rooms, administrative overhead | Hospital-based IVIg $14,124/year  Hospital-based SCIg $4,656/year  Home-based SCIg $3,096/year (costs in US$ at 1993 prices) |
| Högy et al, Germany, German statutory health insurance. Home SCIg versus hospital IVIg | Subgroup analysis: adults (75kg) and children (40kg) | Used result of previous study involving 30 patients that showed no significant differences in infection and AE rates between SCIg and IVIg | Ig, pre-medications, infusion pump, physicians, diagnostic procedures, sick leave for children’s caregivers | Adult: IVIg  € 31,027;  SCIg  €14,893  Children: IVIg  € 17,329;  SCIg  € 8,659  (costs in 2003 prices) |
| Liu et al, British health system, assumptions applied to Högy et al. cost calculations. Home SCIg versus home IVIg and hospital IVIg | Högy et al. subgroup analysis:  adults (75kg) and children (40kg) | As in Högy et al; no significant differences in infection and AE rates between SCIg and IVIg | As in Högy et al; Ig, pre-medications, infusion pump, infusion materials, physicians, diagnostic procedures, sick leave for children’s caregivers | Adult: IVIg at home £11,580  Adult: IVIg at hospital £18,600  Adult: SCIg at home £11,760  Children: IVIg at home £6,540  Children: SCIg at home £6,720 |
| Haddad et al,  France. Costs analysis, Public payer (France). Home SCIg versus hospital SCIg and hospital IVIg. | Not stated | No clinical data provided; authors assume equal effectiveness between SCIg and IVIg | Hospital admission, transportation to and from hospital, Ig acquisition cost (pre-tax), homecare nursing, rental cost of administration pumps and perfusion kits | Hospital IVIg (20g/mo) €1,192.19  Home IVIg (20g/mo) €1,033  Home IVIg (40g/mo)  € 2,034.50  Hospital SCIg (20g/mo)  €2,908.76  Home SCIg (20g/mo)  €1,518  Home SCIg (40g/mo) €2,507–2,729 |

Abbreviations: AEs, adverse events; CA, cost analysis, IMIg, intramuscular immunoglobulin, IVIg = intravenous administration of immunoglobulins, SCIg = subcutaneous administration of immunoglobulins

Source: Membe et al. (2008)

###### Lazzaro et al. (2014)

This economic evaluation compared the costs of SCIG vs IVIG for Italian CIDP patients. A 1-year cost model was developed, with most assumptions derived from neurologist expert opinion. Costs included immunoglobulin, drugs for pre-medication and management of complications (rash, headache, hypertension), time of various health care professionals, pump for SCIG self-administration, and infusion disposables (see Table 63). Non-health care resources were estimated but are not outlined below. Overall costs per patient amount to €49,534.75 (SCIg) and €50,895.73 (IVIg). The major cost was Ig (86-94% of total costs).

Table 63 Health resource identification and quantification (Lazzaro et al, 2014)

|  |  |  |
| --- | --- | --- |
|  | SCIg | IVIg |
| **Health care resources** | | |
| Nursing time for training patient in SCIG self-administration | 2 x 2.5 hours | N/A |
| **Therapy** | | |
| Pre-medication |  | Antihystaminie (10 mg) corticosteroid (4 mg) |
| Immunoglobulin | 960 g per year | 960 g per year |
| GP consultation | 2 per year | 12 per year |
| LHA admittances for receiving immunoglobulin, disposables and self-infusion pump | 4 per year |  |
| LHA pharmacist time for delivering immunoglobulin, disposables and self-infusion pump | 1.32 h per year |  |
| **Administration** | | |
| Number of administrations | 96 per year | 24 per year |
| Neurologist time |  | 0.50 h per administration |
| Nurse time |  | 1 h per administration |
| Self-infusion pump | 1 self-infusion pump 50 ml |  |
| Disposables | 1 50 ml syringe  1 multi subcutaneous drug  delivery device | 1 needle  1 tubing |
| **Follow-up** | | |
| Neurologist time | 2 visits per year, 0.50 h each | 2 visits per year, 0.50 h each |
| Electromyography (12 single nerves) | 1 per year | 1 per year |
| **Complication** | | |
| Neurologist time for rash; headache; hypertension |  | 0.50 h |
| Other specialist time for rash; headache; hypertension |  | 0.025 h |
| Nurse time |  | 0.33 h for rash; headache; hypertension |
| Drug for rash |  | Antihistamine (10mg per os for 1 day corticosteroid (4mg IV for 1 day)) |
| Drug for headache |  | Paracetamol (2g suppositories per diem for 2.5 days) |
| Drug for hypertension |  | Amlodipine besylate (5mg per os for 1 day) furosemide (20mg for 1 day) |

GP = general practitioner, IVIG = intravenous immunoglobulin, LHA = Local Health Authority, SCIG = subcutaneous immunoglobulin

###### Markvardsen and Harbo (2017)

This review of economic studies of SCIG treatment for CIDP and MMN, concluded that cost-effectiveness of the SCIG regimen has been sparsely studied. The Italians studies mentioned earlier in this literature review were included. The 11 published studies examined for clinical effectiveness data included 188 SCIg-treated patients with CIDP, of whom 62 were represented more than once, resulting in 126 unique patients. The authors concluded (ibid, p. 9): “none of the studies have been powered to demonstrate an effect on disability. SCIg can maintain muscle strength for a period of 1 to 2 years and ability seems preserved for a similar period. Quality of life is generally unchanged or improved after switch to SCIG and generalised side effects seem fewer, whereas local reactions at the injection site occur [however] optimal SCIG dosage might be slightly higher than the one used for IVIG therapy”. They also concluded that studies and reports on side effects after SCIG are few. Local reactions such as redness, itching and swelling at the injection site are common, whereas systemic side effects are rare.

###### Hadden and Marreno (2015)

The authors undertook a patient outcomes survey to assess clinical outcomes and satisfaction in CIDP or MMN patients switching from IVIg to SCIg. Most patients were satisfied with the SCIg formulation. They had good outcomes, including fewer adverse event when compared to intravenous administration, increased therapy convenience and no wear-off effect. Most of the patients remained clinically stable on the same mean weekly dose of immunoglobulin when switched from IVIg to SCIg. The authors (p. 18) concluded: “the immunoglobulin cost per gram varies in different countries and different hospitals but is typically slightly more expensive for SCIg than IVIg. SCIg avoids the cost of admission to a hospital day unit with associated staff costs and the costs of the patient taking a day off work but requires the involvement of a home care company for equipment and delivery. Overall, the cost difference is small, and it is not clear which is cheaper.”

###### Le Masson et al. (2018)

Le Masson et al. performed a cost-minimisation analysis for home-based IVIg treatment for MMN and CIDP patients in France. Data were sourced from treating hospital records and claims databases. Data for home-based infusion were collected prospectively over nine months and adjusted to a 1-year figure. One year of treatment cost US$63,755 for home-delivered Ig therapy compared to US$121,448 for hospital delivery. Improved tolerability and absence of AEs were the key drivers in patients choosing home-based therapy.

###### Rajabally and Afzal (2019)

This study examined the cost impacts of different IV treatment regimens among 47 IVIg CIDP patients retrospectively studied over four years in the UK. A standard protocol was compared with an individualised, outcome-measured, dose-modifying protocol. Responder and remission rates, clinical improvement levels, dose requirements, and dosing costs were reported. The IVIg-responder rate was 83% and the 4-year remission rate was 25.6%. Ig costs were £37,660/patient/year and infusion-related costs were £17,115/patient/year, generating a total cost of £54,775/patient/year. The long-term response rate is higher than that outlined in Blackhouse et al. (2010), particularly when the Hughes et al. (2008) responder rate after 25 weeks is projected to five years. Sensitivity analyses are included at the end of Section D where different responder rates are included in the economic model.

###### Högy et al. (2005)

The authors undertook cost-minimisation analysis to compare IVIg and SCIg in Germany. Assuming a body weight of 75kg for adults and 40kg for children and an average monthly Ig dose of 0.4g/kg body weight, yearly doses were calculated to be 360g for adults and 192g for children. Prices per/g of IVIG (€84.60) and SCIg (€38.54) were included (Adult IVIg cost per year of €30,456). The IV price is nearly three times that paid in Australia. Average costs were found to be most sensitive to changes in the immunoglobulin price and changes in the body weight of the patient.

##### Other economic studies

A range of studies identified in the literature review were not Ig intervention economic studies, however, they included cost and utility data relevant to the evaluation and they are summarised in the remainder of this Section.

###### Divino et al. (2018)

The economic and clinical burden of CIDP in the USA was estimated using a matched control group without CIDP. The IQVIA (formerly IMS Health and Quintiles) Real-World Data Adjudicated Claims data was used for adults newly diagnosed with CIDP from 2010 to 2014. The sample comprised 790 cases with matched controls. Healthcare resource use, costs and clinical characteristics were assessed and compared over a 2-year follow-up (see Table 64).

Table 64 Demographic characteristics and clinical characteristics in the 6-month pre-index period and 2-year follow-up

|  | Baseline | | | 2-Year Follow-Up | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | Cases  N = 790 | Controls  N = 790 | p-value | Cases  N = 790 | Controls  N = 790 | p-value |
| **Age (years)** | | | | | | |
| Mean ± SD | 49.7 | 49.7 | NA | NA | NA | NA |
| Median | 52 | 52 | NA | NA | NA | NA |
| **Common (>5%) comorbidities** | | | | | | |
| Asthma/COPD | 19 | 9 | 0.0588 | 65 | 17 | <.0001 |
| Back pain | 241 | 80 | <.0001 | 371 | 150 | <.0001 |
| Cardiac dysrhythmia | 34 | 28 | 0.4386 | 100 | 50 | <.0001 |
| Cerebrovascular disease | 25 | 12 | 0.0280 | 81 | 25 | <.0001 |
| CAD | 22 | 23 | 0.8788 | 62 | 52 | 0.3124 |
| Diabetes | 87 | 112 | 0.0176 | 172 | 147 | 0.0867 |
| Dyslipidaemia | 215 | 237 | 0.1806 | 361 | 363 | 0.9113 |
| Hypertension | 233 | 223 | 0.5543 | 364 | 314 | 0.0064 |
| Hypothyroidism | 80 | 53 | 0.0126 | 128 | 86 | 0.0016 |
| IBD | 16 | 14 | 0.7150 | 46 | 25 | 0.0103 |
| **Characteristic** | | | | | | |
| Leukaemia/lymphoma | 26 | 6 | 0.0004 | 84 | 34 | <.0001 |
| Neuropathic pain | 314 | 23 | <.0001 | 455 | 54 | <.0001 |
| Osteoarthritis | 65 | 26 | <.0001 | 188 | 62 | <.0001 |
| PVD | 17 | 3 | 0.0017 | 50 | 13 | <.0001 |
| Sleep apnoea | 14 | 5 | 0.0290 | 59 | 23 | <.0001 |
| **Common (>5%) therapies of interest:** | | | | | | |
| Anti-anxiety medications | 14 | 5 | 0.0389 | 50 | 17 | <.0001 |
| Anti-convulsant | 242 | 40 | <.0001 | 361 | 57 | <.0001 |
| Anti-depressants | 216 | 108 | <.0001 | 349 | 144 | <.0001 |
| Benzodiazepines | 121 | 43 | <.0001 | 207 | 75 | <.0001 |
| Central muscle relaxants | 93 | 42 | <.0001 | 206 | 71 | <.0001 |
| Lidocaine | 18 | 0 | - | 52 | 10 | <.0001 |
| NSAIDs | 142 | 71 | <.0001 | 253 | 137 | <.0001 |
| Opioids | 264 | 128 | <.0001 | 479 | 212 | <.0001 |

CAD = Coronary artery disease; COPD = chronic obstructive pulmonary disease; IBD = Inflammatory bowel disease; NSAIDs = nonsteroidal anti-inflammatory drugs; PVD = Peripheral vascular disease; SD = standard deviation

Source: Divino et al. (2018)

The authors reported that CIDP patients had greater neuropathic pain, back pain and osteoarthritis, and more commonly utilised opioids and anti-depressants. Average health costs were $116,330 (CIDP) compared to $15,586 (controls). The average cost of CIDP treatment was $59,619.

Table 65 Healthcare cost (US$) per patient over the 2-year follow-up

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cases  N = 790 | Cases  N = 790 | p-value |
| Outpatient Pharmacy | 11,186 | 3,953 | <.0001 |
| Medical | 105,144 | 11,633 | <.0001 |
| Inpatient | 16,357 | 2,862 | <.0001 |
| ER | 1,188 | 468 | <.0001 |
| Physician office | 5,122 | 2,208 | <.0001 |
| Outpatient surgery | 3,204 | 1,157 | <.0001 |
| Lab/pathology | 2,907 | 648 | <.0001 |
| Outpatient ancillary, radiology and HCPCS drugs | 76,366 | 4,292 | <.0001 |
| TOTAL COST | 116,330 | 15,586 | <.0001 |
| Total CIDP Therapy | 59,619 |  |  |

CIDP = chronic inflammatory demyelinating polyneuropathy; ER = emergency room; HCPCS = Healthcare Common Procedure Coding System. All figures in US$.

Source: Divino et al. (2018)

###### Mahdi-Rogers et al. (2014)

Cost-of-illness studies and HRQoL was assessed across southeast England in 2008 using client service receipt inventory and service costs. The EuroQoL (EQ-5D) survey were sent to 50 randomly selected individuals and was completed by 43 of them. Results are outlined in Table 66. The authors reported that mean utility scores (standard devaluation) for CIDP of 0.62 (0.23), PDN of 0.63 (0.22) and MMN of 0.72 (0.14), were lower than the UK average of 0.86 (0.28) but were higher than the score of 0.55 (0.33) for multiple sclerosis in the UK (Kobelt et al. 2006). There was no relationship between the HRQoL in CIDP, PDN and MMN to age, disease duration or gender. The average utility score for those on IVIg was 0.65 and for those not on IVIg it was 0.63 (P = 0.77). Responses to the EuroQoL are outlined in Table 66, with mobility being a major problem for CIDP patients.

Table 66 Responses to each of the domains of the EuroQoL

|  |  |  |  |
| --- | --- | --- | --- |
|  | CIDP  (%) | MMN  (%) | PDN  (%) |
| **Mobility** | | | |
| No problem | 7 (16.7) | 5 (62.5) | 5 (19.2) |
| Some problem | 35 (83.3) | 3 (37.5) | 21 (80.8) |
| Extreme problem | 0 (0) | 0 (0) | 0 (0) |
| **Self-care** | | | |
| No problem | 24 (57.1) | 5 (62.5) | 18 (69.2) |
| Some problem | 17 (40.5) | 3 (37.5) | 8 (30.8) |
| Extreme problem | 1 (2.4) | 0 (0) | 0 (0) |
| **Usual activity** | | | |
| No problem | 9 (21.4) | 2 (25) | 5 (19.2) |
| Some problem | 29 (69.0) | 6 (75) | 20 (76.9) |
| Extreme problem | 4 (9.5) | 0 (0) | 1 (3.8) |
| **Pain and discomfort** | | | |
| No pain | 11 (26.2) | 2 (25) | 6 (23.1) |
| Moderate pain | 28 (66.7) | 6 (75) | 17 (65.4) |
| Extreme pain | 3 (7.1) | 0 (0) | 3 (11.5) |
| **Anxiety and depression** | | | |
| Not anxious or depressed | 25 (59.5) | 5 (62.5) | 14 (53.8) |
| Moderately anxious or depressed | 16 (38.1) | 3 (37.5) | 10 (38.5) |
| Extremely anxious or depressed | 1 (2.4) | 0 (0) | 2 (7.7) |

CIDP = chronic inﬂammatory demyelinating polyradiculoneuropathy; MMN = multifocal motor neuropathy; PDN = paraproteinemic demyelinating neuropathy

Source: Mahdi-Rogers et al. (2014), Table 8, p. 38.

IVIg was the key driver of cost (see Table 67) in all three diseases and the higher frequency of its use in CIDP and MMN accounted for the much greater average cost per patient in these diseases. The total annual cost-of-illness per patient was £22,085 for CIDP, £22,812 for MMN and £7,566 for PDN. The total annual cost per patient was £49,430 for those on IVIg and £9,046 for those not on IVIg (P < 0.01).

Table 67 The annual cost of the components of healthcare provision, social services and productivity per patient

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | CIDP | | | MMN | | | PDN | | |
| Mean | SD | % | Mean | SD | % | Mean | SD | % |
| Hospital services (£) | 2903 | 4313 | 13.1 | 2267 | 2122 | 9.9 | 694 | 446 | 9.1 |
| Primary care services (£) | 191 | 284 | 0.9 | 69 | 48 | 0.3 | 231 | 410 | 3.0 |
| Cost of IVIg (£) | 10,348 | 21,070 | 46.9 | 11,252 | 15,018 | 49.3 | 0 | 0 | 0 |
| Cost of other treatments (£) | 131 | 270 | 0.6 | 0 | 0 | 0 | 113 | 285 | 1.5 |
| Investigations (£) | 104 | 184 | 0.5 | 164 | 294 | 0.7 | 56 | 91 | 0.8 |
| Social services (£) | 2,592 | 5,097 | 11.7 | 3,051 | 4,798 | 13.4 | 2,224 | 3,814 | 29.4 |
| Loss of productivity (£) | 5,815 | 11,479 | 26.3 | 6,009 | 10,660 | 26.3 | 4,247 | 10,158 | 56.1 |

CIDP = chronic inﬂammatory demyelinating polyradiculoneuropathy; MMN = multifocal motor neuropathy; PDN = paraproteinemic demyelinating neuropathy; IVIg = intravenous immunoglobulin.

###### Mengel et al. (2018)

This was a multicentre study cohort in Germany, with 108 patients recruited from three specialised clinics. Costs were calculated for a 3-month period between January 2013 and June 2014. Total quarterly costs were €11,333, with dosing over a range of 20-180g per administration. The following outcomes were assessed: INCAT disability scale, Mini-Mental State Examination, Beck Depression Inventory, Charlson comorbidity index, EuroQoL-5D, World Health Organization QoL instrument, and socioeconomic status. An EQ-5D of 0.68 was reported for CIDP patients.

###### Suryavanshi and Khanna (2016)

Patients with CIDP-related hospitalisations in the United States were matched with four control hospitalisations based on gender and age. There were 31,451 weighted records of CIDP hospitalisation during the study period. The estimated cost of hospitalisations for CIDP from 2010 to 2012 was $US2.1 billion in the United States alone. The mean cost of CIDP-related hospitalisation was $US 68,231.

###### Guptill et al. (2014)

The costs of CIDP were estimated from patients enrolled in nine commercial health plans in the United States in 2011. Average health plan-paid costs were calculated at $US 56,953, medical costs were $US 25,054 and pharmacy costs were $US 31,899.

##### Summary

Only a limited number of economics studies relating to CIDP intervention cost-effectiveness were identified. The key economic study is that by Blackhouse et al. (2010) undertaken in Canada where Ig was compared to steroids. This study used clinical data from the Hughes et al. (2001) trial that included steroid-resistant and -responder patients. One study in Thailand investigated Ig versus azathioprine/mycophenolate mofetil in steroid-resistant patients, based on a small survey of patients (<10) to generate utility values. Most other economic studies compare SCIg with IVIg as part of costing or cost-minimisation analysis. Population-level studies have been undertaken to estimate the costs of CIDP cases in the UK, Germany and the USA. The large share that Ig product costs contribute to overall intervention costs was evident.

### D.3.2. Structure of the economic evaluation

A cost-utility model was developed based on the Markov structure in Figure 4 to estimate the expected costs and QALYs associated with Ig compared to corticosteroids.

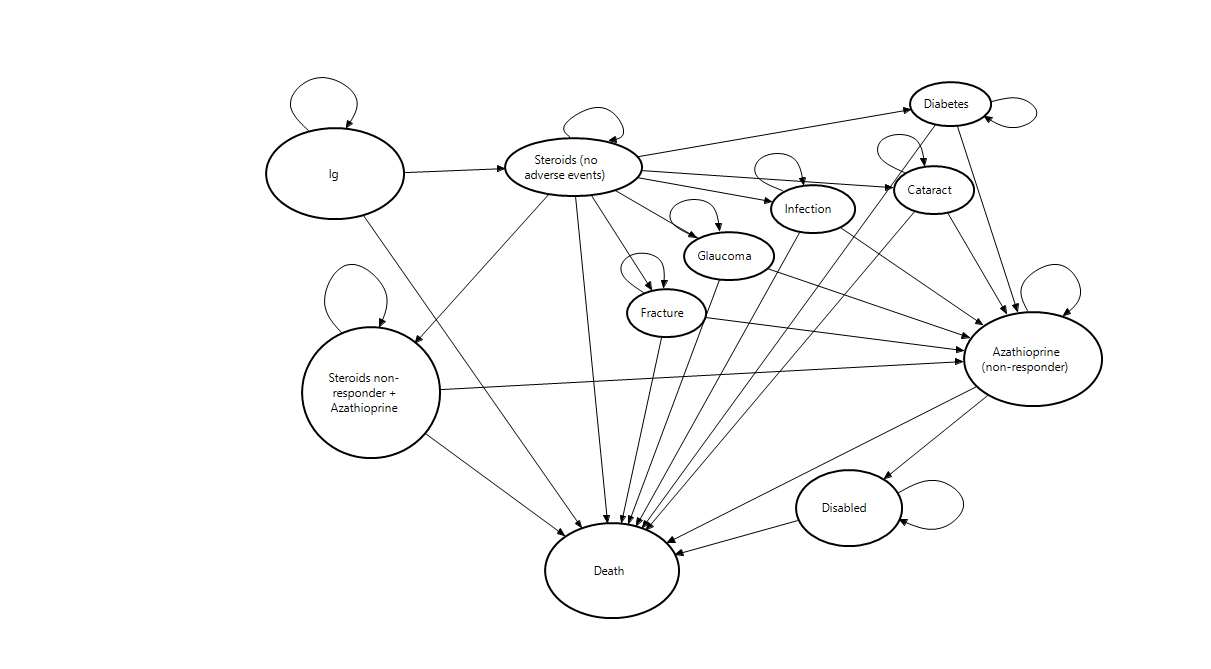
The Microsoft Excel 2010 Markov model (included as an attachment to this Assessment) is based on that developed in Canada by Blackhouse et al. (2010), however is extended to allow for azathioprine use among steroid non-responders and patient progression to disability. The Canadian model is adapted to Australia using local resource costs and a range of updated assumptions based on recent studies. There are eleven states in the model including Ig treatment, corticosteroids (no adverse events) and a range of corticosteroid adverse events including fracture, diabetes, glaucoma, cataract, and infection. Each of the AE states include the use of azathioprine as an immunosuppressant. Second-line treatment states include corticosteroid non-responders treated with azathioprine, azathioprine (non-responder) and disability. Death is an absorbing state to which patients can transition from all states.

A cohort of 1,000 confirmed CIDP patients (as per clinical algorithm Figure 1) begins in the Ig arm of the model in the Ig state. If Ig-responsive, they continue in this state or else transition to corticosteroids (no AEs), and a range of corticosteroid adverse events, azathioprine use as an immunosuppressant, disability and death based on weekly probabilities for each week of the model projection. Patients cannot transition to corticosteroid and related-AE states for the first four months, prior to initial assessment.

The Ig Review Reference Group noted that the economic model is based on a number of assumptions that may not reflect current clinical practice in Australia. Specifically, the Reference Group commented that:

* corticosteroids and Ig may be used concurrently to manage CIDP rather than sequentially as indicated by the model
* the model assumes that patients discontinue corticosteroids if an adverse event occurs; however, in clinical practice a proportion of patients will continue corticosteroids if the adverse event can be appropriately managed.

Figure 4 Makov model structure



Abbreviations: AE = adverse events, Ig = immunoglobulin

et al. The model is for chronic CIDP patients. Ig treatment is assumed to continue for six months or ten years for CIDP patients who continue to respond to Ig. The structure does not allow for withdrawal of Ig in patients who are clinically stable, and hence does not allow for removal of Ig costs in these patients, nor the reintroduction of Ig in patients who relapse. Allowance for temporary cessation of Ig in a proportion of patients in the model would improve the ICER. Clinical evidence is not available to model the clinical pathways for differing CIDP subtypes.

Average Ig use per patient in Australia (497g/patient/year) in part captures patient withdrawal. This amount is less than that in the economic study of Blackhouse et al. 2010 in Canada (around 1,447g[[28]](#footnote-29) in the first year). Assuming an average Australia patient weight of 82.5kg, annual Ig usage would be 1,601g at 19.3g/kg. It is noted that there is some uncertainty surrounding CIDP patient diagnosis. Some patients may enter the model as ‘possible, probable or definite CIDP’ (collectively ‘suspected CIDP’) with response to an initial 4-month dose of Ig a key part of the definitive diagnosis. A proportion of non-responders in this initial assessment will not be CIDP patients, and hence should exit the model. Lower grams of Ig per patient per year reported in Australia, in part capture this issue. Lower and higher dosing assumptions are included as scenarios in trial and extrapolated analyses.

The probabilities of a typical patient transitioning between health states are derived from the clinical evidence outlined in Section B (largely for Ig response and relapse) and assumptions used in Blackhouse et al. (2010) for corticosteroids and corticosteroids adverse events. The Canadian model is extended to include steroid non-response, azathioprine non-response and patient progression to disability. Additional costs of azathioprine , disability and disutilities for the azathioprine non-response and disabled states are included. The model’s baseline year was 2019. All future costs and health benefits are discounted back to this year using a rate of 5%, which is standard MSAC economic evaluation practice. Higher and lower discount rates are included in the sensitivity analysis that concludes Section D.

### D3.3 Assumptions incorporated into the model structure

Assumptions incorporated into the economic evaluation (summarised in Table 68) relate to the model’s perspective and type of economic evaluation, along with the sources of evidence, time horizon and outcomes used to measure the intervention and comparator.

#### Type of economic evaluation

Given the claim of Ig superiority, a cost-utility economic model has been developed, presented as a stepped analysis. The first step estimates costs and clinical benefits over six months, which is the maximum follow-up period for the large ICE trial (Hughes et al. 2008) for which clinical outcomes have been reported. As CIDP is a chronic condition, Ig therapy is likely to have longer-term costs and benefits. The second step of the economic modelling approach extrapolates the period of analysis to a maximum follow-up of 10 years. Incremental costs and clinical benefits (life-years and QALYS) are estimated to calculate the ICER.

#### Sources of evidence

The IVIg response rate for initial treatment is a pooled response rate from the Zinman et al. (2005), Hughes et al. (2008) and Nobile-Orazio et al. (2012) studies. A rate of 61% is estimated which is higher than 47% calculated in Blackhouse et al. (2010). A higher rate is included as the three above studies calculated response at 4-6 months, rather than 0-1 month’s follow-up as in some of the Blackhouse et al. (2010) included studies - so the higher rate is more applicable to Australian Ig use criteria.

The IVIg relapse rate is based on data from Hughes et al. (2008) which was the only study that reported relapse rates over a six-month period. The 25-week relapse rate for IVIg in this study was estimated to be 13%. This is equivalent to a 0.56% constant relapse rate every week. The probabilities of corticosteroid-related AEs are taken from a cost-effectiveness study comparing corticosteroids with Cox-2 inhibitors for the treatment of rheumatoid arthritis, outlined in Blackhouse et al. (2010).

Costs of treatment are based on Ig costs listed on the NBA, MBS Item costs for various diagnostic and medical services, and medicines costs from the PBS. The population entering the model is adult patients with CIDP, assumed to be 55 years of age and weighing 82.5kg. The starting age is based on the average age of patients in the trials by Hughes et al. (2001, 2008) and Nobile-Orazio et al. (2012), along with Australian patient data in McLeod et al. (1999). Patient costs are estimated for an expected patient of the above weight and age. Background mortality is taken from an Australian life table.

#### Perspective

The economic analysis is taken from the perspective of the Australian health system. Health service costs are valued at 100% of fee value for MBS items, the perspective taken by the Federal Government of Australia and the NBA. Budget impact analysis provided in Section E takes NBA, MBS, PBAC, state government and private payer perspectives.

#### Time horizon

The base case of the economic evaluation corresponds with a 6-month trial follow-up period. A second extrapolated analysis is presented over 10 years to capture the adverse effects of corticosteroid use and progression to disability. A longer time horizon than the 5-years used in Blackhouse et al. (2010) is used as it may better capture long-term AEs.

#### Outcomes

As noted in Section C, there are few clinical studies with QoL data that could be transformed into utility. QoL is typically measured in economic studies using utilities derived by survey instruments such as EQ-5D. The incremental gain in utility from IVIg treatment compared with corticosteroid treatment was 0.12 in the Blackhouse et al. (2010) economic model. It was derived from the trial of Hughes et al. (2001), and EQ-5D analysis of McCrone et al. (2003) who measured utility at baseline and at six weeks in patients. It was applied to Ig-responding patients across the 10-year model.

A more recent study by Nobile-Orazio et al. (2012) found no difference in SF36 QoL scale gain between Ig and corticosteroid patients over six months. As noted, there were issues with this study such as imbalance of some baseline characteristics in the two treatment arms. Patients treated with IV methylprednisolone tended to be older and have more functional impairments than did patients treated with IVIg. More patients stopped methylprednisolone (52%) than IVIg (13%), which confounds an intention-to-treat analysis. In the absence of comprehensive data, the 0.12 utility gain for Ig over steroids included in Blackhouse et al. (2010) is used for base calculations. The impact of IVIg therapy on utility is based on a trial that provided six weeks of patient data. Consequently, there is a high degree of uncertainty around this estimate. Alternative utility values are assumed in sensitivity analyses that conclude Section D.

Disutilities for steroid AEs were taken from a range of Australian studies listed in Section C. These disutilities are uncertain. Given the relatively low incidence of corticosteroid-induced AEs, the sensitivity analyses presented at the end of Section D demonstrate that they have limited impact on the estimated ICER. Disutilities are also estimated for azathioprine non-response and disabled CIDP states. There is limited data on which to calculate these parameters. The Thai cost-effectiveness study among steroid-resistant CIDP patient of Bamrungsawad et al. (2016) used the Thai EuroQol 5D (EQ-5D-3L) instrument to survey 11 CIDP patients and estimated utility scores of 0.546 and -0.178 for pre-disabled and disabled CIDP patients. The study defined disabled as a patient with an MRC scale for one muscle group of three or less. In the absence of Australian data for CIDP, the multiple sclerosis health state utility values for Australian MS patients from Ahmad et al. (2017) are used for disabled Australian CIDP patients.

#### Methods used to generate results

The economic model used to generate the results is an expected value cohort analysis for 1,000 patients. A Markov model was developed through which patients transition between each state based on weekly transition probabilities. The simulation begins with the hypothetical cohort of 1,000 in the Ig initial state for the Ig arm, and corticosteroids without AE for the comparator. The evaluation then compares the expected costs and clinical outcomes (Life-years, QALYs) between the treatment options.

#### Health states

The model includes nine states largely based on the Blackhouse et al. (2010) model, with the addition of steroid non-responders, azathioprine non-response and disability states. Death is an absorbing state from which patients cannot transition. The descriptions of each state and possible transitions to other health states are outlined in Table 68.

Table 68 Economic model health states

| Health state | Description | Possible transitions to other health states |
| --- | --- | --- |
| Ig treatment | All patients enter the model in the Ig treatment health state.  Patients who respond to treatment receive maintenance IVIg each week until they relapse and no longer respond to treatment | After 4 months, a proportion of patients are IVIg responders or IVIg non-responders. Non-responders’ transition to corticosteroids (no adverse events) or death |
| Corticosteroids (no adverse events) | Patients start corticosteroid treatment; they are at risk of AEs and non-response in each weekly cycle | Corticosteroids (non-responder), fracture, diabetes, glaucoma, cataract and serious infection  Death |
| Fracture | Patients discontinue steroid treatment with an AE. The patient is assumed to receive treatment specific for the AE, then an azathioprine regimen | Death, Azathioprine non-responder |
| Diabetes | As above. | Death, Azathioprine non-responder |
| Glaucoma | As above. | Death, Azathioprine non-responder |
| Cataract | As above | Death, Azathioprine non-responder |
| Infection | As above | Death, Azathioprine non-responder |
| Corticosteroids non-responder + azathioprine | Corticosteroids non-responder + azathioprine patients transition to non-response based on the weekly risk of non-response | Death, azathioprine non-responder |
| Azathioprine (non-responder) | Non-responding patients transition to disability based on a weekly risk. | Death, disabled |
| Disabled | Patients remain disabled until death. They cannot transition back to pre-disabled states. | Death |
| Death | The proportion of the cohort that dies from any cause. No costs or benefits are accrued in this health state. | None  (this is an absorbing health state) |

Abbreviations: AE = adverse event = IG= immunoglobulin, IV = intravenous

#### Cycle length

The economic model employs a cycle length of one week. Annual and half yearly proportions of responders and non-responders, along with proportions with steroid AEs, are converted to weekly probabilities.

#### Discount rate

Costs and clinical benefits (difference in QALYs between Ig [IV and SC] and corticosteroids) are discounted at 5% per annum. The impact of discounting is explored in sensitivity analyses. A half cycle correction is applied.

#### Comparator

The main comparator for Ig is corticosteroids. Costs are also presented for azathioprine used an immunosuppressant and plasma exchange. As there was limited clinical and QoL evidence to compare these interventions with Ig, they are discussed in terms of cost alone.

## Inputs to the economic evaluation

The following sections summarise the clinical and economic input parameters included in the economic evaluation. Variables used in the economic evaluation can be grouped into the following categories:

### D.4.1. Clinical Input Parameters

#### Baseline patient demographics

Table 69 summarises baseline patient characteristics of the modelled patient population. Starting age has a limited impact given that background mortality differs across a life table. This variable does not affect the treatment effectiveness or natural history of the disease in the model. Average weight was taken from the patient profile in key trials. Given that Ig costs are a large (80%+) component of total intervention costs, weight and dosing have a large impact on the estimated ICER.

Table 69 Baseline patient and disease characteristics of the modelled patient cohort

| Parameter | Input | Source |
| --- | --- | --- |
| Age of population at baseline | 55 | Based on Hughes et al. (2001, 2008) and NBA data. Average age 64 years in 2017-18 in NBA supplied data for 2017-18. |
| Weight | 82.5kg | Based on NBA data for 2017-18. |

#### Transition probabilities

Section B is used for Ig transition probabilities, while corticosteroid and associated AE probabilities are derived from Blackhouse et al. (2010). Annual values are converted to weekly equivalents using the formulae -(LN(1-annual probability))/52. Weekly probabilities are specified in Table 70.

Table 70 Health state transition probabilities

| Parameter | Study | Weekly rates | | |
| --- | --- | --- | --- | --- |
| >1 year | 1 to 5 years | 5+ years |
| Ig response probability | The IVIg response rate for initial treatment is a pooled response rate from the Zinman et al. (2005), Hughes et al. (2008) and Nobile-Orazio et al. (2012) studies. It is higher than the pooled estimate in Blackhouse et al. 2010 of 0.473. The calculation included response rates from the IVIg treatment arms of Zinman (2005), Thompson (1996), Mendell (2001), Hughes (2008), Vermuelen (1993) and Hahn (1996) which had limited months of follow-up. The response rate is included at 12 weeks in line with Australia Ig use assessment timing. | 0.61000  At 4 months | NA | NA |
| Ig relapse probability | The IVIg relapse rate was based upon data from the ICE study. The 25-week relapse rate for IVIg in this study was estimated to be 13%. It is converted to a weekly probability using -(LN(1-0.13))/25. The ICE study does not extrapolate beyond 1-year; therefore, no additional relapse is assumed beyond 12 months. | 0.00557 | 0.00000 | 0.00000 |
| Corticosteroids (non-responder) probability | van Lieverloo et al. 2018 indicated 60% responded to corticosteroids and of the 75 responders, 61% remained in remission, during a median follow-up of 55 months Eftimov et al. 2012 reported long-term results of PREDICT study for 5 years. 33% of patients had cure or remission, 33% had stable active disease and 10% had unstable active disease. Patient baseline population characteristics vary among trials, with some precluding those who were contraindicated to steroids, and others not. Correspondingly, there is uncertainty about steroid response rates among trials for the Australian patient population. Weekly non-response probably is included so 40% of the steroid arm is responsive after 5-years. Non-responsive patients and those with AEs transition to azathioprine used an immunosuppressant. This assumption is subject to sensitivity analysis. | 0.00246 | 0.00246 | 0.00000 |
| Azathioprine used an immunosuppressant non-responder probability | Bamrungsawad et al. (2016) included a zero probability of response to immunosuppressant plus corticosteroids. A 99.99% non-response at 1-year is converted to weekly rate of 0.66422 for steroid-resistant patients. It is assumed that 75% of patients in steroid adverse events state would be non-respondent to azathioprine used an immunosuppressant after one year | 0.66422 | 0.66422 | 0.66422 |
| Disability among azathioprine non-responder’s probability | Bamrungsawad et al. 2016 defined a disabled as those with an MRC scale for one muscle group of three or less. Using this criterion 24/29 (82.76 %), of CIDP patients were disabled. The probability of becoming disabled in patients not responding to therapy in all health states was 0.098 over 12 weeks, or 0.0086 per week, or 37.4% per year. | 0.00860 | 0.00860 | 0.00860 |

|  |  | Weekly rates | | |
| --- | --- | --- | --- | --- |
| Parameter | Study | >1 year | 1 to 5 years | 5+ years |
| Fracture probability | A fracture annual probability of 0.0098, or 0.00019 per week for Corticosteroids patients, was taken from Bae et al. 2003 in the Blackhouse et al. (2010) study. Fractures were not reported in the Van Schaik et al. 2010 description of PREDICT, however they were reported in Eftimov et al. 2012. A total of 2 of the 39 (Table 3. p. 1083) (5.13%) were reported to have fractures, equating to 8.3% of the dexamethasone group and none of the prednisolone group. This value is converted to a weekly probability. | 0.00023 | 0.00023 | 0.00023 |
| Diabetes probability | A diabetes annual probability of 0.0043, or 0.00008 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). Impaired glucose tolerance was found in 3 (20%) patients after 10 years of follow-up in the Boru et al. 2014 study. The dexamethasone arm of PREDICT had adverse event prevalence of 8.3% for hypertension, 54.1% increased body weight, 8.3% diabetes, 33.3% Cushing appearance and 4.2% impaired glucose tolerance. A higher 5-year value of around 10% is included in this study, which corresponds to a weekly probability of 0.00045. | 0.00045 | 0.00045 | 0.00045 |
| Glaucoma probability | A glaucoma annual probability of 0.0008, or 0.00002 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). | 0.00002 | 0.00002 | 0.00002 |
| Cataract probability | A cataract annual probability of 0.0114, or 0.00022 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). | 0.00022 | 0.00022 | 0.00022 |
| Infection probability | An infection annual probability of 0.0035, or 0.00007 per week for Corticosteroids patients, was taken from Blackhouse et al. (2010). The 5-year probability of fracture probability associated with this estimate is less than 2%. | 0.00007 | 0.00007 | 0.00007 |
| Ig mortality odds ratio | CIDP was not assumed to results in increased mortality. The ABS annual mortality rate for 55-year olds in Australia in 2017 was 0.0045 for men and 0.0027 for women. These are converted to weekly values using a gender balance of 0.49. | 1.0000 | 1.0000 | 1.0000 |
| Corticosteroids mortality odds ratio | CIDP was not assumed to result in increased mortality. | 1.0000 | 1.0000 | 1.0000 |
| Fracture mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.0127 for first-year fractures. This is included as an odds ratio of 1.0142 for 55-59 year olds and applied to weekly base mortality. | 1.01420 | 1.01420 | 1.01420 |
| Diabetes mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.001160 for first year diabetes for 55-59-year-olds. This is included as an odds ratio of 1.001160 and applied to weekly base mortality. | 1.00116 | 1.00116 | 1.00116 |
| Glaucoma mortality odds ratio | Not assumed to result in increased mortality | 1.0000 | 1.0000 | 1.0000 |
| Cataract mortality odds ratio | Not assumed to result in increased mortality | 1.0000 | 1.0000 | 1.0000 |
| Infection mortality odds ratio | Blackhouse (2010) included an incremental mortality of 0.018 for 25-64 year olds in hospital. This is included as an odds ratio of 1.018 and applied to weekly base mortality. | 1.01800 | 1.01800 | 1.01800 |

Abbreviations: AE= adverse event. CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

**Trial period**

Weekly probabilities are taken from Table 70 and applied across six months for the base trial analysis. Results of the analysis are included in the Markov trace presented in Figure 5. It is evident that all the cohorts start in the initial Ig treatment state. After four months they are assessed for Ig response, then move to either Ig responder or corticosteroid states.

Figure 5 Ig patient distribution between health states – 6 month follow-up trial period

Abbreviations: AE= adverse event, Ig= Immunoglobulin

**Extrapolation after the trial period**

Results of the extrapolations are presented as a series of Markov traces for the Ig and steroid arms, along with a trace that shows the difference in patient numbers by state as a result of Ig use. Based on the Ig response (61%) at 4 months and Ig relapse rate assumed in the model, around half of Ig patients remain on Ig treatment after 10 years. Nearly 30% have progressed to disability due to non-response to first and second-line treatments.

Figure 6 Ig arm patient distribution between health states – 10 year follow-up

Abbreviations: AE= adverse event, Ig= Immunoglobulin

Figure 7 Steroid arm patient distribution between health states – 10 year follow-up

Abbreviations: AE= adverse event

The difference between steroid AEs on the model arms is limited, given incidence rates. Fracture and diabetes are the largest AEs by patient number but are less than 1% of total patients at 10-years. Given the small numbers relative to those in Ig and steroid states, these patients have limited impact on estimated ICER

A higher proportion of steroid arm patients are estimated to progress to disability. After 10-years it is estimated that nearly 60% of patients on the steroid arm reside in this state. The key difference between Ig and steroid (see Figure 8) arms is the higher number of patients who transition to azathioprine non-response then disability over the 10-year projection. The incremental utility of Ig over the steroid health state and, greater proportion of patients suffering disability are the key drivers of economic value.

Figure 8 Difference between Ig and steroid patient distribution between health states – 10 year follow-up

Abbreviations: Ig= Immunoglobulin

### D.4.2. Economic Input Parameters

Changes in health system resource utilisation associated with the intervention include cost estimates for Ig and steroid products; infusion equipment; administrative, nursing and clinician time; medication to treat adverse events; training of patients for SCIg; and follow-up and/or monitoring visits, including regular neurology visits.

#### Cost of Ig product and delivery services

##### IVIg treatment

Costs of Ig product and medical services for IVIg delivery are outlined in Table 69 for an 83kg patient. Costs are specified for the initial and maintenance IVIg treatment phases. The dose and frequency of IVIg treatment assumed in the model are based on NBA product use. Actual product use in Australia is less than the recommended dosing, possibly due to relapse and remission in Australian patients. Correspondingly ICERs are presented assuming Australian Ig use of 497g per patient per year, and a trial maintenance dose (based on Hughes et al. 2008) of 17.33g/kg per year (1g/kg every 3 weeks), equating to 1,430g for an average 82.5kg Australian CIDP patient, as reported by the NBA. The cost per gram of IVIg ($60.41) was provided by the NBA. Additional sensitivity analyses are high, low and weighted Ig prices. Some pre-medication may be needed (eg 10mg oral cetirizine and 1g (oral or IV) paracetamol), though clinical feedback indicated pre-medication usage is limited.

Medical services include specialist (neurologist) and nurse inputs for administration. Most Ig cases would be billed using MBS Item 132 for the first specialist consultation, then MBS Item 133 or 116 (depending on duration, clinical context) for subsequent attendances. The cost per hour for a nurse ($85) is based on data from NSW awards and an overhead factor of 1.67. Blood tests for electrolytes, urea, creatinine, liver function and full blood counts may be ordered every 4-6 weeks during the first few months of treatment, though this is more closely checked during steroid or adjuvant immunosuppression use (e.g. azathioprine, methotrexate) than with Ig. Nerve conduction studies at four months may be arranged to assess response, though if clinically improving this may not be necessary. These costs are shown in Table 71.

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The analysis assumed 497g per patient based on NBA data. The cost of IVIg use per patient was $30,024 ($10,007.9 over 4 months + $20,015.8 over 8 months).

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Blackhouse et al. (2010) estimated Canadian IVIg costs to be $27,307.50 for the initial model 12 weeks of treatment, then $18,205 in subsequent 12-week cycles. The cost difference is a result of higher dosing and slightly higher Ig unit cost in the Canadian study. A higher dose (17.33g per patient) is included in this report, with the ICER being similar to that of Blackhouse et al. (2010). The costs for Ig in the economic model are based on Intragam but are subject to sensitivity analysis.

Table 71 Resources associated with IVIg

| **MBS Item** | **Provider** | **Price per unit**  **(AU$)** | **Number of grams or products** | **Proportion availing** | **Total cost**  **(AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **Initial IVIg product cost and delivery (over first 4 months)** | | | | | | |
| Pre-medication, Antihistamine, Cetirizine hydrochloride 10mg tablet, 30 pack | PBS | $0.9 | 4.00 | 10% | $0.4 | Antihistamine, Cetirizine hydrochloride 10mg tablet, 30 from PBS website. Pack cost divided by 30 |
| Ig product, grams per infusion, $60.41 per gram | NBA-listed | $60.4 | 165.67 | 100% | $10,007.9 | Dosing assumes for 497g per patient per year. At 82.5kg per patient, equivalent to 6.024g per kg. 33% of dose provided in first 4 months |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| GP Consultations | MBS | $34.9 | 1.00 | 100% | $34.9 | MBS 23. Professional attendance by a general practitioner. Assumes 1 GP visit in first 4 months of IVIg |
| Neurologist Specialist Consultations | MBS | $267.9 | 1.00 | 100% | $267.9 | MBS 132. Professional attendance by a consultant. Assumes 1 specialist visit in first 4 months of IVIg |
| Liver function tests, Urea, Electrolytes, Creatinine | MBS | $17.1 | 1.00 | 100% | $17.1 | MBS 66512. Liver function tests, Urea, Electrolytes, Creatinine |
| Full Blood Examination | MBS | $17.0 | 1.00 | 100% | $17.0 | MBS 65070. |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1.00 | 100% | $227.6 | MBS 11018. Neuro muscular electro diagnosis, 4 nerves |
| **Subtotal**  **(4 months)** |  |  |  |  | **$12,056.8** |  |
| **Subtotal (weekly equivalent)** |  |  |  |  | **$709.2** |  |

| **Responder IVIg product cost and delivery (4-12 months)** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Pre-medication, Antihistamine, Cetirizine hydrochloride 10mg tablet, 30 | PBS | $0.9 | 9.20 | 10% | $0.9 | Antihistamine, Cetirizine hydrochloride 10mg tablet, 30 from PBS website. Pack cost divided by 30 |
| Ig product, grams per infusion, $60.41 per gram. | NBA-listed | $60.4 | 331.33 | 100% | $20,015.8 | Up to 0.4 to 1g/kg once every 2-6 weeks. Assumed 4.07g per kg provided over 8-12 months, which generates annual use of 497g per patient. This is the Australian average |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Nurse time for infusion. Assumes 2 hour per administration | Hospital | $85.5 | 18.40 | 100% | $1,573.6 | NSW State Award. 2018. Clinical Nurse, Grade 2, $1,946 per week. Loaded at 1.67. 2 hours per administration. Assumes total of 13.2 administrations per year |
| GP Consultations | MBS | $34.9 | 2.00 | 100% | $69.8 | MBS 23. Professional attendance by a general practitioner |
| Neurologist Specialist Consultations | MBS | $136.3 | 1.00 | 100% | $136.3 | MBS 133. Professional attendance |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11012. Neuro muscular electro diagnosis |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| **Subtotal**  **(8 months)** |  |  |  |  | **$25,167.1** |  |
| **Subtotal (weekly equivalent)** |  |  |  |  | **$719.1** |  |
| **Total IVIG per year** |  |  |  |  | **$37,223.9** |  |

##### Cost of Corticosteroids product and delivery services

The estimated cost of prednisone is shown in Table 72. Medicine costs are taken from the PBS website. Based on loading dose assumptions, the total cost per year is $3,220.4. This includes a medicine cost of $1,452 per year. The cost of medicines in Blackhouse et al. (2010) was $51.19, $43.57, and $39.87 for the first, second and all following 12-week cycles. This amounts to around $200 per year. The medicines cost in Table 72 include proton pump inhibitor therapy, vaccination and prophylaxis with trimethoprim and sulfamethoxazole which increases the cost for the steroid intervention.

Clinical feedback during the evaluation indicated that a patient on steroids is likely to require closer monitoring than does a patient on Ig, due to the risk of steroid side effects, monitoring required for steroid-sparing agents that are commonly used in this setting, and management of complications (e.g. diabetes). Patients on long-term steroids treatment would need regular (at least 6-monthly) reviews for blood pressure, blood sugar, weight, skin integrity, infectious complications and dental review, etc. Patients on steroid-sparing agents also require regular blood tests that need to be monitored.[[29]](#footnote-30)

Additional costs for patients on long-term steroids include proton pump inhibitor therapy (e.g. pantoprazole 40mg daily) for prevention of gastric ulcers, DEXA scan for bone density at initiation and after one year. Ongoing monitoring depends on stability and ongoing steroid use, and possible additional immunisations including annual influenza vaccination and 5-yearly pneumococcal vaccination. Costs for many of these items are included in Table 72.

Table 72 Resources associated with corticosteroids

| **MBS Item** | **Provider** | **Price per unit**  **(AU$)** | **Number** | **Proportion availing** | **Total cost**  **(AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **Corticosteroids No AE—first 4 weeks** | | | | | | |
| Pantoprazole 40mg enteric tablet, 30 | PBS | $13.9 | 28 | 100% | $13.0 | 40mg per day while on treatment PBAC 8007K (40 mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBAC 1917X (5mg tablet, 60). | PBS | $14.3 | 56.00 | 100% | $13.4 | 60mg per day of prednisone for the first 4 weeks of treatment. PBAC 1917X (5mg tablet, 60), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBAC 1916W (25 mg tablet, 30). | PBS | $15.6 | 56.00 | 100% | $29.1 | 60mg per day of prednisone for the first 4 weeks of treatment. PBAC 1916W (25mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Alendronate 70mg + colecalciferol 140ug PBAC 2224C | PBS | $18.2 | 4.00 | 100% | $18.2 | PBAC 2224C. https://www.pbs.gov.au/medicine, 29 April 2019 |
| GP Consultations | MBS | $34.9 | 3.00 | 100% | $104.7 | MBS 23. Professional attendance by a general practitioner at consulting rooms |
| Neurologist Specialist Consultations | MBS | $267.9 | 1.00 | 100% | $267.9 | MBS 132. Professional attendance at consulting rooms or hospital |
| Liver function tests, Urea, Electrolytes, Creatinine | MBS | $17.1 | 1.00 | 100% | $17.1 | MBS 66512. Liver function tests, Urea, Electrolytes, Creatinine |
| Full Blood Examination | MBS | $17.0 | 1.00 | 100% | $17.0 | MBS 65070. Full Blood Examination |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis, 4 nerves |
| **Subtotal** |  |  |  |  | **$707.8** |  |
| **Subtotal weekly** |  |  |  |  | **$176.9** |  |
| **Corticosteroids No AE—4-24 weeks** | | | | | | |
| Pantoprazole 40mg enteric tablet, 30 pack | PBS | 13.88 | 140 | 100% | 64.77 | 40mg per day while on treatment PBAC 8007K (40mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Pneumococcal vaccination, PBS 10210J | PBS | $49.2 | 1 | 100% | $49.2 | Pneumococcal vaccination for patients on prednisolone > 20mg/day for > 4 weeks. https://www.pbs.gov.au/medicine, 29 April 2019 |
| Trimethoprim 160 mg + sulfamethoxazole 800 mg tablet, 10 pack, PBS 2951H | PBS | $13.4 | 546 | 100% | $730.0 | PJP prophylaxis, trimethoprim+sulfamethoxazole 160+800 mg orally, 3 times weekly; continued until 6 weeks’ post cessation for prednisolone patients > 20mg/day for > 4 weeks, https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBS 1917X (5 mg tablet, 60 pack) | PBS | $14.3 | 280.00 | 100% | $66.9 | Steroids would typically be tapered from 1mg/kg/day down to 10mg/day over 6-8 months. Average of 37mg/day over weeks 4-24. PBS 1917X (5 mg tablet, 60), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBS 1916W (25 mg tablet, 30 pack) | PBS | $15.6 | 140.00 | 100% | $72.8 | As above. PBS 1916W (25 mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBS 3152X (1 mg tablet, 100 pack) | PBS | $14.0 | 280.00 | 100% | $39.3 | As above. PBS 3152X (1 mg tablet, 100), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Alendronate 70 mg + colecalciferol 140 microgram, 4 pack, PBS 2224C | PBS | $18.2 | 20.00 | 100% | $90.9 | PBS 2224C, https://www.pbs.gov.au/medicine, 29 April 2019 |
| GP Consultations | MBS | $34.9 | 2.00 | 100% | $69.8 | MBS 23. Professional attendance by a general practitioner at consulting rooms |
| Neurologist Specialist Consultations | MBS | $136.3 | 1 | 1 | $136.3 | MBS 132 for initial then MBS 133 (professional attendance of at least 20 minutes’ duration subsequent to the first attendance) for subsequent visits |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis, 4 or more nerves |
| **Subtotal** |  |  |  |  | **$1,547.5** |  |
| **Subtotal per week** |  |  |  |  | **$77.4** |  |
| **Corticosteroids No AE—following 24-52 weeks** | | | | | | |
| Pantoprazole 40mg enteric tablet, 30 | PBS | $13.9 | 196 | 100% | $90.7 | 40mg per day while on treatment PBAC 8007K (40mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBAC 1917X (5mg tablet, 60). Number of tablets | PBS | $14.3 | 196.00 | 100% | $46.8 | 5mg per day. PBAC 1917X (5mg tablet, 60), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Prednisolone PBAC 1916W (25mg tablet, 30). Number of tablets | PBS | $15.6 | 0.00 | 100% | $0.0 | PBAC 1916W (25mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Alendronate 70mg + colecalciferol 140ug PBAC 2224C | PBS | $18.2 | 28.00 | 100% | $127.3 | PBAC 2224C, https://www.pbs.gov.au/medicine, 29 April 2019 |
| GP Consultations | MBS | $34.9 | 3.00 | 100% | $104.7 | MBS 23. Professional attendance by a general practitioner at consulting rooms |
| Neurologist Specialist Consultations | MBS | $136.3 | 1 | 1 | $136.3 | MBS 116. Professional attendance at consulting rooms or hospital |
| DEXA Scan | MBS | $102.4 | 1.00 | 100% | $102.4 | MBS 12321. Bone densitometry, using dual energy X‑ray absorptiometry |
| Liver Function, Urea, Electrolytes, Creatinine Tests | MBS | $17.1 | 3.00 | 100% | $51.3 | MBS 66512. Liver function tests, Urea, Electrolytes, Creatinine |
| Full Blood Examination | MBS | $17.0 | 3.00 | 100% | $50.9 | MBS 65070. |
| Test for Open Angle Glaucoma | MBS | $40.8 | 1.00 | 5% | $2.0 | MBS 11200. Glaucoma test |
| Test for Diabetes | MBS | $16.8 | 3.00 | 50% | $25.2 | MBS 66841. Quantitation of HbA1c |
| Neuro Muscular Electro Diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis |
| **Subtotal** |  |  |  |  | **$965.0** |  |
| **Total per year** |  |  |  |  | **$3,220.4** |  |

##### Azathioprine used as an immunosuppressant for steroid non-responders

Immunosuppressants are generally used with corticosteroids or following tapering of steroid dosage. They are included in the economic model for corticosteroid non-responders on both arms of the model. The annual cost of an azathioprine regimen, including service delivery, is estimated to be $2,603. Costs are presented in Table 73.

Table 73 Costs of Azathioprine regimen for steroid non-responders

| **MBS Item** | **Provider** | **Price per unit (AU$)** | **Number** | **Proportion availing** | **Total cost (AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| Pantoprazole 40 mg enteric tablet, 30 pack | PBS | $13.9 | 196 | 100% | $90.7 | 40 mg per day while on treatment PBS 8007K (40 mg tablet, 30), https://www.pbs.gov.au/medicine, 29 April 2019 |
| Azathioprine PBS. 2688L (25mg tablet, 100 pack) | PBS | $23.5 | 21.90 | 100% | $514.4 | 150 mg day. 6 tablet per day or 2,190 tablets per year for 25mg tablets. http://www.pbs.gov.au/ medicine/item/2688L. Accessed 29 April 2019 |
| Prednisolone PBS 1917X (5mg tablet, 60) | PBS | $14.3 | 12.17 | 100% | $174.3 | 10mg/day. http://www.pbs.gov.au/medicine/item/2688L. Accessed 29 April 2019 |
| Prednisolone PBS 1916W (25mg tablet, 30) | PBS | $15.6 | 24.33 | 100% | $379.8 | 50mg/day. http://www.pbs.gov.au/medicine/item/2688L. Accessed 29 April 2019 |
| Alendronate 70 mg + colecalciferol 140 microgram, 4 PBS 2224C | PBS | $18.2 | 28 | 100% | $127.3 | PBS 2224C, https://www.pbs.gov.au/medicine, 29 April 2019 |
| GP Consultations. Assumes 4 GP visits per year | MBS | $34.9 | 8.00 | 100% | $279.2 | MBS 23. Professional attendance by a general practitioner |
| Neurologist Specialist Consultations. Assumes 1 specialist visit per year | MBS | $267.9 | 2.00 | 100% | $535.7 | MBS 132. Professional attendance at consulting rooms or hospital, by a consultant physician |
| DEXA Scan | MBS | $102.4 | 1.00 | 100% | $102.4 | MBS 12321. Bone densitometry, using dual energy X‑ray absorptiometry |
| Liver Function, Urea, Electrolytes, Creatinine Tests | MBS | $17.1 | 4.00 | 100% | $68.4 | MBS 66512. Liver function tests, Urea, Electrolytes, Creatinine |
| Full Blood Examination | MBS | $17.0 | 4.00 | 100% | $67.8 | MBS 65070. Blood examination |
| Test for Open Angle Glaucoma | MBS | $40.8 | 1.00 | 5% | $2.0 | MBS 11200. Glaucoma test |
| Test for Diabetes | MBS | $16.8 | 4.00 | 50% | $33.6 | MBS 66841. Quantitation of HbA1c |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis |
| **Annual total** |  |  |  |  | **$2,603.3** |  |
| **Weekly equivalent** |  |  |  |  | **$50.1** |  |

AR-DRG = Australian Refined Diagnosis Related Group, AU$ = Australia dollar, MBS=Medical Benefits Schedule.

##### Corticosteroid AE costs

Costs are included for the first and following years following corticosteroid adverse events. Patients who experience an AE are assumed to take up immunosuppressants. Costs for treating adverse events and the following years of treatment are outlined in Table 74.

Table 74 Corticosteroid adverse event costs

| **MBS Item** | **Provider** | **Price per unit (AU$)** | **Number** | **Proportion availing** | **Total cost (AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **Corticosteroids AEs** | | | | | | |
| **Initial cost Fracture** | | | | | | |
| Average cost per fracture | Health system | $12,902.0 | 1.00 | 100% | $12,902.0 | From Watts, J. et al. 2012. Osteoporosis costing all Australians A new burden of disease analysis – 2012 to 2022. Osteoporosis Australia. Average cost per fracture in 2020. |
| **Total** |  |  |  |  | **$12,902.0** |  |
| **Initial cost Diabetes** | | | | | | |
| Average cost per case of early stage diabetes | Health system | $2,081.0 | 1.00 | 100% | $2,081.0 | From Ying Lee, et al. 2013. Annual direct per person costs were A$1898 for those with normal glucose tolerance to A$2,081 for new diabetes |
| **Total** |  |  |  |  | **$2,081.0** |  |
| **Initial cost Glaucoma** | | | | | | |
| Average cost per case for surgery | Health system | $1,118.0 | 1.00 | 100% | $1,118.0 | Dirani et al. 2011. Australia $1,118.15 for topical application in 50-year-old male. Costs include costs of side effect |
| **Total** |  |  |  |  | **$1,118.0** |  |
| **Initial cost Cataract** | | | | | | |
| Average cost per case for surgery | Health system | $7,000.0 | 1.00 | 100% | $7,000.0 | A cost of $6,218 was taken from Hopkins et al. study and primarily comprises surgery costs. |
| **Total** |  |  |  |  | **$7,000.0** |  |
| **Initial cost Infection** | | | | | | |
| Average cost per case for community-acquired pneumonia treatment | Health system | $7,171.0 | 1.00 | 100% | $7,171.0 | The average Australian Refined Diagnosis Related Group (AR-DRG) for patients admitted for respiratory infections was $7,171 (weighted average of AR-DRGs E62AB). |
| **Total** |  |  |  |  | **$7,171.0** |  |
| **Follow-on Fracture** | | | | | | |
| Average cost per fracture | Health system | $258.0 | 1.00 | 100% | $258.0 | From Watts, J. et al. 2012 |
| Annual cost of medicines regimen | Health system | $2,603.3 | 1.00 | 100% | $2,603.3 | From Azathioprine regimen costing |
| **Weekly equivalent** |  |  |  |  | **$55.0** |  |
| **Follow-on Diabetes, Glaucoma, Cataract, Infection** | | | | | | |
| Annual cost of medicines regimen | Health system | $2,603.3 | 1.00 | 100% | $2,603.3 | From Azathioprine regimen costing |
| **Weekly equivalent** |  |  |  |  | **$50.1** |  |

AR-DRG = Australian Refined Diagnosis Related Group, AU$ = Australia dollar, MBS=Medical Benefits Schedule.

Fracture

The Blackhouse et al. (2010) economic model used a weighted cost per fracture noting that the most common sites of osteoporosis-related fractures were in the vertebra, followed by the hip and forearm. Average fracture cost ranged from $3,926 in the first year for 40-year olds, to $10,880 for those age 70 years and older (estimates in Australia in 2012 from Watts et al, 2012). The cost decreased to $63 per year (40-year-old) to $744 (70+ years) in the following year. The total cost of osteoporosis and osteopenia in Australians over 50 years of age was $2.75 billion. Costs included ambulance services, hospitalisations, emergency department and outpatient services, rehabilitation, aged care and community services. Total direct costs were $12,902 per fracture. Patients are assumed to take-up immunosuppressants for the remaining period of the projection once a steroid AE has occurred.

Diabetes mellitus

The cost of diabetes was estimated using the Ontario Diabetes Model (O'Reilly et al. 2006) in the Blackhouse et al. (2010) study. First year costs ranged from $12-$27 and second-year costs $24-$341 per case of diabetes. Costs for diabetes cases were recently estimated in Australia, with the annual direct per person cost (Ying Lee, et al. 2013) being AU$1898 for those with normal glucose tolerance to AU$2,081 for those with newly diagnosed diabetes. Costs were substantially higher in diabetes patients with macrovascular complications. A cost of $2,081 with new diabetes is included as the AE cost in this study. Patients are assumed to take-up immunosuppressants for the remaining period of the projection once a steroid AE has occurred.

Cataract

Blackhouse et al. (2010) used the cataract case cost of $Canadian 6218 from the North American study by Hopkins et al. 2008. Resources were mainly associated with surgery. In 2009, total Australian health system expenditure on disorders of the eye and adnexa were estimated at $A 2.98 billion or $A 5,183 per person with vision loss aged over 40 (Centre for Eye Research Australia and Access Economics 2004 and 2009). A cost of $A7,000 is included as the AE cost in this CIDP Ig study for 2019. Patients are assumed to take-up immunosuppressants for the remaining period of the projection once a steroid AE has occurred.

Glaucoma

Blackhouse et al. (2010) estimates for glaucoma ($152) were based on those used by Bae et al. 2003, Gottlieb et al. 1983 and Stewart et al. 1997. Resource utilisation and direct costs associated with glaucoma progression have been estimated more recently in Europe (Traverso et al. 2005). Costs were calculated for 194 patients stratified by disease severity using a six-stage glaucoma staging system based on static threshold visual field parameters. The direct cost of treatment increased by an estimated €86 for each incremental step, ranging from €455 per person per year for stage 0 to €969 per person per year for stage 4 disease.

Data outlining the economic impact of glaucoma in Australia is limited, but a 2011 study by the Centre for Eye Research Australia (CERA) estimated that health system costs related to primary open-angle glaucoma could reach $A 784 million by 2025 (Dirani et al. 2011). Treatment cost was estimated at $A 1,118.15 for 50-year-old male. Costs of side effects for patients on b blockers were included, and the overall cost is included in the CIDP model.

Infection

Costs in Blackhouse et al. (2010) that related to steroid AE serious infection ($Canadian 24,334) were based on the estimates used by Bae et al. 2003 with a risk of infection of 0.0035. Community-acquired pneumonia can be managed with oral antibiotics at home, with the cost of home care being estimated around $A1,000 (Rhew et a; 1998). This cost included transport, staff time, equipment, pharmaceuticals and support services (administrative, laboratory and radiology costs) for each patient. The Canadian CIDP model included costs for serious infection (generally hospitalised). The average Australian Refined Diagnosis Related Group (AR-DRG) for patients admitted for respiratory infections was $7,171 (weighted average of AR-DRGs E62AB). A cost of $7,171 is included in the economic model.

Immunosuppressants non-response and disabled

Bamrungsawad et al. (2016) included annual outpatient and inpatients cost for pre-disabled and disabled CIDP patients from medical records in Thailand. Pre-disabled and disabled CIDP cost data are not readily available for Australian patients. Equipment, nursing, community services and alterations to home costs reported for mild, moderate and severe patients in the Palmer et al. (2013) economic impact of multiple sclerosis in Australia in 2010 study are used for pre-disabled CIDP (equivalent to mild multiple sclerosis) and moderate/severe for disabled CIDP patients. Health service costs (GP visits, specialist visits and testing) in pre-disabled and disabled patients are assumed to the same as for CIDP patients availing immunosuppressants. Costs for immunosuppressantnon-responders and disabled states are summarised in Table 75.

Table 75 Azathioprine immunosuppressant non-response and disabled costs

| **Item** | **Provider of resource** | **Price per unit (AU$)** | **Number of grams, products or services** | **Proportion availing service / product** | **Total cost**  **(AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **immunosuppressant non-responder (pre-disabled)** | | | | | | |
| Immunosuppressant health services | MBS | $1,316.7 | 1.00 | 100% | $1,316.7 | See immunosuppressants Costs |
| Equipment, nursing, community services, and alterations to home for pre-disabled non-responders | DSS, community | $2,155.0 | 1.00 | 100% | $2,155.0 | Bamrungsawad et al. (2016) included annual pre-disabled outpatient service cost of US$1363 from medical records. Inpatient costs were estimated to be US$ 528 per year. Mild MS costs in Palmer et al. (2013) for equipment, nursing, community services, and alterations to home were $A 1,826 in 2010. The 2019 equivalent is $A 2,155 |
| **Annual total** |  |  |  |  | **$3,471.7** |  |
| **Weekly equivalent** |  |  |  |  | **$66.8** |  |
| **Disabled CIDP patient** | | | | | | |
| Health services | MBS | $1,316.7 | 1.00 | 100% | $1,316.7 | Medical services similar to immunosuppressants |
| Equipment, nursing, community services, and alterations to home for disabled non-responders | DSS, community | $6,995.0 | 1.00 | 100% | $6,995.0 | Bamrungsawad et al. (2016) included annual disabled outpatient service cost of US$1402 and US $528 for inpatients from medical records. Moderate and severe MS costs in Palmer et al. (2013) are used for equipment, nursing, community services and alterations to home costs assuming 15% are severe. Using this proportion, they were $A 5,928 in 2010. The 2019 equivalent is $A 6,995. |
| Nursing home | DSS, community | $5,162.2 | 1.00 | 100% | $5,162.2 | CIDP disabled person home and nursing home care were estimated at US$ 403 and 1137 per year in Bamrungsawad et al. (2016). Palmer et al. (2013) moderate and severe nursing home costs for Australian MS patients are inflated to 2019 |
| **Annual total** |  |  |  |  | **$13,473.9** |  |
| **Weekly equivalent** |  |  |  |  | **$259.1** |  |

Abbreviations: AE = adverse event, CIDP = Chronic Inflammatory Demyelinating Polyneuropathy, MS = Multiple Sclerosis

#### Utility values

The derivation of utilities was outlined in Section C and presented here in Table 76. Given the uncertainties they are subjected to a range of sensitivity analyses presented at the end of Section D Table 76

Table 76 Utility value used in the model

| **Health state** | **Utility/ Disutility** | **Nature of estimate** | **Source** | **Utility values used in sensitivity analysis** |
| --- | --- | --- | --- | --- |
| Ig Initial Treatment | -0.120 | McCrone et al. (2004) reported these changes using changes in quality of life using the EuroQol EQ-5D instrument from the 6-week Hughes trial | McCrone et al. (2003) | 0/+10% |
| Ig Responder | -0.120 | McCrone et al. (2003) | 0/+10% |
| Corticosteroids  (no adverse events) | -0.240 | Cross-sectional analysis from the south-east of England | Mahdi-Rogers et al. (2014) | 0/+10% |
| Corticosteroids Non-Response + Azathioprine | -0.240 | Assumed to be the same as steroid responder | Study Assumption | 0/+10%. |
| Fracture | -0.377 | The non-hip fracture multiplier of 0.84 was applied to a general population utility of 0.85 and added to steroid disutility. | Karnon et al. (2016) | 0/+10%. |
| Diabetes | -0.240 | The disutility in the Canadian model is added too steroid CIDP patient disutility. The lower value -0.000160 from the Canadian study is combined with steroid disutility to generate a disutility of -0.240160 | Blackhouse et al. (2010) disutilities for steroid AEs | 0/+10%. |
| Glaucoma | -0.301 | Blackhouse et al. (2010) disutilities for steroid AEs of 0.061. It is added to steroid disutility | Blackhouse et al. (2010) | 0/+10%. |
| Cataract | -0.330 | The disutility in Abell and Vote 2014 is added to steroid disutility | Abell and Vote (2014) | 0/+10%. |
| Infection | -0.279 | A disutility of -0.04 is added to steroid patient disutility | Blackhouse et al. (2010) | 0/+10%. |
| Azathioprine non-responder (pre-disabled) | -0.240 | In the absence of utility data for this state, assumed to be the same as Corticosteroids Non-Response + Azathioprine. | Study Assumption | 0/+10% |
| Disabled | -0.360 | CIDP disabled utility is estimated to be 0.49, or a disutility of -0.36 for a general population 50-year-old utility of 0.85 | Assumption based on Ahmad et al. (2017). utility weights for Australian Multiple Sclerosis patients. | 0/+10% |

Abbreviations: AE = adverse event, CIDP = Chronic Inflammatory Demyelinating Polyneuropathy

## Results of the Economic Evaluation

### D.5.1. Health Care Costs by Resource Type

The costs per patient for Ig and corticosteroids are presented for the trial period analysis in Table 77 and Table 78 for the extrapolated 10-year horizon. Costs are averages generated for one patient in the model. It is evident that the cost of Ig product and its delivery are the dominant costs for Ig, and resources associated with corticosteroids AEs are minor.

Table 77 Health care costs by resource type for IVIg trial analysis (average per patient)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **IVIg** | **Corticosteroids** | **Incremental Cost** |
| **Trial period (6 months)** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | $16,624 | $0 | $16,624 |
| Corticosteroids no AE | $356 | $2,150 | -$1,794 |
| Fracture | $6 | $74 | -$68 |
| Diabetes mellitus | $2 | $28 | -$26 |
| Cataract | $3 | $40 | -$37 |
| Glaucoma | $0 | $1 | -$1 |
| Infection | $1 | $12 | -$11 |
| Corticosteroid non-responder +azathioprine | $0 | $4 | -$4 |
| Azathioprine non-responder | $1 | $49 | -$48 |
| Disabled | $0 | $13 | -$13 |
| **Total** | **$16,992** | **$2,371** | **$14,622** |

Table 78 Health care costs by resource type for IVIg 10-year extrapolated analysis (average per patient)

|  |  |  |  |
| --- | --- | --- | --- |
| **10-years** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | $193,328 | $0 | $193,328 |
| Corticosteroids no AE | $3,873 | $7,827 | -$3,954 |
| Fracture | $430 | $886 | -$456 |
| Diabetes mellitus | $219 | $452 | -$233 |
| Cataract | $245 | $506 | -$261 |
| Glaucoma | $6 | $12 | -$6 |
| Infection | $76 | $158 | -$81 |
| Corticosteroid non-responder +azathioprine | $15 | $32 | -$17 |
| Azathioprine non-responder | $2,154 | $4,640 | -$2,486 |
| Disabled | $19,153 | $43,507 | -$24,354 |
| **Total** | **$219,499** | **$58,020** | **$161,480** |

Abbreviations: IVIg = Intravenous Ig, AE = adverse event

### D.5.2. Health Outcomes per Patient by Step and by Health State

Average outcomes (per patient) generated by the economic model are estimated for life years (LY) and Quality-Adjusted Life Years (QALY). Table 79 presents the analysis for the 6-month trial period and Table 80 shows the 10-year extrapolated analysis. It is evident that most QALYs are generated in the Ig-responder state for the Ig arm, while most in the corticosteroid arm are associated with the corticosteroids no AE state. As in the resource use analysis, corticosteroids no AE states have limited impact on model results. The difference between the utilities assumed for the Ig responder and corticosteroid no-AE states is a key driver of estimated health benefit. This was estimated to be 0.12 in favour of Ig for the base analysis. It is included in the sensitivity analysis and shown to have a significant impact on model results.

Table 79 Average patient health outcomes by health state and by outcome measure for trial analysis

| **Trial period (6 months)** | **Ig** | **Corticosteroids** | **Incremental** |
| --- | --- | --- | --- |
| **# Life Years (LYs)** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | 0.45 | 0.00 | 0.45 |
| Corticosteroids no AE | 0.05 | 0.48 | -0.43 |
| Fracture | 0.00 | 0.00 | 0.00 |
| Diabetes mellitus | 0.00 | 0.00 | 0.00 |
| Cataract | 0.00 | 0.00 | 0.00 |
| Glaucoma | 0.00 | 0.00 | 0.00 |
| Infection | 0.00 | 0.00 | 0.00 |
| Corticosteroid non-responder +azathioprine | 0.00 | 0.00 | 0.00 |
| Azathioprine non-responder | 0.00 | 0.02 | -0.02 |
| Disabled | 0.00 | 0.00 | 0.00 |
| **Total** | **0.50** | **0.50** | **0.00** |
| **# QALYs** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | 0.33 | 0.00 | 0.33 |
| Corticosteroids no AE | 0.03 | 0.29 | -0.26 |
| Fracture | 0.00 | 0.00 | 0.00 |
| Diabetes mellitus | 0.00 | 0.00 | 0.00 |
| Cataract | 0.00 | 0.00 | 0.00 |
| Glaucoma | 0.00 | 0.00 | 0.00 |
| Infection | 0.00 | 0.00 | 0.00 |
| Corticosteroid non-responder +azathioprine | 0.00 | 0.00 | 0.00 |
| Azathioprine non-responder | 0.00 | 0.01 | -0.01 |
| Disabled | 0.00 | 0.00 | 0.00 |
| **Total** | **0.36** | **0.30** | **0.05** |

Abbreviations: LY = life year; QALY = quality-adjusted life year

Table 80 presents the average outcomes (per patient) generated by the economic model for LYG or QALY over the 10-year period. A greater number of QALYs are generated in the corticosteroid AE states for the steroid arm, however, they are a relatively small proportion (<10%) of all QALYs.

Table 80 Health outcomes for 10-year analysis (per patient)

| **10-year** | **Ig** | **Corticosteroids** | **Incremental** |
| --- | --- | --- | --- |
| **# Life Years (LYs)** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | 5.20 | 0.00 | 5.20 |
| Corticosteroids no AE | 2.44 | 5.02 | -2.58 |
| Fracture | 0.02 | 0.04 | -0.02 |
| Diabetes mellitus | 0.04 | 0.08 | -0.04 |
| Cataract | 0.02 | 0.04 | -0.02 |
| Glaucoma | 0.00 | 0.00 | 0.00 |
| Infection | 0.01 | 0.01 | -0.01 |
| Corticosteroid non-responder +azathioprine | 0.01 | 0.01 | -0.01 |
| Azathioprine non-responder | 0.62 | 1.34 | -0.72 |
| Disabled | 1.42 | 3.23 | -1.81 |
| **Total** | **9.77** | **9.77** | **0.00** |
| **# QALYs** | **Undiscounted** | **Undiscounted** | **Undiscounted** |
| Ig | 3.80 | 0.00 | 3.80 |
| Corticosteroids no AE | 1.49 | 3.06 | -1.57 |
| Fracture | 0.01 | 0.02 | -0.01 |
| Diabetes mellitus | 0.02 | 0.05 | -0.03 |
| Cataract | 0.01 | 0.02 | -0.01 |
| Glaucoma | 0.00 | 0.00 | 0.00 |
| Infection | 0.00 | 0.01 | 0.00 |
| Corticosteroid non-responder +azathioprine | 0.00 | 0.01 | 0.00 |
| Azathioprine non-responder | 0.38 | 0.82 | -0.44 |
| Disabled | 0.70 | 1.58 | -0.89 |
| **Total** | **6.41** | **5.57** | **0.85** |

Abbreviations: LY = life year; QALY = quality-adjusted life year

### D.5.3. Incremental Costs and Effectiveness

The incremental cost and the incremental effectiveness of IVIg versus corticosteroids for an average patient is presented in Table 81. The ICER is presented as the incremental cost of achieving an additional QALY. The trial period ICER is $269,038 per QALY at average Australia Ig use (497g) and $742,576 per QALY at Ig use of 1,430g per patient per year. The 10-year ICER is $197,472 per QALY at average Australia Ig use (497g) and $549,897 per QALY at Ig use of 1,430g per patient per year

Table 81 Incremental cost-effectiveness ratio of IVIg versus corticosteroids (average patient)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Cost** | **Incremental cost** | **Effectiveness (QALYs)** | **Incremental effectiveness** | **ICER** |
| **Trial period** |  |  |  |  |  |
| Ig, 497g per patient per year | $16,808 | $14,459 | 0.35 | 0.05 | $269,038 |
| Ig, 1,430 g per patient per year | $42,257 | $39,907 | 0.35 | 0.05 | $742,576 |
| Corticosteroids | $2,349 | NA | 0.30 | NA | NA |
| **10-year** |  |  |  |  |  |
| Ig, 497g per patient per year | $174,469 | $130,714 | 5.10 | 0.66 | $197,472 |
| Ig, 1,430 g per patient per year | $407,752 | $363,997 | 5.10 | 0.66 | $549,897 |
| Corticosteroids | $43,755 | NA | 4.44 | NA | NA |

ICER = Incremental Cost-Effectiveness Ratio, NA = Not applicable, QALY = quality-adjusted life year

## Sensitivity analyses

Sensitivity analyses for the 10-year extrapolation analyses are undertaken. Only limited incremental clinical benefits accrue during the trial period, as patients transition to non-responder and adverse event health states after the first six months of Ig treatment. Sensitivity analyses are presented using the 10-year extrapolation at average Australian Ig use of 497g per year. Parameters included in sensitivity analyses include background assumptions (age gender, discount rate and weight), unit costs, transition probabilities, utilities and odds ratio for steroid adverse event state mortalities. Results are presented in Table 82, followed by discussion.

Table 82 Sensitivity analysis for IVIg versus corticosteroids 10-year analysis

| **Parameter** | **Analysis** | **Incremental cost** | **Incremental effect** | **ICER** |
| --- | --- | --- | --- | --- |
| ***10-year extrapolation*** | Base | $130,714 | 0.66 | $197,472 |
| ***Background assumptions*** | | | | |
| Years of follow-up (10 years) | Trial duration | $14,459 | 0.05 | $269,038 |
| 5-year | $81,083 | 0.34 | $236,378 |
| Starting age (55 years) | 40 years | $132,414 | 0.67 | $197,001 |
| 70 years | $123,862 | 0.62 | $199,593 |
| Male (49%) | 40% | $130,829 | 0.66 | $197,439 |
| 60% | $130,580 | 0.66 | $197,510 |
| Average weight (83kg) | 50 kg | $81,760 | 0.66 | $123,516 |
| 60 kg | $96,823 | 0.66 | $146,272 |
| 70 kg | $111,886 | 0.66 | $169,028 |
| 90 kg | $142,011 | 0.66 | $214,539 |
| Discount rate (5%) | 0% | $161,480 | 0.85 | $190,986 |
| 7% | $121,115 | 0.61 | $200,034 |
| ***Ig delivery costs*** | | | | |
| Ig price ($60.41 per g) | $140.18 | $294,807 | 0.66 | $445,370 |
| $44.94 | $98,891 | 0.66 | $149,397 |
| $94.51 | $200,860 | 0.66 | $303,443 |
| SCIg | Same dose as IV | $110,458 | 0.66 | $166,870 |
| 120% of IV dose | $135,311 | 0.66 | $204,417 |
| Nurse cost per infusion | +10% | 131,679 | 0.66 | 198,930 |
| -10% | 129,749 | 0.66 | 196,014 |
| Trial IVIG dose for first 4 months (471g, 33% of 1,430 g per patient per year), then average Australian dose (equivalent to 497g per patient per year) | 802g in Year 1, 497g following years | $151,831,986 | 660.22 | $229,970 |
| Maintenance IVIG dose | 5% | $136,359 | 0.66 | $206,000 |
| -5% | $125,069 | 0.66 | $188,944 |
| 10% | $142,004 | 0.66 | $214,527 |
| -10% | $119,425 | 0.66 | $180,417 |
| 20% | $153,293 | 0.66 | $231,582 |
| -20% | $108,135 | 0.66 | $163,362 |
| ***Unit costs*** | | | | |
| Corticosteroids no AE | +10% | $130,360 | 0.66 | $196,937 |
| -10% | $131,068 | 0.66 | $198,007 |
| Fracture | +10% | $130,660 | 0.66 | $197,390 |
| -10% | $130,768 | 0.66 | $197,553 |
| Diabetes mellitus | +10% | $130,703 | 0.66 | $197,456 |
| -10% | $130,725 | 0.66 | $197,488 |
| Cataract | +10% | $130,691 | 0.66 | $197,437 |
| -10% | $130,737 | 0.66 | $197,507 |
| Glaucoma | +10% | $130,708 | 0.66 | $197,463 |
| -10% | $130,720 | 0.66 | $197,481 |
| Infection | +10% | $130,707 | 0.66 | $197,462 |
| -10% | $130,721 | 0.66 | $197,482 |
| Disability | +10% | $128,939 | 0.66 | $194,791 |
| -10% | $132,489 | 0.66 | $200,153 |
| ***Utilities*** | | | | |
| Ig disutility | Ig and steroid the same | $130,714 | 0.16 | $807,898 |
| 0% | $130,714 | 1.16 | $112,483 |
| 90% | $130,714 | 0.71 | $183,600 |
| Corticosteroids no AE disutility | 0% | $130,714 | 0.14 | $948,762 |
| 90% | $130,714 | 0.61 | $214,454 |
| Fracture disutility | 0% | $130,714 | 0.66 | $199,460 |
| 90% | $130,714 | 0.66 | $197,669 |
| Diabetes mellitus disutility | 0% | $130,714 | 0.65 | $199,968 |
| 90% | $130,714 | 0.66 | $197,719 |
| Cataract disutility | 0% | $130,714 | 0.66 | $197,590 |
| 90% | $130,714 | 0.66 | $197,484 |
| Glaucoma disutility | 0% | $130,714 | 0.66 | $199,006 |
| 90% | $130,714 | 0.66 | $197,624 |
| Infection disutility | 0% | $130,714 | 0.66 | $197,904 |
| 90% | $130,714 | 0.66 | $198,057 |
| Disability disutility | 0% | $130,714 | 0.19 | $696,121 |
| 90% | $130,714 | 0.61 | $212,709 |
| Disable stroke  -0.39 | $130,714 | 0.79 | $164,777 |
| ***Transition probabilities*** | | | | |
| 4-month Ig responder (61%) | +10% | $142,771 | 0.72 | $198,012 |
| -10% | $118,657 | 0.60 | $196,826 |
| Weekly probability based on Ig responder weekly relapse (25.15% at 1 year) | 10% | $144,551 | 0.73 | $198,262 |
| 20% | $135,538 | 0.69 | $197,766 |
| 50% | $105,170 | 0.54 | $195,460 |
| 100% | $11,972 | 0.08 | $141,681 |
| Steroid responder | +10% | $129,871 | 0.67 | $193,882 |
| -10% | $131,593 | 0.65 | $201,304 |
| Steroid adverse events | 0% | $135,012 | 0.63 | $215,420 |
| Wilson et al | $131,752 | 0.65 | $201,540 |
| Immunosuppressants non-response and Disability | No Immunosuppressants non-response | $145,510 | 0.53 | $274,132 |
| No probability of disability | $143,888 | 0.50 | $285,559 |
| ***Mortality odds ratio*** | | | | |
| Fracture, diabetes and infection | 0% | $130,714 | 0.66 | $197,473 |

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY, = quality-adjusted life year.; AE = adverse event

* A base projection of 10 years is used in the economic model. This is longer than the base time frame used in Canada by Blackhouse et al. (2010). Decreasing the extrapolation to 5 years is undertaken in a sensitivity analysis. This increases the ICER to $236,378 per QALY. The average age of entry in the baseline is 55 years based on participants in key trials (range 48-55 years). Changes in the assumed gender balance and starting age have a limited impact on the estimated ICER.
* The cost of Ig is a key cost driver of the model. Consequently, changes in assumed patient weight have a large impact on the estimated ICER. Most economic studies include a weight of 75kg. But Australian general population weights are higher than this. For example, the average Australian weight at 50 years of age is 90.4 kg for males and 75.1 kg for females (Australian Bureau of Statistics[[30]](#footnote-31)). The estimate of 497g of Ig per patient per year equates to 6.02g/kg for an average Australian CIDP patient weighing 82.5kg (NBA data 2017-18). The model was not run for children due to the absence of clinical data for this age group. Based on a similar dose per kg and clinical outcomes in adults, the ICER decreases to $89,383 per QALY for a patient weighing 35 kg (average weight for 8- to 11-year old in 2017-18 ABS Health survey).
* A base discount rate of 5% was used. Higher and lower rates of 0% and 7% were also included. Changes in discount rate have limited impact, although the cumulative costs associated with disability toward the end of the projection are less using the higher discount rate of 7%.
* The cost of Ig product accounts for 80%+ of health cost resources. Changes in assumed dose per kg or product price are key drivers of cost-effectiveness. The base cost of Ig assumes a price per gram of $60.41. This is varied by high ($140.81), low ($44.94) and a weighted value of $94.51. Inclusion of Ig costs of this range vary the ICER from $445,370 to $149,397 per QALY for IVIg compared to steroids at the average Australia dose per patient.
* The Blackhouse et al. (2010) study estimated a 10-year ICER of $Canadian $670,396 ($Australian 732,344 at current exchange rate of 1.09) per QALY gained. It included a base scenario of initial treatment provided as two 1g/kg doses and maintenance treatment as a single 1g/kg dose every three weeks. Correspondingly, the ICER is more than three times that of $197,472 per QALY estimated in this economic study. The assumed dosing in Blackhouse et al. (2010) is higher than that in Section D (497g Ig per person in Australia from NBA reporting).
* Sensitivity analysis was included in the Blackhouse et al. (2010) Canadian economic study where patients received 0.4mg/kg every 3 weeks and 0.4mg/kg every 6 weeks for maintenance, resulting in ICERs of $Canadian 181 to 314 thousand per QALY over 5-years. The cost for the Ig arm was $32,000-$56,000, which is more in line with the results of this study where the five-year ICER is estimated to be $A236,378 per QALY. Varying other Ig treatment costs, such as nurse time for Ig delivery had limited impact on estimated ICER. Similarly, unit costs for steroids, immunosuppressants and AEs were also varied and have limited impact on the estimated ICER.
* SC Ig is costed in Table 70. Based on a patient of 82.5kg and the same weighted Ig cost of $60.41/g, SCIg had an annual total cost per year of $33,136. The cost for SCIg is around $4,000 less than for IVIg [REDACTED].   
  If the cost of SCIg delivery is substituted for IVIg and a similar clinical outcome assumed, the ICER for Ig compared to steroids is more cost-effective, i.e. at 10 years it decreases to $166,870 per QALY as a result of reduced hospital admission and adverse event costs associated with SCIg.

Table 83 Resources associated with SCIg

| **Item** | **Provider** | **Price per unit (AU$)** | **Number per period** | **Proportion availing** | **Total cost (AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **Initial SCIg product cost and delivery (over first 4 months)** | | | | | | |
| Nurse time for self-administration education. 2 x 2.5 hours in first 4 months of SCIg | Hospital | $85.5 | 5.00 | 100% | $427.6 | NSW State Award. 2018. Clinical Nurse, Grade 2, $1,946 per week. Loaded at 1.67. |
| Assumed same as IV price of $60.41 per g | NBA | $60.4 | 165.67 | 100% | $10,007.9 | Dosing assumed for 497g per patient per year. 6.024g per kg |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| GP Consultations. Assumes 2 GP visits in first 4 months of IV Ig | MBS | $34.9 | 2.00 | 100% | $69.8 | MBS 23. Professional attendance by a general practitioner |
| Neurologist Specialist Consultations. | MBS | $267.9 | 1.00 | 100% | $267.9 | MBS 132. Professional attendance at consulting rooms or hospital. Assumes 1 specialist visit in first 4 months |
| Liver function tests, Urea, Electrolytes, Creatinine | MBS | $17.1 | 1.00 | 100% | $17.1 | MBS 66512. Liver function tests, Urea, Electrolytes, Creatinine |
| Full Blood Examination | MBS | $17.0 | 1.00 | 100% | $17.0 | MBS 65070. |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis |
| **Subtotal,**  **(4 months)** |  |  |  |  | **$11,434.8** |  |
| **Subtotal**  **(weekly equiv.)** |  |  |  |  | **$672.6** |  |
| **Responder SCIg product cost and delivery (4-12 months)** | | | | | | |
| Assumed same as IV price of $60.41 per g | NBA-listed | $60.4 | 331.33 | 100% | $20,015.8 | Dosing assumed for 497g per patient per year. 6.024g per kg |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| GP Consultations (MBS 23) | MBS | $34.9 | 2.00 | 100% | $69.8 | MBS 23. Professional attendance by a general practitioner |
| Neurologist Specialist Consultations | MBS | $136.3 | 1.00 | 100% | $136.3 | MBS 133. Professional attendance at consulting rooms or hospital |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| **Subtotal**  **(8 months)** |  |  |  |  | **$21,701.0** |  |
| **Total per year** |  |  |  |  | **$33,135.8** |  |

* Once patients become resistant to steroids or suffer steroid-related AEs, they are assumed to switch to immunosuppressants. Plasma exchange is also used following corticosteroids and involves exchange of three to five litres of plasma to reduce IgG levels by 45%. To achieve adequate venous access, patients may have large-bore peripheral cannulation or insertion of a central venous catheter, or implantation of an arteriovenous fistulae for longer-term treatment, such as required for CIDP patients. None of the RCTs included in the clinical evidence repeated plasma exchange. Case series data reported by Choudray (1995) indicated 10-70 exchanges were undertaken over 8-60 months for patients requiring extended treatment, however, 16 of 23 responders did not need long term treatment. Codron (2017) indicated that 11 patients had 368 sessions over approximately 9.5 years, with a median of 28 sessions per patient, equating to around 3 per year. The costs of plasma exchange are outlined in Table 84 for five procedures over 1 year. Substitution of plasma exchange for immunosuppressants decreases the estimated ICER to $180,308 per QALY. At around $8,210.9 per year, plasma exchange is three times the cost of immunosuppressants.

Table 84 Costs of plasma exchange

| **Item** | **Provider** | **Price per unit (AU$)** | **Number per period** | **Proportion availing** | **Total cost (AU$)** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| **Plasma Exchange** | | | | | | |
| Albumex, 4% albumin, 40 ml/kg | NBA | $67.6 | 33.00 | 100% | $2,231.5 | 82.5 kg patient × 5 procedures = 15,000 ml = 33 vials of 500 ml 4% albumin. https://www.blood.gov.au/national-product-list |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Nurse time for exchange. Assumes 5 exchanges x 2 hour per exchange | Hospital | $85.5 | 10 | 100% | $855.2 | NSW State Award. 2018. Clinical Nurse, Grade 2, $1,946 per week. Loaded at 1.67. |
| Therapeutic haemapheresis | MBS | $136.7 | 5.00 | 100% | $683.3 | MBS Item 13750 Removal of plasma or cellular (or both) elements of blood, utilising continuous or intermittent flow techniques |
| Insertion of non-tunnelled central venous catheter | MBS | $857.3 | 1.00 | 100% | $857.3 | MBS Item 34112, Arteriovenous fistula of an extremity, dissection and ligation |
| TPE equipment amortization | Hospital costs | $52.6 | 5.00 | 100% | $263.0 | Winter et al. (2011) Included cell separator system, blood warmer and medical recliner chair, with useful lives of 6, 7 and 10 years (200 procedures per year) and costs of $59,320, $3,840 and $829 |
| Service contract amortization | Hospital costs | $22.0 | 5.00 | 100% | $110.0 | $4,450 annually per cell separator system (CaridianBCT device in 2011); assumes 200 procedures per year per device. Winter et al. 2011 |
| GP Consultations. Assumes 4 GP visits per year | MBS | $34.9 | 4.00 | 100% | $139.6 | MBS 23. Professional attendance by a general practitioner at consulting rooms (other than a service to which another item in the table applies), lasting less than 20 minutes |
| Neurologist Specialist Consultations. Assumes 1 specialist visit per year | MBS | $267.9 | 1.00 | 100% | $267.9 | MBS 132. Professional attendance at consulting rooms or hospital |
| Neurologist Specialist Consultations (MBS 133). | MBS | $136.3 | 2.00 | 100% | $272.5 | MBS 132 for initial then MBS 133 (professional attendance of at least 20 minutes’ duration subsequent to the first attendance) for subsequent visits |
| Neuro muscular electro diagnosis | MBS | $227.6 | 1 | 1 | $227.6 | MBS 11018. Neuro muscular electro diagnosis |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| **Annual total** |  |  |  |  | **$8,210.9** |  |
| **Weekly equivalent** |  |  |  |  | **$157.9** |  |

* Patients who do not respond to steroids and immunosuppressants have the potential to become disabled. This potential was modelled in the Thai study of Bamrungsawad et al. (2016), which included a probability of 0.098 for disability among non-responsive patients and costs of care in the hospital and at home. A utility of -0.178 was included for disabled patients, however, the survey was based on four patients. The 10-year extrapolated analysis includes the progression of resistant and contraindicated steroid patients to disability. The disutility included in the analysis is based on a survey of MS patients in Australia. The disutility is far less than that of Bamrungsawad et al. (2016), and the estimated ICER is higher.
* A sensitivity analysis was included in Table 82 using disabling stroke utility of 0.39 from studies such as Wu et al. (2014) and Shah and Gage (2011) as a proxy for disabled CIDP quality of life. This represents a disutility of around -0.46 for a general population utility of 0.85. Inclusion of this disutility has a large impact on the estimated ICER. It decreases to $164,777 per QALY gained.
* Transition probabilities are varied for Ig response, steroid response and steroid-related AEs. The odds ratios associated with each of the AEs are also varied. As only limited numbers of patients are estimated to transition to steroid-related AEs, variation in these odds ratios has limited impact on economic results. Steroid adverse event rates are also taken from the Wilson et al. (2007) study. Inclusion of these annual rates of 0.42%, 0.41%, 1.14%, 0.50%, and 1.20% for fracture, diabetes, cataract, glaucoma and infection probability has limited impact on the estimated ICER.
* Utilities are specified for Ig responders, steroids and steroid AE patients. There is uncertainty around these estimates as they are derived from trials with limited follow-up and small patient numbers. The difference between steroids and Ig of 0.12 was taken from Hughes et al. (2001) which followed-up patients for six weeks. More recent studies, such as that by Nobile-Orazio and colleagues, found no difference in SF-36 gain between steroid and Ig patients. This study is confounded by intention-to-treat analysis, with high non-response on the steroid arm. A sensitivity analysis is included where utility values are changed by 10%. It is evident the ICER varies considerably with changes in utility assumptions.
* The economic model is based on assumptions derived from Ig versus steroid comparison trials that included steroid-resistant and -responsive patients. The cost-effectiveness of Ig in these mixed patient groups is likely to be less than if Ig was used in steroid-resistant patents alone. For steroid resistant patients alone[[31]](#footnote-32), an ICER of $125,260 per QALY gained is estimated.

Key results from the sensitivity analysis are summarised in Table 85.

Table 85 Key drivers of the economic model

| Description | Method/Value | Impact |
| --- | --- | --- |
| Utilities for Ig responders and steroids | The utility gain of 0.12 employed in Blackhouse et al. (2010) was used to estimate the difference between Ig and steroids. It was based on the small study by McCrone et al. (2003). A more recent study by Nobile-Orazio found no utility gain, however there were high drop-outs in study arms, which confound generalisability of results. | Large. Decreasing this value has a large impact on estimated ICER. The Reference Group noted that that in McCrone et al. (2003) health-related quality of life (or the utility difference) was not significantly different for Ig compared to steroids |
| Cost of Ig | The cost of Ig accounts for more than 80% of intervention costs. Correspondingly, variation in this cost has a large impact on the estimated ICER. | Large. Lower Ig price reduces the ICER. Sensitivity analyses are undertaken using high and low Ig costs of $140.18 and $44.94 per gram. The 10-year ICER varies between $445,370 and $149,397 |
| Ig dosing | Induction and maintenance dosing frequencies and grams per dose have a large impact on the estimated ICER. The grams of Ig included in this study of 497 g are less than that of Blackhouse et al. (2010). | Large. The estimated ICER of $197,472 per QALY in this analysis is far less than Blackhouse et al. (2010) of $Canadian 670,396 per QALY ($Australian 732,344 at current exchange rate of 1.09) gained due to lower Ig use. Australian average Ig use of 497g per patient per year versus initial treatment provided as two 1g/kg doses and maintenance treatment as a single 1g/kg dose every three weeks in the Canadian study. |
| Steroid non-response probability | The model is based on assumptions from trials with steroid-resistant and -responsive patients. The Thai economic study (Bamrungsawad et al. 2016) demonstrated that Ig is cost-effective in steroid-resistant populations as patients transition to disability and costs of treatment are higher than steroids alone. | Possibly Large. The ICER for Ig is less in steroid-resistant patients, as disability has a large disutility. For steroid-resistant patients alone, an ICER of $125,260 per QALY gained is estimated |

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY, = quality-adjusted life year.; AE = adverse event

# Section E Financial Implications

## Justification of the Selection of Sources of Data

Section E presents the financial budget impact of a scenario where CIDP patients use of Ig is projected over a five-year period using the 2012-2018 trend in patient numbers. As Ig is already funded in Australia, total patient numbers and Ig utilisation data are available in the *National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16,* presented by the NBA. However, the number of CIDP patients in Australia, including those not using Ig, is uncertain. Similarly, data relating to the proportions of Ig patients in Australia that are steroid-resistant or pure motor CIDP types are not available.

Data sources used to estimate the number of CIDP patients and those being treated with Ig are provided in Table 86 and Table 87. Prevalence estimates for CIDP vary considerably. Rajabally et al. (2009) estimated patient numbers using EFNS/PNS criteria (2006 version) resulting in a prevalence of 4.77 per 100,000 and using the AAN criteria resulting in a prevalence of 1.97 per 100,000. Lefter et al. (2017) reported CIDP prevalence of 5.87 per 100,000 adults in Ireland using EFNS/PNS criteria. McLeod et al. (1999) estimated Australian CIDP patient numbers using AAN criteria, resulting in a prevalence of 1.9 per 100,000.

The estimated number of CIDP patients in Australia ranges from 578 to 1593 in 2017/2018 based on these prevalence rates, which is less than the figure of 2,595 CIDP patients using Ig as reported by the NBA. The PICO noted that around half of CIDP patients currently use steroids. There is a great deal of uncertainty surrounding CIDP patient numbers in Australia.

The number of CIDP patients using Ig has increased in recent years. NBA data indicates that the number of patients using Ig for CIDP has increased by 67% between 2011/12 and 2017/18. The rationale for this increase is unclear. A regression analysis was undertaken to project CIDP patient numbers to 2024 for use in this budget impact analysis. The analysis includes the increase in patient numbers, but not changes in average Ig per patient per year. Average use per patient will change with adoption of the new criteria. A sensitivity analysis is also included, which corresponds with higher and lower CIDP patient number estimates based on Rajabally et al. (2009) prevalence rates.

The budget impact analysis includes financial impacts for the NBA (Commonwealth and State), MBS, PBS and state hospitals. The base case analysis uses a domestic unit cost of Ig excluding plasma of $60.41, while other unit costs are taken from the MBS and PBS - along with hospital costs detailed in the economics section. Out-of-pocket health services costs are not included for patients due to data limitations, however, they would be relatively small compared with Ig costs.

## E.2. Use and Cost of Ig For CIDP

### E.2.1. Number of patients with the medical condition

Table 86 shows number of patients using Ig as reported by the NBA (*National Report on the Issue and Use of Immunoglobulin (Ig) Annual Report 2015-16*). It is evident that patient numbers increased by 57% between 2012 and 2018, however, the reasons underpinning this trend are unclear.

Table 86 Historical patient numbers using IVIg for CIDP in Australia (total) by year

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Financial Year | 2011-12 | 2012-13 | 2013-14 | 2014-15 | 2015-16 | 2017-18 |
| Patient no. | 1,551 | 1,753 | 1,903 | 2,054 | 2,250 | 2,595 |

**Source:** NBA Annual Report

Table 87 shows the number of patients projected to use Ig treatment in 2020 to 2024 following the trend from 2012 to 2018. Regression analysis was undertaken using the patients in each year over the 2012-2018 period. The equation comprised an intercept of - 344648.4 and coefficient per year of 172.07 (R2=0.998766). Based on the regression analysis, Ig patient numbers increase from 2,250 in 2016 to 2,936 for the 2020 starting year of the projection. By 2024 it is estimated that there will be 3,624 patients using Ig in Australia, which represents an annual increase in patient numbers of around 5% per year.

Table 87 Projected CIDP patient uptake of Ig in Australia, 2020-2024 (based on utilisation data from 2012-2018)

| **Description** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| --- | --- | --- | --- | --- | --- | --- |
| Australian population | 25,992,413 | 26,408,291 | 26,830,824 | 27,260,117 | 27,696,279 | ABS[[32]](#footnote-33) Australian population 2018 and 1.6% population growth |
| Lefter et al. (2017), EFNS/PNS Ireland | 1,125 | 1,143 | 1,161 | 1,180 | 1,199 | Lefter et al. (2017) 5.87 per 100,000 in adult Irish population. Estimate for Australia assumes 75% of population 18 years+ |
| Rajabally et al. (2009) EFNS/PNS CIDP patients | 1,240 | 1,260 | 1,280 | 1,300 | 1,321 | Rajabally et al. (2009) estimated patient numbers using EFNS/PNS criteria of 4.77 per 100,000 |
| McLeod et al. (1999) AAN CIDP patients | 494 | 502 | 510 | 518 | 526 | McLeod et al. (1999) estimated patient numbers using AAN criteria of 1.9 per 100,000 |
| CIDP patients using Ig, from NBA annual report trend | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Regression analysis of 2012-18 CIDP patients using NBA reporting projected 2020-2024 |

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. NBA = National Blood Authority.

### E.2.2. Number who would be eligible for the requested restriction

The current Ig use criteria specify that confirmed CIDP patients with significant disability or compromised walking (measured by ONLS score of at least two points, and MRC sum score for patients >10 years and 6MWT and/or Modified Rankin Scale sum score for patients ≤ 10 years) and those who relapse within six months of commencing a trial off Ig therapy are eligible for Ig. Neurologist reviews should be undertaken annually to support continued IVIg therapy. Patients are also eligible for Ig therapy in the event that relapse has occurred within six months of the last Ig dose. The PICO notes that IVIg is often a first-choice treatment option for patients with moderate too severe CIDP in Australia. CIDP patients access Ig treatment in Australia according to NBA Criteria eligibility. The total number of CIDP patients in Australia is unknown, thus the proportion using Ig is unclear, but regression analysis indicates that the number of CIDP patients using Ig will increase to 3,624 by 2024.

### E.2.3. Number of patients

Clinical feedback provided during the evaluation indicated that 60% of patients have chronic progressive CIDP requiring lifelong treatment, 30% have a relapsing-remitting form requiring recurrent treatment for relapses (often treated lifelong after second relapse), and 10% are monophasic and could be taken off treatment. Clinical feedback indicated that about 5% of CIDP patients have the pure motor form of the disease. Steroid studies indicated that half of CIDP patients could be contraindicated or non-responsive to steroids. It is unclear what proportion of Ig-using CIDP patients in Australia are steroid-resistant. The numbers of CIDP patients (all sub-groups) who are projected to avail Ig over a five-year period are summarised in Table 87 using the 2012-2018 trend in patient numbers.

### E.2.4. Estimated Cost per Patient Who Receives Ig

Average Ig use of 497g per patient per year (NBA reporting) is used for Ig cost estimates in the budget impact analysis. Four Ig price scenarios are included in the analysis. The base case analysis: domestic unit cost of IVIg excluding plasma, $60.41; in addition to sensitivity analyses based on:

1) Highest cost Ig: domestic IVIg including plasma, $140.18;

2) Lowest cost Ig: imported IVIg, $44.94; and

3) The weighted average cost across all indications when plasma is included, which is estimated to be $94.51.

Costs of Ig delivery were presented in Section D. They are outlined again in Table 88with an allowance for MBS and PBS proportions of total cost.

Table 88 Unit costs of Ig Delivery: IVIg product cost and delivery (maintenance)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MBS Item** | **Provider** | **Price per unit** | **Per year** | **% of Patients** | **Total cost** | **State, NBA, MBS, PBS proportion of total cost** | **State, NBA, MBS or PBS cost** | **Source** |
| Antihistamine, Cetirizine hydrochloride 10mg tablet, | PBS | $0.9 | 13.2 | 10% | $1.2 | 100% | $1.2 | PBS website. Pack cost divided by 30 |
| Ig product, grams per infusion, domestic unit cost of IVIg excluding plasma, $60.41, | NBA | $60.4 | 497.0 | 100% | $30,023.8 | 100% | $30,023.8 | 497 g per patient per year from NBA for 2017-18 |
| GP Consultations. | MBS | $34.9 | 3.0 | 100% | $104.7 | 100% | $104.7 | MBS 23. Professional attendance |
| Neurologist Specialist Consultations. | MBS | $267.9 | 1.0 | 100% | $267.9 | 75% | $200.9 | MBS 132. Professional attendance |
| Neurologist Follow-up Consultations. | MBS | $136.3 | 1.0 | 100% | $136.3 | 75% | $102.2 | MBS 133. Professional attendance |
| Liver function tests, Urea, Electrolytes, Creatinine | MBS | $17.1 | 1.0 | 100% | $17.1 | 75% | $12.8 | MBS 66512. |
| Full Blood Examination | MBS | $17.0 | 1.0 | 100% | $17.0 | 75% | $12.7 | MBS 65070. |
| Neuro muscular electro diagnosis | MBS | $227.6 | 2.0 | 100% | $455.1 | 75% | $341.3 | MBS 11018, 4 or more nerves. |
| Hospital admission and consumables for IV | State Hospital | $100.0 | 26.4 | 100% | $2,640.0 | 100% | $2,640.0 | 13.2 x 2 hour for IV Ig |
| Nurse time for infusion. | State Hospital | $85.5 | 26.4 | 100% | $2,257.7 | 100% | $2,257.7 | 13.2 x 2 hour for IV Ig |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| **Total** |  |  |  |  | **$37,223.9** |  | **$37,000.6** |  |

Abbreviations: CIDP= Chronic Inflammatory Demyelinating Polyneuropathy: MBS = Medicare Benefits Schedule; PBS= Pharmaceutical Benefits Schedule.

It is evident that Ig accounts for more than 80% of overall treatment costs. MBS costs are estimated assuming services are delivered on an inpatient basis. State level hospital costs include hospital, nurse and infection control costs. These costs are included in the impact analysis where overall government health budget impacts are estimated.

### E.2.5. Projected Cost of Ig for CIDP, 2020-2024

Projected Ig costs for CIDP are presented in Table 89. The projected number of patients, average Ig grams per patient and base Ig price are combined to estimate projected total Ig costs. Ig costs for CIDP are estimated to be $88.1 million in 2020, increasing to $108.8 million in 2024.

Table 89 Estimated costs of Ig for CIDP, 2020-2024

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unit** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| Projected Ig patients | Number | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Projected using 2012-2018 trend |
| Grams Ig per patient per year | grams | 497 | 497 | 497 | 497 | 497 | Current Ig per patient per year |
| Total projected Ig grams per year | grams | 1,459,121 | 1,544,641 | 1,630,160 | 1,715,680 | 1,801,199 | Calculated, based on Ig patient numbers |
| Ig cost per gram | $ per gram | 60.41 | 60.41 | 60.41 | 60.41 | 60.41 | NBA price list |
| **Total Ig product costs** | **$** | **88,145,500** | **93,311,733** | **98,477,966** | **103,644,199** | **108,810,432** | **Unit cost multiplied by Ig patients** |
| Commonwealth Ig costs | $ | 55,531,665 | 58,786,392 | 62,041,118 | 65,295,845 | 68,550,572 | 63% funded by Commonwealth |
| State Ig costs | $ | 32,613,835 | 34,525,341 | 36,436,847 | 38,348,353 | 40,259,860 | 37% funded by states and territories |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. Ig = immunoglobulin;

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

## E.3. Changes in Use and Cost of Other Medical Services

The uptake of Ig incurs additional costs associated with service delivery. These costs are projects for MBS, PBS and state budgets. Ig use among CIDP patients substitutes for other CIDP treatments that otherwise would have been utilised. These costs are included in the budget impact as cost offsets. The analysis assumes Ig substitutes for steroids.

### E.3.1. Estimated Cost per CIDP Patient for Corticosteroids

The cost of steroid treatment (prednisone) is estimated inTable 90. Medicine costs are taken from the PBS website and included at the longer-term dose of 5mg per day the total cost per year is $1,701. Delivery costs which include doctor visits and tests are also included.

Table 90 Unit costs of steroids delivery

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **MBS Item** | **Provider of resource** | **Price per unit** | **Number per year** | **Proportion of patients** | **Total cost** | **State, MBS, PBS proportion of total cost** | **State, MBS or PBS cost** | **Source** |
| Pantoprazole 40mg per day | PBS | $13.9 | 365 | 100% | $168.9 | 100% | $168.9 | PBS website |
| Prednisolone 5mg day. | PBS | $14.3 | 365 | 100% | $87.2 | 100% | $87.2 | PBS website |
| Alendronate colecalciferol | PBS | $18.2 | 52.00 | 100% | $236.3 | 100% | $236.3 | PBS website |
| GP Consultations | MBS | $34.9 | 8.00 | 100% | $279.2 | 100% | $279.2 | MBS 23. general practitioner |
| Neurologist Specialist Consultations | MBS | $267.9 | 1.00 | 100% | $267.9 | 75% | $200.9 | MBS 132. Professional attendance |
| Neurologist Follow-on Consultations | MBS | $136.3 | 2.00 | 100% | $272.5 | 75% | $204.4 | MBS 133. Professional attendance |
| DEXA Scan | MBS | $102.4 | 1.00 | 100% | $102.4 | 75% | $76.8 | MBS 12321. |
| Liver Function Test | MBS | $17.1 | 4.00 | 100% | $68.4 | 75% | $51.3 | MBS 66512. |
| Full Blood Examination | MBS | $17.0 | 4.00 | 100% | $67.8 | 75% | $50.9 | MBS 65070. |
| Test for Open Angle Glaucoma | MBS | $40.8 | 1.00 | 5% | $2.0 | 75% | $1.5 | MBS 11200. Glaucoma test |
| Test for Diabetes | MBS | $16.8 | 4.00 | 5% | $3.4 | 75% | $2.5 | MBS 66841. |
| Neuro Muscular Electro Diagnosis | MBS | $227.6 | 2.00 | 100% | $455.1 | 75% | $341.3 | MBS 11018. |
| **Subtotal** |  |  |  |  | **$2,011.0** |  | **$1,701.2** |  |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. MBS = Medicare Benefits Schedule, PBS= Pharmaceutical Benefits Scheme

### E.3.2. Projected Costs of MBS Services

Increases in MBS-funded medical services are projected for CIDP patients availing Ig and cost offsets included for services that otherwise would have been availed with steroids. The unit costs are outlined in Table 88 for Ig and Table 90 for steroids. They are multiplied by projected Ig patient numbers to generate the total costs outlined in Table 91.

Table 91 Projected cost changes for the MBS, 2020-2024

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unit** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| **Ig MBS-related services** | | | | | | | |
| Projected Ig patients | No. | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Projected using 2012-2018 trend |
| GP Consultations  (3 x MBS 23), $69.80 yr | $ | 307,384 | 325,400 | 343,416 | 361,432 | 379,448 | Calculated, based on Ig patient numbers |
| Neurologist Consultations  (1 x MBS 132 + 1 x MBS 133, $303.08 yr) | $ | 889,785 | 941,935 | 994,086 | 1,046,237 | 1,098,387 | Calculated, based on Ig patient numbers |
| Liver function & other tests (1 x MBS 66512), $12.83 yr | $ | 37,652 | 39,859 | 42,066 | 44,273 | 46,480 | Calculated, based on Ig patient numbers |
| Full Blood Examination  (1 x MBS 65070), $12.71 yr | $ | 37,322 | 39,510 | 41,697 | 43,884 | 46,072 | Calculated, based on Ig patient numbers |
| Neuro muscular electro diagnosis  (2 x MBS 11018), $341.33 yr | $ | 1,002,081 | 1,060,814 | 1,119,546 | 1,178,278 | 1,237,011 | Calculated, based on Ig patient numbers |
| **Subtotal** | $ | **2,274,225** | **2,407,518** | **2,540,811** | **2,674,104** | **2,807,397** |  |
| **Steroid MBS-related services** | | | | | | | |
| GP Consultations (8 x MBS 23, $279.2 yr) | $ | -819,691 | -867,734 | -915,776 | -963,818 | -1,011,861 | Calculated, based on less steroid patients |
| Neurologist Specialist Consultations  (1 x MBS 132 + 2 x MBS 133, $405.26 yr) | $ | -1,189,793 | -1,259,527 | -1,329,261 | -1,398,995 | -1,468,729 | Calculated, based on less steroid patients |
| DEXA Scan (1 x MBS 12321, $76.8 yr) | $ | -225,474 | -238,689 | -251,904 | -265,119 | -278,334 | Calculated, based on less steroid patients |
| Liver function & other tests (4 x MBS 66512), $51.3 yr | $ | -150,609 | -159,437 | -168,264 | -177,091 | -185,919 | Calculated, based on less steroid patients |
| Full Blood Examination (4 x MBS 65070), $50.85 yr | $ | -149,288 | -158,038 | -166,788 | -175,538 | -184,288 | Calculated, based on less steroid patients |
| Test for Open Angle Glaucoma (1 x MBS 11200, $1.53 yr) | $ | -4,492 | -4,755 | -5,018 | -5,282 | -5,545 | Calculated, based on less steroid patients |
| Test for Diabetes (1 x MBS 66841, $2.52 yr) | $ | -7,398 | -7,832 | -8,266 | -8,699 | -9,133 | Calculated, based on less steroid patients |
| Neuro muscular electro diagnosis (2 x MBS 11018), $341.33 yr | $ | -1,002,081 | -1,060,814 | -1,119,546 | -1,178,278 | -1,237,011 | Calculated, based on less steroid patients |
| **Subtotal** | $ | **-3,548,827** | **-3,756,825** | **-3,964,823** | **-4,172,821** | **-4,380,819** | Calculated |
| **Net cost offset** | $ | **-1,274,602** | **-1,349,307** | **-1,424,012** | **-1,498,717** | **-1,573,422** | Calculated |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. MBS = Medicare Benefits Schedule, PBS= Pharmaceutical Benefits Scheme

### E.3.3. Projected Costs of PBS Medicines

The PICO noted that around 50% of Australian patients not receiving Ig therapy will receive corticosteroids. In the absence of Ig, steroid use would have increased. These costs offsets are outlined in Table 92.

Table 92 Projected cost changes for PBS medicines, 2020-2024

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unit** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| Projected Ig patients | No. | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Projected using 2012-2018 trend |
| Ig IV Pre-medication, Cetirizine hydrochloride 10 mg | $ | 3,656 | 3,870 | 4,084 | 4,299 | 4,513 | Calculated, based on Ig patient numbers |
| Prednisolone, 5mg per day | $ | -255,931 | -270,931 | -285,931 | -300,931 | -315,932 | Calculated, based on less steroid patients |
| Pantoprazole 40 mg | $ | -495,788 | -524,846 | -553,905 | -582,963 | -612,021 | Calculated, based on less steroid patients |
| Alendronate 70 mg + colecalciferol 140 microgram | $ | -693,860 | -734,528 | -775,195 | -815,863 | -856,530 | Calculated, based on less steroid patients |
| **Net cost offset** | $ | **-1,441,924** | **-1,526,435** | **-1,610,947** | **-1,695,458** | **-1,779,970** | NA |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. Ig =Immunoglobin, IV= Intravenous, MBS = Medicare Benefits Schedule, PBS= Pharmaceutical Benefits Scheme

### E.3.4. Projected State Hospital Costs of Ig IV Delivery

Ig is typically delivered intravenously in hospital settings. Costs of hospital admission and nurse time, along with the costs of treating infection are assumed to be borne by state hospital budgets. These costs are projected in Table 93 based on unit costs presented in Section D (See Table 77) and projected Ig patient numbers over 2020-2024.

Table 93: Projected cost changes for state hospital delivery of Ig, 2020-2024

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Unit** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| Projected Ig patients | No. | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Projected using 2012-2018 trend |
| Hospital admission and consumables (13.2 IV administrations), $2,640 yr | $ | 7,750,663 | 8,204,931 | 8,659,200 | 9,113,469 | 9,567,737 | Calculated, based on Ig patient numbers |
| Nurse time for infusion (13.2 IV administrations), $2,258 yr | $ | 6,628,367 | 7,016,857 | 7,405,348 | 7,793,838 | 8,182,329 | Calculated, based on Ig patient numbers |
| REDACTED | $ | 3,826,009 | 4,050,253 | 4,274,496 | 4,498,739 | 4,722,983 | Calculated, based on Ig patient numbers |
| **State costs** | $ | **18,205,039** | **19,272,041** | **20,339,044** | **21,406,046** | **22,473,049** |  |

Abbreviations: Ig =Immunoglobin, IV= Intravenous

## E.4. Financial Implications For Government Health Budgets

Table 94 shows the 5-year budget impact underpinned by the assumptions above. Net costs increase from $103.4 million in 2020 to $127.9 million in 2024.

Table 94 Estimated net costs to government, 2020-2024

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Total net government costs** | **Unit** | **2020** | **2021** | **2022** | **2023** | **2024** | **Source** |
| Projected Ig patients | No. | 2,936 | 3,108 | 3,280 | 3,452 | 3,624 | Calculated |
| **Ig costs for CIDP** | | | | | | | |
| Commonwealth Ig costs | $ | 55,531,665 | 58,786,392 | 62,041,118 | 65,295,845 | 68,550,572 | Calculated |
| State Ig costs | $ | 32,613,835 | 34,525,341 | 36,436,847 | 38,348,353 | 40,259,860 | Calculated |
| **Commonwealth MBS and PBS Costs** | | | | | | | |
| MBS-supported service delivery | $ | -1,274,602 | -1,349,307 | -1,424,012 | -1,498,717 | -1,573,422 | Calculated |
| PBS costs | $ | -1,441,924 | -1,526,435 | -1,610,947 | -1,695,458 | -1,779,970 | Calculated |
| **State Hospital Costs** | | | | | | | |
| Ig delivery, nurse and adverse events | $ | 18,205,039 | 19,272,041 | 20,339,044 | 21,406,046 | 22,473,049 | Calculated |
| **Net Government Costs** | | | | | | | |
| Commonwealth costs | $ | 52,815,139 | 55,910,649 | 59,006,160 | 62,101,670 | 65,197,180 | Calculated |
| State costs | $ | 50,818,874 | 53,797,382 | 56,775,891 | 59,754,400 | 62,732,909 | Calculated |
| Total costs to government | $ | 103,634,012 | 109,708,032 | 115,782,051 | 121,856,070 | 127,930,089 | Calculated |

CIDP= Chronic Inflammatory Demyelinating Polyneuropathy. MBS = Medicare Benefits Schedule, PBS= Pharmaceutical Benefits Scheme

## E.5. Identification, Estimation and Reduction of Uncertainty

The budget impact model presented in this Section provided a base case. Key base assumptions are included in a sensitivity analysis in Table 95. The budget impact is most sensitive to the assumed price for Ig. Financial impact is also sensitive to varying the prevalence rates by Rajabally et al. (2009). REDACTED.

Table 95 Net government cost sensitivity analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **2020** | **2021** | **2022** | **2023** | **2024** |
| **Base-case net cost** | 103,634,012 | 109,708,032 | 115,782,051 | 121,856,070 | 127,930,089 |
| Rajabally et al. (2009) estimated patient numbers using EFNS/PNS criteria of 4.77 per 100,000 | 43,837,187 | 46,406,497 | 48,975,807 | 51,545,118 | 54,114,428 |
| McLeod et al. (1999) estimated patient numbers using AAN criteria resulting in 1.9 per 100,000 | 17,514,148 | 18,540,657 | 19,567,167 | 20,593,676 | 21,620,185 |
| REDACTED | REDACTED | REDACTED | REDACTED | REDACTED | REDACTED |
| Price of Ig product $140.18 | 220,028,095 | 232,924,004 | 245,819,914 | 258,715,824 | 271,611,733 |
| Price of Ig product $44.94 | 81,061,410 | 85,812,443 | 90,563,475 | 95,314,508 | 100,065,540 |
| Price of Ig product $94.51 | 153,390,038 | 162,380,273 | 171,370,507 | 180,360,741 | 189,350,975 |
| Average grams per person 497 (+10%) | 112,448,562 | 119,039,205 | 125,629,847 | 132,220,490 | 138,811,132 |
| Average grams per person 497 (-10%) | 94,819,462 | 100,376,858 | 105,934,254 | 111,491,650 | 117,049,046 |

Abbreviations: Abbreviations: AAN = American Academy of Neurology, CIDP = chronic inflammatory demyelinating polyneuropathy, EFNS/PNS = European Federation of Neurological Societies/Peripheral Nerve Society, Ig= Immunoglobulin. REDACTED.

# Section F Other relevant considerations

*Access/equity considerations*

The intervention (Ig) and all the comparators, excluding no active treatment, have issues of access for patients in rural or remote locations.

IVIg can only be received at a hospital that has been accredited to administer blood products under the National Safety and Quality Health Services Standard for Blood Management. It is unlikely that small rural hospitals would have this accreditation, requiring patients to travel to large rural or metropolitan centres to receive IVIg. Access to SCIg may possibly alleviate these travel issues as patients could store and administer Ig at home. According to the NBA, SCIg is initially supplied monthly, and repeat prescriptions can be accessed without seeing a doctor at an agreed pharmacy or medical centre that does not have to be a treating hospital (NBA 2016a).

Access to plasma exchange is likely to be more difficult than IVIg for patients living in rural or remote locations. A clinical expert to the PICO reported that, in Australia, plasma exchange is only provided in major teaching hospitals in capital cities (DoH 2019a).

Treatment with steroids, both oral and IV, would be easier for rural and remote patients to access than either IVIg or plasma exchange. Oral steroids can be administered by the patient at home, and although IV steroids must be infused at a hospital, this is usually feasible at small hospitals (Expert Neurologist 2019), alleviating the need to travel to large metropolitan centres. While treatment with steroids may be easier to access, the potential side effects of steroids mean that patients must be monitored more closely than do patients on Ig or plasma exchange (Expert Neurologist 2019). Patients on steroids must undergo frequent blood tests (Table 15, Section A7) and reviews for blood pressure, blood sugar, weight, skin integrity and infectious complications (Expert Neurologist 2019; Hsu and Katelaris 2009). Although these tests could be carried out at small country hospitals, the frequency with which tests are required may inconvenience rural patients who may still need to travel a significant distance. Immunosuppressants have similar access challenges to steroids. While they can be taken orally and administered by the patient at home, the risk of significant adverse effects means patients must undergo constant surveillance and tests (Table 17, Section A7).

*Social/ethical considerations*

Patients who belong to the Jehovah’s Witness religion do not accept blood transfusion or blood products. They are unlikely to undergo plasma exchange but might be willing to accept Ig, depending on the individual (Chand et al. 2014).

*Clinical trials*

A search of ClinicalTrials.gov on 16 May 2019 identified seven clinical trials on Ig and CIDP (either recruiting or active but not recruiting). Two trials of unknown status were also identified. Details of the clinical trials and their completion dates are summarised in Table 96.

Table 96 Clinical trials identified on CIDP and Ig search of ClinicalTrials.gov (searched 16th May 2019)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Trial ID**  **Country** | **Status** | **Intervention and Comparator(s)** | **Study design** | **Primary outcome(s)** | **Completion date** |
| NCT02549170  Argentina, Austria, Canada, Colombia, Czechia, Denmark, France, Germany, Greece, Israel, Italy, Norway, Poland, Serbia, Slovakia, Spain, Sweden, Switzerland, Turkey and UK | Recruiting | HYQVIA  Placebo | RCT | Relapse rate (proportion of patients who experience worsening of functional disability)  Responder rate (proportion of patients with clinically meaningful improvement in function disability) | December 2021 |
| NCT03684018  USA | Recruiting | IVIg (Privigen) single dose  IVIg (Privigen)  Multiple dose | RCT | Percentage of patients with CIDP relapse | January 2023 |
| NCT02372149  Canada | Unknown | IVIg (Gamunex)  Placebo | RCT (crossover) | Change in Overall Neuropathy Limitations Score | February 2018 |
| NCT02638207  Bulgaria, Canada, Czechia, Germany, Hungary, Polan, Romania, Russian Federation and Ukraine | Active, not recruiting | IVIg (Panzyga) dose 1  IVIg (Panzyga) dose 2  IVIg (Panzyga)  dose 3 | RCT | Decrease in the Inflammatory Neuropathy Cause and Treatment Disability Score | December 2019 |
| NCT02955355  Canada, Czechia, Denmark, France, Greece, Italy, Serbia, Slovakia, Spain, Turkey and UK | Recruiting | HYQVIA | Case series | Adverse events | September 2024 |
| NCT02629796  France | Recruiting | IVIg  Healthy subjects | Case control | Blood levels of biomarkers of Ig response | December 2020 |
| NCT02465359  USA | Active, not recruiting | SCIg (Hizentra) | Case series | Relapse of CIDP symptoms | December 2019 |
| NCT02414490  USA | Active, not recruiting | IVIg | Case series | Daily grip strength measurements | May 2020 |
| NCT03166527  Canada | Unknown | IVIg (Panzyga) | Case series | Adverse events | December 2018 |

CIDP: = chronic inflammatory demyelinating polyneuropathy; Ig = immunoglobulin; IVIg = intravenous immunoglobulin; RCT = randomised controlled trial; SCIg = subcutaneous immunoglobulin

**Appendix A Clinical Experts and Assessment Group**

## Assessment group

**RACS Research and Evaluation (ASERNIP-S)**

* REDACTED
* REDACTED
* REDACTED
* REDACTED
* REDACTED
* REDACTED

**Noted conflicts of interest**

There were no conflicts of interest.

# Appendix B Search strategies

## Bibliographic databases

|  |  |
| --- | --- |
| Electronic database | Time period searched |
| Embase | Inception to 25 March 2019 |
| PubMed | Inception to 25 March 2019 |

# 

# Appendix C Studies included in the Systematic Review

**Randomised controlled trials**

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Donofrio, PD, Bril, V, Dalakas, MC, Deng, C, Hanna, K, Hartung, HP, Hughes, R, Latov, N, Merkies, I & Van Doorn, P 2010, 'Safety and tolerability of immune globulin intravenous in chronic inflammatory demyelinating polyradiculoneuropathy', Archives of Neurology, vol.67, pp. 1082-88.

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Hughes, RA, Donofrio, P, Bril, V, Dalakas, MC, Deng, C, Hanna, K, Hartung, HP, Latov, N, Merkies, IS & van Doorn, PA 2008, 'Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial', The Lancet Neurology, vol.7, pp. 136-44.

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# Appendix D Evidence Profile Tables

Table 97 Key features of the randomised controlled trials on the treatment and maintenance of CIDP included in the systematic literature review

| Study ID  Location | Study overview | Key inclusion criteria | Baseline characteristics | Disease characteristic | Baseline disability | Intervention details | Comparator details | Completeness of safety reporting  Period of safety monitoring |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Studies investigating treatment of CIDP |  |  |  |  |  |  |  |  |
| Hahn et al. (1996b) | Ig (I) vs Pl (C)  MC DB CO | Definite or probable CIDP.A Continually progressive (>8 weeks). static or recently progressed disease. Muscle weakness interferes with ambulation (NDS ≥ 40). Ig naïve patients. | I: n = 16  C: n = 14  Whole group  Age: 52 (range 9-79)  % male: 37 | Whole group  Status: definite: 21, probable: 9  Type: progressive: 16, relapsing: 14  Time since diagnosis: NR | NDS  I: 78.3 ± 27.5  C: 76.6 =- 27.7  Clinical grade  I: 4.6 ± 1.9  C: 4.2 ± 1.9 | IVIg  Cutter Biological Product, Miles Inc. 5% human protein in 9-11% mannose  0.4 g/kg daily for 5 days | Placebo  10% dextrose daily for 5 days | Low  4 weeks |
| ICE Study (Hughes et al. (2008), Donofrio et al. (2010), Bril et al. (2009) Merkies et al. (2009) | Ig (I) vs Pl (C)  MC DB CO | Adult patients with diagnosed CIDP (motor and sensory dysfunction) with significant disability (INCAT 2-9). Patients treated for CIDP in last 3 months excluded. | I: n = 59  C: n = 58  Age  I: 50 ± 17 y  C: 53 ± 16  % male  I: 53%  C: 79% | Status: NR  Type: NR  Time since diagnosis  I: 2.4 ± 3.7 yr  C: 1.8 ± 2.9 yr | INCAT  I: 4.2 ± 1.4  C: 4.1 ± 1.5  MRC  I: 49.3 ± 6.9  C: 50.0 ± 7.2 | IVIg  IGIV-C (Gamunex, Talecris Biotherapeutics, Research Triangle Park, NC, USA)  loading dose 2g/kg over 2-4 days  maintenance 1g/kg over 1-2 days every 3 weeks | Placebo  0.1% albumin every 3 weeks | High  at least 24 weeks |
| Dyck et al. (1982)  USA | St (I) vs Pl (C) | Patients with CIDP for > 6 months and untreated with immunosuppressive therapy | I: n = 14  C: n = 14  Age  I: med 46.5 range 22-76  C: med 50 (range 9-83)  % male  I: 71%  C: 64% | Status: NR  Type: chronic progressive: 14, recurrent: 14  Time since diagnosis  I median 25 mo (range 6-84)  C median 32 mo (range 8-168) | NDS  I: med 74 (range 31-123)  C: med 74 range 28-137 | Prednisone 120 mg alternate days; 5 mg alternate days tapering to 0 mg over 13 weks | No treatment |  |
| Zinman et al. (2005) | Ig (I) vs Ia (C) | Patients aged 18-70 years with motor and/or sensory CIDP > 2 months. Patients treated with Ig, Is or PE in last 6 months excluded. | I: 9  C: 5  Age  I: 63.5± 8.7  C: 63.8 ± 9.3  % male  I: 62.5%  C: 100% | Status: NR  Type: NR  Time since diagnosis  I: 2.32 ± 2.05 yrs  C: 1.32 ± 1.30 yrs | TCNS  I: 13.3 ± 4.7  C: 11.2 ± 3.5  Hughes score  I med 2.5  C: med 2.0  AMS  I: 273 ± 28.2  C: 294 ± 12.3 | IVIg (brand NR) 1g/kg/day, two days per month for 6 months | Ia (Excorim system Citem 10 device) with Protein A matrix column (2 in parallel, 10 min cycles). Access via antecuital or forearm vein. 3 plasma volumes over 7 days monthly for 6 months | Low  24 weeks |
| PREDICT study van Schaik et al. (2010), Eftimov et al. (2012) | St (I) vs St (C)  MC, DB, | Patients aged ≥ 18 years with newly diagnosed definite or probable CIDPB Required to have signs and symptoms severe enough to warrant treatment. Treatment naïve. | I: 24  C: 17  Age  I: med 59.9 [IQR 25.8-80.2]  C:med 60.8 [IQR 25.3 to 87.7]  % male  NR | Status: NR  Type: NR  Time since diagnosis  I: med 13.5 mo IQR 5.3-28.5  C: 8.5 mo IQR 6-15 | INCAT  I: med 8.5 IQR 1-15  C:med 9 IQR 0-17  ALDS  I: 69.9 ± 16.1  C: 63.2 ± 21.2  MRC  I: med 50 IQR 24-57  C: med 50 IQR 35-59 | Oral dexamethasone 40 mg/day for four days then placebo for 24 days. 6 cycles | Oral prednisolone  60 mg per day for 5 weeks then tapering to 0mg over 27 weeks | High  52 weeks |
| Hahn et al. (1996a) and Ashworth et al. (2000) | PE vs Pl  SC, CO, DB | Patients aged >18 years with newly diagnosed CIDPA, progressive for 8-104 weeks. Significant muscle weakness (NDS ≥ 50). Treatment naïve. | I: 9  C: 9  Age:  NR  % male  72% | Status:18/18 definite  Type:  Chronic progressive n = 9  Chronic relapsing n = 9  Time since diagnosis  Mean 4.5 mo range 3-18 mo | NDS  I: 73.3 ± 5.3  C: 69.4 ± 6.4  Clinical grade  I: 4.6 ± 0.4  C: 4.3 ± 0.4 | PE antecubital access using continuous or intermittent cell separator (Cobe TPE Cobe Spectra and V-50 Haemonetics apheresis system) 10 exchanges over 4 weeks | Sham exchange  10 exchanges over 4 weeks | Low  9 weeks (some patients followed for much longer) |
| Dyck et al. (1994) | Ig vs PE  CO | CIDP diagnosis with static or worsening neurological disability. NDS-W ≥ 5 points. | I: 10  C: 9  Age  I: 51 ± 18  C: 39 ± 17  % male  I; 60%  C: 44% | NR | NDS  I: 68 ± 28  C: 83 ± 40 | IVIg (Gamimune, Miles Biological Products) 0.4 g/kg/wk for 3 weeks then 0.2 g/kg/wk for 3 weeks | PE (machine NR)  Twice weekly for 3 weeks then weekly for 3 weeks | Low  up to 12 weeks with washout period (some patients followed for much longer) |
| Hughes et al. (2001) | Ig (I) vs St (C)  CO, DB | Diagnosis of CIDP by neurologist, progressive or relapsing motor and sensory dysfunction of >1 limb resulting from neuropathy developing over > 2 months. Significant disability in upper or lower limb functions. stable or worsening clinical condition | I: 17  C: 15  Age  I: 55.8 ± 16.2  C: 52.1 ± 18.3  % male  I: 71%  C: 60% | Status: NR  Type: progressive n = 12, relapsing n = 20  Time since diagnosis  I: 5.3 ± 7.8 yrs  C: 5.2 ± 6.5 yrs | INCAT  I: 4.11 ± 2  C: 3.47 ± 1.3 | IVIg (Sandoglobulin)  1 g/kg/day for 2 days  + placebo St | Oral prednisolone  60 mg daily tapering to 10 mg daily over 6 weeks  + placebo Ig | Moderate  < 8 weeks |
| Mendell et al. (2001) | Ig vs Pl | Patients fulfilling diagnostic criteria for definite or probable CIDP. Patients receiving treatment in past 3 months excluded | I: n = 29  C: n = 21  Age  I: 54 ± 20  C: 50 ± 18  % male  55% | Status: NR  Type: NR  Time since diagnosis: NR | AMS:  I: 7.06 ± 1.31  C: 7.28 ± 1.18 | IVIg (Pasteurised Gammar IV (Aventis Behring LLC)) 1.0 g/kg on days 1, 2 and 21 | Placebo 5% albumin on days 1, 2 and 21 | Moderate  6 weeks |
| Vermeulem et al. (1993) | Ig vs Pl | Newly diagnosed CIDP with progression of weakness over >8 weeks. Disability ≥ 3 on modified Rankin Scale. Treatment naïve. | I: n = 15  C: n = 13  Age  I: mean 45 yrs  C: mean 50 years  % male  I: 73%  C: 69% | Status: NR  Type: NR  Time since diagnosis: mean 1 years 2 months | MRC  I: median 52  C: median 43  Rankin scale  I: median 3  C: median 3 | IVIg (Prepared by the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam)  0.4 g/kg/day for 5 consecutive days | Placebo (Prepared from 20% albumin solution in which less than 0.1% IgG could be detected)  5 consecutive days |  |
| Dyck et al. (1986) | PE vs sham | Patients with CIDP and a neurologic status that was static or worsening. NDS ≥ 50 points. No change to immunotherapy, in preceding six weeks. | I: n = 15  C: n = 14  Age  R  % Male NR | Status: NR  Type: NR  Time since diagnosis: NR | NR | PE (intermittent or continuous flow cell separator) (Haemonetics model 30 or IBM 2997)  47 ml/kg, mean 3.5 L exchanged per session)  Access via antecubital or subclavian veins | Sham (same schedule as for PE) |  |
| Dyck et al. (1985) | St + Is vs St | Static or worsening CIDP with symptoms for ≥ 6 months, NDS ≥ 50 points, no treatment with prednisone or immunotherapy for at least 3 months | I: n = 15  C: n = 14  Age  I: median 41 (range 18-63)  C: median 46 (range 19-70)  % male  I: 46%  C: 70% | Status: NR  Type: NR  Time since diagnosis:  I median 29 ms (range 8-168 mo)  C: 21 mo (range 6-84 mo) | NDS  I median 119 range 70-203  C: median 110 (range 53-164) | Prednisone 120 mg alternate days tapering over 13 weeks + azathioprine 2 mg/kg/day | Prednisone 120 mg alternate days tapering over 13 weeks |  |
| Nobile-Orazio et al. (2012) | Ig vs St | Definite typical CIDP.C ONLS or modified Rankin core ≥ 2. Active or stationary disease phase but not in remission. | I: n = 24  C: n = 21  Age  I: med 54 range 19-83  C: med 66 range 39-79  % male  I: 63%  C: 71% | Status: all definite  Type:  Progressive 17/45  Relapsing 18/45  Time since diagnosis:  I: Median 4 years range 0-12  C: Median 6 years range 0-29 | Modified Rankin score  I median 2 range 1-4  C: median 3 range 2-5  ONLS  I: median 3 range 2-5  C: median 4 range 2-9 | IVIg (IgVena, Kedrion, Italy)  0.5 g/kg/day for 4 consecutive days each month for 6 months | IV methylprednisolone 0.5g for 4 consecutive days each month for 6 months | High  52 weeks |
| Markvardsen et al. (2017) note IVIg vs SCIg | IVIg vs SCIg | Patients aged 18-80 with definite or pure motor CIDP naïve to immune modulatory therapy and fulfilling EFN/PNS criteria. | I: n = 10  C: n = 10  Age  I: 52.3 ± 12.8 yrs  C: 56.7 ± 8.1  % male  I: 80%  C: 90% | Status: NR  Type: NR  Time since diagnosis:  I: 23 ± 20.7  C: 8.5 ± 7.3 | MRC  I: 84.0 ± 5.3  C:83.9 ± 5.1  ODSS  I: 3.5 ± 1.4  C: 3.5 ± 1.6 | IVIg (Privigen, CSL Behring) 2g/kg for 5 days | (Hizentra, CSL Behring, Sockholm, Sweden) 0.4 g/kg delivered in 2-3 infusion weekly weekly for 5 weeks |  |
| Studies investigating maintenance of treatment |  |  | I: |  |  |  |  |  |
| Kuitwaard et al. (2010) | Ig vs Ig | Patients aged ≥ 18 with CIDPA observed and documented improvement of muscle function after first use of Gammagard S/D; ODSS ≥ 2 or MRC grade ≤ 4 before start of trial or following reduction of IVIg dose within last 12 months. Ongoing intermittent treatment with Gammagard leads to stable condition; stable does for last 8 weeks. | I: n = 13  C: n = 14  Age  I: 54 ± 12 yrs  C: 54.6 ± 13.8  % male  I: 62%  C: 86% | Status: NR  Type: NR  Time since diagnosis:  NR  Current treatment:  Ig (mean 5 years, range 5 months – 13 years) | MRC  I: 53.6 ± 4.4  C:54.6 ± 3.4  ODSS  I: median 3.0 range 0-7  C: median 3.7 range 1-5 | IVIg (Gammagard S/D, Baxter AG, Vienna, Austria, 5% (50g/l) freeze dried)  Dose: 8-30 g per week, mean interval 18.8 days ± 5.3 days | IVIg (Koivig, Baxter AG, Vienna, 10% 10g/l liquid)  Dose: 10-38 g per week, mean interval 15.5 days ± 4.1 days |  |
| van Schaik et al. (2018) | Ig vs Pl | Patients aged 18 year and over, definite or probable CIDP.C Last IVIg treatment within 8 weeks of study; Ig-dependent disease. | I1: n = 57  I2: n = 58  C: n = 57  Age: median (IQR)  I1: 58.9 (50.5-66.5)  I2:55.2 (49.2-66.4)  C: 57.6 (46.7-56.9)  % male  I1: 74%  I2: 53%  C: 65% | Status:  Definite vs probable  I1: 98% vs 11%  I2: 91 vs 9%  C: 93% vs 7%  Type:  NR  Time since diagnosis median (IQR)  I1: 2.8 yrs (1.4-5.0)  I2: 3.3 yrs (1.3-8.6)  C: 2.7 yrs (1.1-4.7)  Current treatment:  100% on IVIg | All median (IQR)  INCAT  I1: 2 (1-3)  I2: 2 (1-3)  C: 2 (1-3)  I-RODS  I1: 63 (51-73)  I2: 69 (54-80)  C: 68 (51-83)  MRC  I1: 75 (70-78)  I2: 76 (70-79)  C: 76 (72-78) | I1: SCIg (low dose)  IgPro20 (Hizentra, CSL Behring, Bern, Switzerland) 0.2 g/kg given weekly in 2 sessions  I2: SCIg (high-dose)  IgPro20 (Hizentra, CSL Behring, Bern, Switzerland) 0.4 g/kg given weekly in 2 sessions | Placebo (2% human albumin) given in 2 sessions weekly. |  |
| Markvardsen et al. (2013) | Ig vs Pl | CIDPC patients aged 18-80 years in maintenance therapy with IVIg. All were Ig responders and received treatment every 3-10 weeks. | I: n = 15  C: n = 15  Age  I: 53.4 ± 11.9  C: 61.4 ± 9.4  % male  I: 73%  C: 73% | Status: NR  Type: NR  Time since diagnosis:  I: 4.6 ± 3.2 yrs  C: 5.4 ± 6.1 yrs  Current treatment:  IVIg mean dose 0.31 ± 0.1 g/kg/week | ODSS  I: 3.07 ± 1.91  C: 3.00 ± 1.46  NIS  I: 40.4 ± 26  C: 48.5 ± 22  MRC  I: 84.7 ± 6.19  C: 83.2 ± 5.02 | SCIg (Subcuvia 16% Baxter A/S, Fresenius-Kabi AB, Uppsla, Sweden)  Dose: equivalent to previous IVIg dose (range 4.8-48 g)  2-3 times weekly for 12 weeks | Placebo (saline) in equal volume to prior IVIg usage, 2-3 infusion weekly for 12 weeks |  |
| Mahdi-Rogers et al. (2009) | Is vs Pl as Ig and St-sparing agent | Diagnosed CIDPD with chronically progressive, stepwise, or recurrent weakness of all extremities, developing over ≥ 2 months and present for ≥ 6 months. ONLS ≥ 2 and MRC ≤4. Patients must have responded to and still be receiving stable dose of IVIg (equivalent to at least 0.4 g/kg every 4 weeks and given at least every 8 weeks) or corticosteroids (equivalent to at least 15 mg daily prednisolone). Ig- or steroid-dependent disease demonstrated in last 12 months.. | I: n = 28  C: n = 32  Age (median (IQR)):  I: 57 (48-63)  C: 59 (46-66)  % male  I: 57%  C: 84% | Status: NR  Type: NR  Time since diagnosis:  NR  Current treatment:  See intervention and comparator columns for details | All median (IQR)  MRC  I: 71 (61-76)  C: 72 (68-77)  ONLS  I: 4 (2-5)  C: 4 (3-5)  ISS  I: 9 (3-22)  C: 8.5 (4-20) | Methotrexate (2.5 mg tablets; Pharmacia Maxtrex) 7.5 mg weekly increasing to 15 mg over 32 weeks  Used in conjunction with  IVIg n = 21/28  Mean dose 0.34 ± 0.21 g/kg/week  Steroids n = 7/28  Mean dose 210 ± 74 mg/week | Placebo  Used in conjunction with  IVIg n = 28/32  Mean dose 0.33 ± 0.19 g/kg/week  Steroids n = 4/32  Mean dose 186 ± 88 mg/week | High  39-42 weeks |
| Hughes et al. (2018) | Switch to Is or Pl | Patients with typical or atypical CIDPC with INCAT disability score of 1-9, receipt of either IVIg (minimum dose equivalent to 0.4 g/kg every 4 weeks for a minimum of 12 weeks) or corticosteroids (minimum dose equivalent to prednisone 10 mg/day) documented clinically meaningful deterioration on interruption or reduction of therapy in the 18 months before screening. Sttable disease without a substantial change in treatment for the 6 weeks before randomisation. | I: n = 54  C: n = 52  Age  I: 54.3 ± 13.3  C: 55.6 ± 11.7  % male  I: 69%  C: 58% | Status: NR  Type: NR  Time since diagnosis:  I: 5.6 ± 5.7 yrs  C: 7.2 ± 6.5 yrs  Current treatment:  IVIg (77%)  Steroids (23%)  Note patients on steroids tapered their dose to 0 over 8 weeks | INCAT  I: 2.7 ± 1.5  C: 2.7 ± 1.7  MRC  I: 55.3 ± 5.3  C: 55.8 ± 5.5  SF-36  I: 40.4 ± 9.2  C: 41.2 ± 8.8  R-ODS  I: 65.7 ± 17.7  C: 66.3 ± 19.6 | Oral fingolimod (0.5 mg) daily. | Placebo (daily) |  |
| Studies investigating treatment refractory patients |  |  |  |  |  |  |  |  |
| Lieker et al. (2017) | PE vs Ia | Met EFN/PNS 2010 diagnostic criteria for possible, probable or definite CIDP. | I: n = 10  C: n = 10  Age  I: 65.44 ± 12.6  C: 65.4 ± 12.3  % male  I: 55.5%  C: 77.8% | Status: definite n = 9, probable/possible n = 9  Type:  Typica n = 7, atypical n = 11  Time since diagnosis:  I: 5.2 ± 4.3 years  C: 3.1 ± 2.3 yrs | INCAT  I: 3.6 ± 1.7  C: 3.1 ± 1.7  MRC  I: 61.7 ± 5.6  C: 61.8 ± 4.1 | PE (tryptophan-linked polyvinyl alcohol adsorber TR-350, after membrane plasma separation with the polyethylene plasma separator (OP-05) (Asahi Kasei Kuraray Tokyo, Japan) in combination with the Octo Nova extracorporeal circuit technology (SW 4.30.2, front 4.30.0, Dimed Medizintechnik, Cologne, Germany))  6 sessions with volume 2.5L over 12 days | IA (tryptophan-linked polyvinyl alcohol adsorber TR-350, after membrane plasma separation with the polyethylene plasma separator (OP-05) (Asahi Kasei Kuraray Tokyo, Japan) in combination with the Octo Nova extracorporeal circuit technology (SW 4.30.2, front 4.30.0, Dimed Medizintechnik, Cologne, Germany))  6 sessions with volume 2.5L over 12 days |  |

Abbreviations: I = intervention; C = comparator; MC = multicentre, DB = double blind; CO = crossover; TCNS = Toronto clinical neuropathy score; AMS = average muscle score.

Table 98 Summary of effectiveness data for other comparisons

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study ID | Follow-up  N | INCAT | MRC | NDS | Grip strength | Clinically meaningful response | Other outcomes |
| **Ig vs Ig** |  |  |  |  |  |  |  |
| Markvardsen et al. (2017) note IVIg vs SCIg | 10 weeks  I: 10  C: 10 |  | I: 0.5 ± 5.5  C: 1.1 ± 5.1  *P* = NS (NR) |  | 2.1 kg ± 14.71  C: 1.2 kg ±14.84  P = NS (NR) |  | 9PHT (s)  I: -4.3 ± 40.65, C: -2 ± 20.31, p = NS (NR)  40MWT (s)  I: -1.2 ± 7.763, C: -1.2 ± 6.62, p = NS (NR)  ODSS  I: -0.2 ± 1.56, C: -0.6 ± 1.64, p = NS (NR) |
| Kuitwaard et al. (2010) | Ig vs Ig  NR | MD 0.59 (95% CI -0.7, 1.8)  P = NS |  |  | MD (95% CI)  0.54 kPa (-0.7, 1.8) |  | All MD (95% CI)  ODSS  0.004 (-.4, 0.4) p = NS  FSS  0.18 (-1.9, 0.6) p = NS  Clinical grading  -0.58 (-1.9, 0.7) p = NS |
| **Ig vs Ia** |  |  |  |  |  |  |  |
| Zinman et al. (2005) | 26 weeks  I: 6  C: 4 |  |  |  |  | I: 3/6  C: 4/4  P = 0.2 |  |
| **St vs Pl** |  |  |  |  |  |  |  |
| Dyck et al. (1982)  USA | 6 weeks  I: 14  C: 14 |  |  | I: -20.64 ± 29.26  C: -3.5 ± 28.87  P = NR |  | I: 5/14  C: 3/14  P = NR |  |
| **St vs St** |  |  |  |  |  |  |  |
| PREDICT study van Schaik et al. (2010), Eftimov et al. (2012) | 32 weeks  I: 24  C: 16 | I: -1.46 ± 2.72  C: -0.1 ± 2.44  *P* = 0.19 | I: 4 ± 6.24  C: 1.6 ± 6.29  *P* = 0.24 |  | I: 8.1 kPa ± 28.79  C: 13.4 kPa ± 35.21  P = 0.61 | I: 13/24  C: 8/16  P = NS | ALDS  I: 13.5 ± 14.57, C: 16.9 ± 11.95, P = 0.47  SF36  I: 7.4 ± 12.07, C: 4.5 ± 12.48, P = 0.69 |
| **St vs St + Is** |  |  |  |  |  |  |  |
| Dyck et al. (1985) | 26 weeks  I: 10  C: 13 |  |  | I: -30 [-104, 20]  C: -29 [-84, 49]  P = NR | I: 1.2 kg [0.2, 15.3]  C: 4.5 kg [-0.3, 18.3]  P = NR |  |  |
| **PE vs pl** |  |  |  |  |  |  |  |
| Hahn et al. (1996a) and Ashworth et al. (2000) | 4 weeks  I: 15  C: 15 |  |  | I: -38 ± 6.95  C: 1.7 ± 9.86  P < 0.001 | I: 12.7 kg ± 3.63  C: 0.1 ± 4.11  P < 0.003 |  | Clinical grade  I: -1.6 ± 0.56, C: 0.4 ± 0.64, P < 0.001 |
| Dyck et al. (1986) | 3 weeks  I: 15  C: 14 |  |  | I -20.93 ± 31.93  C: -5.07 ± 14.47  P = NR |  |  |  |

Abbreviations: St = steroids; PE = plasma exchange; pl = placebo; Ia = immunoabsorption; I = intervenition; C = comparator; 9PHT = nine peh-hole test; 40MWT = 40 metre walk test; ALDS = Academic Medical Centre Linear Disability Score; SF36 = Short-Form-36; MRC = Medical Research Council Sum Score; INCAT = Inflammatory Neuropathy Cause and Treatment; NDS = Neurological Disability Score; ODSS = INCAT overall disability sum score; FSS = Fatigue Severity Scale.

Table 99 Studies included for the extended assessment of harms, key characteristics and safety data

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID**  **Level of evidence**  **Retrospective (R) / Prospective (P)**  **N** | **Inclusion criteria (simplified)** | | | | **Intervention**  **Comparator (if relevant)** | **Observation period**  **Comments regarding safety analyses** | **Any adverse event (AE), n/N (%)**  **Any serious adverse event (SAE), n/N (%)**  **Details of SAE** |
| **Level IV studies reporting on IVIg** | |  | | |  |  |  |
| Cocito 2014 (Cocito et al. 2014)  IV  R  66 | CIDP and Myasthenia gravis (EFNS/PNS criteria(Van den Bergh et al. 2010)) | | | | SCIg : 1-2g/kg, 1-3 Subcutaneous injections per week | < 6 months of follow-up  Authors report frequent and transient skin reactionsa butn/N not reported | 13/66 (20%)  1/66 (2%)  SAE: skin reaction (1) |
| Debes 2007 (Debes et al. 2007)  IV  P  36 | Multiple indications including CIDP (Criteria NR) | | | | IVIg: Individualised treatment | Mean follow-up: 440 days  AEs occurred in 4.2% of all patients and 0.35% of all infusions.  Non-serious (94.8%), mild/moderate (90.2%). Rigors were reported most frequently, followed by fever, headache, nausea and flush. n/N NR | 3/36 (8%)  NR |
| Grehl 1997 (Grehl et al. 1997)  IV  P  13 (with CIDP) | CIDP or MMN (AAN criteria(1991)) | | | | IVIg: *Induction*: 400 mg/kg/day for 5d  *Maintenance*: After 4 weeks or when symptoms returned 1 day of IVIg was givenb | 2-65 months follow-up  Erythrocyte sedimentation rate and serum IgG increased for a short period. All other laboratory values remained within the normal range. There was no hepatitis in any patient. Only one patient suffered from headache and nausea for some hours after  every day of IVIg infusions. n/N NR for general AEs | NR  0/13 (0%)  SAE: no severe side effects were observed |
| Jann 2005 (Jann et al. 2005)  IV  P  31 | Idiopathic CIDP +/- diabetes mellitus | | | | IVIg: *Induction*: 2g/kg over five days  *Maintenance*: repeated if the patient was initially a responder and they had a relapse | >24 months  The most frequent minor side effect was headache, which was easily controlled with symptomatic medications. n/N NR for general AEs. | NR  0/31 (0)  SAE: no severe side effects were observed |
| Katzberg 2013 (Katzberg et al. 2013)  IV  P  10 | CIDP (Koski criteria) for at least 3 months + at least on IVIg treatment in hospital w/o a major complication | | | | Home IVIg: *Induction*: in hospital  *Maintenance*: 1-2 g / kg every 3-4 weeks as per their protocols in the medical day unit. | 6 months  AEs NR except for mild headache (7/10); and nausea and leg heaviness (12.2% of infusions). n/N NR for general AEs. | NR  1/10 (10%)  SAE: polypharmacy with pain medications |
| Kuitwaard 2015 (Kuitwaard et al. 2015)  IV  R  281 | CIDP (EFNS/PNS criteria) + treatment naïve.[[33]](#footnote-34)  . | | | | IVIg: *Induction*: 2g/kg over 2-5 days  *Maintenance*: When required, regular attempts to reduce the dosage were performed to check whether patients were in remission or were still IVIg dependent | Mean 5.2 years  AEs resulting in discontinuation: 10/281 (3.6%). Authors note that most were relatively minor including headache. n/N NR for general AEs. | NR  3/281 (1%)  SAE: Steven Johnson syndrome (1), acquired haemolytic anaemia (2) |
| Kuwabara 2017 (Kuwabara et al. 2017)  IV  P  49 | CIDP (EFNS/PNS criteria), 43% had typical CIDP and the remainder had atypical CIDP | | | | IVIg: *Induction*: 0.4 g/kg/day for 5 days. *Maintenance*: 1.0 g/kg/day for 1 day | Unclear  Comprehensive AE reporting. Frequent adverse events were headache (32.7%), nasopharyngitis (28.6%) and skin rash (12.2%). No death occurred during the study. | 46/49 (94%)  6/49 (12%)  SAE: cerebral infarction  (2), aggravation of CIDP (2), cryptococcal pneumonia (1), cholesteatoma (1), inguinal hernia (1), anxiety neurosis (1) |
| Leger 2013 (Leger et al. 2013)  IV  P 28 | CIDP (EFNS/PNS criteria) | | | | IVIg: *Induction*: 2g/kg over 2-5 days  *Maintenance*: up to 7 infusions of 1g/kg at 3 weekly intervalsd | NR  A total of 108 AEs in 22 patients were recorded. Overall rate of AE per infusion of 0.47. 88% of all AEs were mild or moderate in intensity. n/N NR for general AEs. | 22/28 (79%)  4/28 (14%)  SAE: Haemolysis (2), CIDP deterioration (1), worsening of chronic sigmoid diverticulitis (1). The cases of haemolysis were considered related to the intervention. |
| Markvardsen 2014 (Markvardsen et al. 2014b)  IV  P 17 (data only presented for those who completed 6 months of follow-up) | CIDP (EFNS/PNS criteria) | | | | SCIg: Treatment regimen was individualised | 12 months  Authors state side effects were mild and limited to reactions at the injection sites with rash, redness and swelling. No new side effects to treatment nor any systemic reactions were observed. n/N NR for general AEs. | NR  0/17 (0%) |
| Merkies 2018 (Merkies et al. 2019)e  IV  P  207 (including PATH only, as the PRIMA study is reported by Leger) | CIDP (EFNS/PNS criteria) | | | | IVIg: *Induction*: 2.0 g/kg over 2-5 consecutive days. *Maintenance*: up to 7 doses of 1.0 g/kg every 3 weeks on 1-2 consecutive days | NR  A total of 284 AEs in 100 (48.3%) subjects (0.175/infusion). AEs reported. | 100/207 (48%)  7/207 (3%)  SAE: Hypersensitivity (1), pulmonary embolism (1), increased blood pressure (1), exacerbation of CIDP (1), respiratory failure (1), rash (1), migrane (1). |
| Querol 2013 (Querol et al. 2013)  IV  R  87 | CIDP (EFNS/PNS criteria) | | | | IVIg: Seventy-nine patients (91.9%) started IVIg at the 2-g/kg dose. The others received 1 g/kg. The most common course was administration over 5 days (73 patients, 84.9%). | Median 3.9 years  Authors report: No severe adverse reactions related to IVIg were reported during follow-up. | NR  0/87 (0%) |
| Rajabally 2006 (Rajabally et al. 2006)  IV  R  15 | CIDP (diagnosed on the basis of a relapsing-remitting sensory-motor disturbance with hyporeflexia or areflexia) | | | | IVIg: Most patients had been started on an approximate dose of 2 g/kg/course. | NR  Authors report incidents were rare (occurring in 9 administered IVIg, 2.2%) and minor, consisting mainly of rapidly resolving headaches. | NR  0/15 (0) |
| Rigas 2008(Rigas et al. 2008)  IV  R  44 (with CIDP) | Patients with neuroimmunologic disorder | | | | Home-based IVIg: Varied according to patient | NR  AEs reported. | 15/44 (34%)  NR |
| Robert 2015 (Robert et al. 2015)  IV  R  26 | CIDP (according to the clinical criteria of CIDP) | | | | IVIg: 2 g/kg body weight over 3 to 5 days via IV. The cycle of IV Ig could be repeated based on the physician's assessment and at a frequency decided by him/her, most often at 4-week intervals | Mean 9.4 months  AEs reported. | 17/26 (65%)  1/26 (4%)  SAE: Not related to the treatment or disease (generalised epileptic seizure secondary to discontinuation of medication prescribed for paraesthesia) |
| Sharma 2002 (Sharma et al. 2002)  IV  P  26 | Diabetes Mellitus + CIDP  (AAN criteria + chronic, progressive, or relapsing motor sensory or sensory-motor polyneuropathy > two months duration). | | | | IVIg: *Induction:* 400 mg/kg for 5 days  *Maintenance:* none reported | Median 25 months  AEs reported. | 14/26 (54%)  NR |
| Souayah 2011 (Souayah et al. 2011)  IV  R  167 | Neuroimmunology disorders | | | | Home-based IVIg: details NR | NR  Nature of AEs NR | 39/167 (23%)  NR |
| Wietek 2018 (Wietek 2018)  IV  R  58 | Patients with CIDP, myasthenia gravis, MS and MMN (criteria NR) | | | | Hospital or home-based IVIg  The mean dose per course for patients with CIDP was 0.8 g/kg bodyweight; the full dose was split over 2 or more days in 23.2% of courses. The mean dose per single infusion per day was 0.3 g/kg bodyweight. | NR  Nature of AEs NR | 5/58 (9%)  1/58 (2%)  SAE: NR |
| **Level III-3 studies considered as level IV evidence for each comparator** | | | |  |  |  |  |
| Choudry 1995 (Choudhary and Hughes 1995)  III-3 (IVIg v PE)  R  22 | CIDP considered by the consultant neurophysiologist to have demyelinating neuropathy | | | | IVIg: Either 0.4 g/kg/day for 5 days or 1 g/kg/day for 2 days. Frequency NR.  PE: Frequency NR however, initial treatment was 5 exchanges over 8-14 days. | NR  Nature of AEs only partially reported. The only AE detailed for PE was septicaemia arising from a tunnelled central venous catheter. | 6/22 (27%) vs 7/33 (21%)  1/22 (5%) vs NR  SAE: incomplete reporting. |
| Christiansen 2018 (Christiansen et al. 2018)  III-3 (IVIg v SCIg)  P  24 (12 in each group) | CIDP and MMN (EFNS/PNS criteria) | | | | IVIg: 3 or 6 weeks with an unchanged weekly dose of IVIg (NR).  SCIg: Injections were given 2 or 3 times weekly at a maximal volume of 20 ml at each injection site, with the total volume of immunoglobulin ranging from 76 to 303 ml weekly. | 20 weeks  Authors state: no patients reported any adverse events | 0/12 (0) vs 0/12 (0)  0/12 (0) vs 0/12 (0) |
| Cocito 2010 (Cocito et al. 2010)  III-3  R  IVIg: 153  Steroids: 155  PE: 21  Note: patients could switch between therapies so the numbers in each group are considered as all patients treated with the option as a first or second-line therapy | CIDP (EFNS/PNS criteria) | | | | Details of the interventions were not reported. | Highly varied according to patient and treatment.  AEs with each treatment are reported. | 6/153 (4%) vs steroids: 19/155 (12.5%) and PE: 4/21 (19%)  SAE: NR |
| Hung et al. 2018 (Hung et al. 2018)  III-3  R  31  IVIg: 15  Steroids: 10  Plasma exchange: 1  No treatment: 5 | CIDP (EFNS/PNS criteria) | | | | IVIg: Induction: 0.4 g/kg/day over 5 days. Maintenance: every 4-6 weeks  Comparators included oral prednisolone and plasma exchange however, **safety is only reported for IVIg patients** | >12 months  Some adverse events are reported, however, there is substantial uncertainty about patient numbers and interventions not reported in the study methods are reported in the text. | 5/8 (63%) – numbers in outcomes do not match demographic data  NR |
| Lopate et al. 2005 (Lopate et al. 2005)  III-3  R  39  IVIg: 27  IVMP: 16  Prednisone: 24  Cyclosporin: 13  methotrexate: 8 | CIDP (EFNS/PNS criteria) | | | | IVIg: 2g/kg over 2 days every 1-6 months  IV methylprednisolone (IVMP): 1000 mg/d of IVMP on each of 3 to 5 consecutive days, followed by 1000 mg IV on 1 day each week for the next month. IVMP was then tapered in frequency and dose over a period of 2 months to 2 years. All patients continued to receive IVMP no more than once a week.  Oral immunosuppressive including prednisone, cyclosporine further details not reported. | IVIg: 3.6 years, IVMP: 4.6 years, Oral agents: 4.7 years  Nature of AEs reported. | NR  NR  Nature of adverse events but not overall n/N experiencing them are reported |
| **Level II evidence** |  | | | |  |  |  |
| Hughes 2008 (Hughes et al. 2008)  II (crossover study decide)  117  IVIg:113  Placebo: 95  Patients could be counted in > 1 group | CIDP patients (motor and sensory dysfunction) with significant disability (INCAT 2-9) | | | | IVIg 2g/kg over 2-4 days followed by 1g/kg over 1-2 days every 3 weeks  Placebo infusion | > 24 weeks  Nature of AEs reported, distinction between SAE and non-SAE unclear. | 85/113 (75%) vs 45/95 (47%)  6/113 (5%) vs 8/95 (8%)  SAE: All SAEs NR |
| Hughes 2001(Hughes et al. 2001)  II (crossover study decide)32  Patients could be counted in > 1 group | Diagnosis of CIDP by neurologist, progressive or relapsing motor and sensosory dysfunction of > one limb resulting from neuropathy developing over > 2months. | | | | IVIg: 1.0g/kg on 2 consecutive days  Oral prednisolone 60 mg each morning for 2 weeks, 40 mg each morning for 1 week, 30 mg each morning for 1 week, 20 mg each morning for 1 week and then 10 mg each morning for 1 week. | <8 weeks  Nature of AEs reported. | 18/30 (60%) IVIg courses vs 11/27 (41%) prednisolone  1/30 (3%) vs 1/27 (4%)  SAE: IVIg - heart failure (1), prednisolone – psychosis (1) |
| Mendell 2001 (Mendell et al. 2001)  II  Parallel assignment  53 | Patients fulfilling diagnostic criteria for definite or probable CIDP | | | | IVIg 1.0 g/kg on 2 consecutive days, on day 21 a single dose.  Placebo infusion | 6 weeks  Nature of AEs reported. | NR  NR  Overall AEs NR however specific AEs reported |
| Nobile-orazio 2012 (Nobile-Orazio et al. 2012b)  II  Parallel assignment  45 | Definite typical CIDP according to EFNS/PNS criteria | | | | IVIg 0.5 g/kg daily for 4 consecutive days (+IV steroid placebo) then every 28 days for 6 months. After 6 months therapy was discontinued.  IVMP 0.5 g in 250 mL daily for 4 consecutive days (+IVIg placebo) then every 28 days for 6 months. After 6 months therapy was discontinued. | 12 months  Nature of AEs reported. | 11/24 (46%) vs 14/21 (67%)  2/24 (8%) vs 1/21 (5%)  SAE: IVIg – cardiac arrest (1), respiratory failure (1) both resulting in death, methylprednisolone – gastritis (1) |
| Van Schaik 2010 (van Schaik et al. 2010)  II parallel assignment  40 | Definite or probable CIDP according to EFNS/PNS criteria | | | | Oral dexamethasone 40 mg per day for 4 consecutive days then placebo for 24 days repeated 6 times as a 28 day cycle  Oral prednisolone 60 mg per day for 5 weeks tapering to alternative day doses then zero over 27 weeks | 12 months  Nature of AEs reported. | NR  NR  Overall AEs NR however specific AEs reported |
| **Level IV evidence for active comparators** | | |  | |  |  |  |
| Barnett 1998 (Barnett et al. 1998)  IV  R  19 | Patients with CIDP diagnosed by an accepted combination of neurophysiological, and biopsy criteria. MGUS (n = 5), polyclonal gammopathy (n = 1) | | | | Cyclosporin: 8-11 mg/kg per day in n = 8, 3-7 mg/kg per day in n = 10. A stepwise reduction in dose was made at 1 month, 3 months, and 6 months, generally to 2–3 mg/kg. | 4-7 years (progressive – relapsing disease)  Nature of AEs reported. | 13/19 (68%)  NR |
| Benedetti 2011 (Benedetti et al. 2011)  IV  R  13 | Patients with CIDP (EFNS/PNS criteria), four patients had comorbid haematological disease | | | | Rituximab: 375 mg m2 IV weekly for 4 consecutive weeks. One patients with severe Waldenstrom macroglobulinemia received 1000 mg IV every 6 months for four years | 1-5 years  Nature of AEs reported. | 2/13 (15%)  0/13 (0%) |
| Boru 2014 (Boru et al. 2014)  IV  R  15 | CIDP based on clinical examination, laboratory findings, electrophysiologic examination and nerve biopsy (at least one set of AAN criteria) | | | | IVMP: 1000 mg/day for 10 days followed by 1000 mg/day IV once every 4 weeks for 5 years. | 10 years  Nature of AEs reported. | 7/15 (47%)  0/15 (0%) |
| Cocito 2011 (Cocito et al. 2011)  IV  R  110 | CIDP patients (EFNS/PNS criteria) who had not responded to conventional therapy | | | | Azathioprine :100–200 mg/daily  cyclophosphamide: 1 g/m2 IV/monthly, or 2 mg/kg/daily  Mycophenolate mofetil: 1– 2 g/daily Cyclosporine 100–300 mg/daily Methotrexate 7.5–15 mg/weekly Rituximab 375 mg/m2/  week · 4 weeks or 1 g twice, at 2 week intervals; interferon-alpha 800 000–3 million U · 1–3 weeks; and interferon beta-1a 6 million U. | Median 5.4 years  Nature of AEs NR | Any AE: Azathioprine (n = 16/77); rituximab (n = 2/18); Cyclosporin (n = 6/12); Cyclophosphamide (n = 2/13); Methotrexate (n = 1/12); Mycophenolate Mofetil (n = 2/12); interferon beta (n = 0/3); interferon-alpha (n = 1/11)  SAE: Azathioprine (n = 10/77); Cyclosporin (n = 5/12); Cyclophosphamide (n = 1/13) |
| Dorst 2018 (Dorst et al. 2018)  IV  P  17 | CIDP (EFNS/PNS criteria) who had not responded to steroids, IVIg or both treatments. | | | | Immunoadsorption: Shaldon catheter (jugular vein). One cycle of IA consisted of five treatments on 5 consecutive days. Range of cycles was 1-9 per patient. | NR  Nature of AEs reported | 2/17 (12%)  NR |
| Fialho 2006 (Fialho et al. 2006)  IV  R  10 | CIDP fulfilling recognised clinical criteria and neurophysiological evidence of demyelination | | | | Methotrexate: according to patient needs from 10-15 mg weekly for as long as clinically appropriate | NR  Nature of AEs reported | 3/10 (30%)  1/10 (10%)  SAE: death (1) due hypotension and fever of unknown origin. |
| Galldik 2011 (Galldiks et al. 2011)  IV  R  14 | CIDP patients (according to current diagnostic guidelines) who had an unsatisfactory response to at least two of steroids, IVIg or plasma exchange. | | | | Immunoadsorption: Double-lumen central venous catheter in the jugular or subclavian vein: frequency adjusted according to clinical signs and fibrinogen levels. If necessary, treatment intervals were extended depending on the degree of fibrinogen depletion. Ten patients were treated in-hospital. Four of these 14 patients were treated in outpatient clinics using long-term maintenance IA with 1–2 treatments per week. | NR  Authors report in all patients, Immunoadsorption was safe and well tolerated, and no  severe side effects occurred. | NR  0/14 (0%) |
| Good 1998 (Good et al. 1998)  IV  P  15 | CIDP according to established criteria | | | | IV Cyclophosphamide: 1 g/m2 over 1.5-2 hours as initial treatment and as monthly pulse treatments unless they showed sustained improvement over three courses of pulse. In patients failing to show a significant leukocyte count drop the dose was increased by 25% on subsequent pulses. | Mean 36.6 months  Nature of AEs reported. | Overall AEs NR |
| Gorson 2004 (Gorson et al. 2004)  IV  R  21 | Patients with demyelinating polyneuropathy fulfilling criteria for CIDP | | | | Mycophenolate Mofetil: Mean dose 2.1 g/day, and the average duration of therapy was 13 months (range, 9 to 18 months) | NR Nature of AEs reported. | 5/21 (24%)  NR |
| Molenaar 1997(Molenaar et al. 1997)  IV  R  10 | CIDP patients (electrophysiological criteria of the AAN) | | | | Dexamethasone: 40 mg per day for four days in weeks 1, 4, 7, 11, 15 and 19 | NR Nature of AEs reported. | 6/10 (60%)  NR |
| Muley 2008 (Muley et al. 2008)  IV  P  10 | CIDP patients (criteria NR) | | | | Pulsed oral prednisolone: 500 mg once a week for 3 months with dose adjustment every 3 months by 50 to 100 mg depending on the clinical  status | NR  Nature of AEs reported. | Overall AEs NR |
| Roux 2018 (Roux et al. 2018)  IV  R  28 | CIDP patients (EFNS/PNS criteria) | | | | Rituximab: Varied. The most frequent was a first injection (1 g) followed by a second one (1 g) 2 weeks later (for 13 patients). Two patients received weekly infusions of 375 mg/m2 for 4 weeks; and nine patients received 375 mg/m2/month for 4 or 6 months, five of whom received rituximab with another chemotherapy because of a haematological indication. One patient (with lupus) received one infusion of 375 mg/m2 every 3 months for 3 years. | Median 2 years  Nature of AEs reported. | 3/28 (11%)  1/28 (4%)  SAE: CNS lymphoma (1) 7 months after rituximab infusion. |
| Vucic 1998 (Vucic and Davies 1998)  IV  R  32 | CIDP patients (criteria NR) undergoing plasmapheresis | | | | Plasma exchange: The duration of each procedure was 1.5-2 hours. Five per cent human serum albumin (5% NSA) alone or formulated with normal saline was the usual replacement fluid. Anticoagulant citrate dextrose (ACD) was the anticoagulant used in all procedures | NR  Nature of AEs incompletely reported. | 13/32 (41%)f  NR |
| Wertman 1988 (Wertman et al. 1988)  IV  R  16 | CIDP (Author modified criteria) | | | | High-dose steroids: 1-1.5 mg/kg/day of prednisone. Patients who on efforts to withdraw experienced relapse were treated with medium dose steroid therapy (0.5-.75 mg.kg/day) for prolonged periods. | Mean 5.2 years  General AEs NR | NR  7/16 (43%)  SAE: Cushingoid appearance (3); GI bleeding (2); infection complications (3); death (1, urinary sepsis) |

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society; AAN: Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force. a without generalised symptoms and localised to the injection sites; b If after induction + 2 maintenance doses there was no response treatment stops, otherwise each patient received monthly maintenance treatment; c Six patients experienced eight serious adverse events; d All patients had interruption of IVIg (if they were allready in receipt) for up to 10 weeks until deterioration occurred that allowed eligibility; e Also includes data reported by another publication (Merkies et al. 2019); f The 24.7 per cent of patients who experienced one adverse reaction had a mean of 12 episodes of plasmapheresis. In patients experiencing two to five complications the mean was 18 and one patient with six episodes of complication had 30 treatments. There was a linear relationship between the frequency of adverse reactions and the number of treatment episodes for an individual patient. No adverse reactions were recorded in 60.3 per cent of patients. There were no fatalities in the study group. Complications rated as severe occurred in 0.7 per cent of procedures. The most frequent of these was infection of the venous access site, occurring in 0.5 per cent of procedures. Sepsis was an accompanying feature in 0.2 per cent of procedures. None of the three patients so affected was judged to have any deterioration in their underlying neurological condition.

# Appendix E Excluded Studies

## Studies on CIDP excluded:

**Randomised controlled trials excluded due to lack of safety data (note these studies were included for the effectiveness section)**

Ashworth NL, Zochodne DW, Hahn AF, Pillay N, Chalk C, Benstead T, et al. Impact of plasma exchange on indices of demyelination in chronic inflammatory demyelinating polyradiculoneuropathy. Muscle and Nerve. 2000;23(2):206-10.

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Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, crossover study. Brain. 1996b;119(4):1067-77.

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Lieker I, Slowinski T, Harms L, Hahn K, Klehmet J. A prospective study comparing tryptophan immunoadsorption with therapeutic plasma exchange for the treatment of chronic inflammatory demyelinating polyneuropathy. Journal of Clinical Apheresis. 2017(pagination).

**Randomised controlled trials excluded due to overlap with another study included**

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**Non-RCT comparative studies that were excluded due to a lack of safety data**

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van Lieverloo GGA, Peric S, Doneddu PE, Gallia F, Nikolic A, Wieske L, et al. Corticosteroids in chronic inflammatory demyelinating polyneuropathy: A retrospective, multicentre study, comparing efficacy and safety of daily prednisolone, pulsed dexamethasone, and pulsed intravenous methylprednisolone. Journal of Neurology. 2018;265(9):2052-9.**Case series studies of IVIG excluded due to lack of safety data**

Berg R, Fuellenhals E. Aseptic meningitis following therapy with immune globulins: a combination of product features and patient characteristics? Transfusion. 2016;56(12):3021-8.

Cirillo G, Todisco V, Tedeschi G. Long-term neurophysiological and clinical response in patients with chronic inflammatory demyelinating polyradiculoneuropathy treated with subcutaneous immunoglobulin. Clinical Neurophysiology. 2018;129(5):967-73.

Dyer WB, Tan JC, Day T, Kiers L, Kiernan MC, Yiannikas C, et al. Immunomodulation of inflammatory leukocyte markers during intravenous immunoglobulin treatment associated with clinical efficacy in chronic inflammatory demyelinating polyradiculoneuropathy. Brain Behav. 2016;6(10):e00516.

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Jann S, Bramerio MA, Facchetti D, Sterzi R. Intravenous immunoglobulin is effective in patients with diabetes and with chronic inflammatory demyelinating polyneuropathy: Long term follow-up. Journal of Neurology, Neurosurgery and Psychiatry. 2009;80(1):70-3.

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**Case series of comparators excluded due to lack of safety data**

Barnett MH, Pollard JD, Davies L, McLeod JG. Cyclosporin a in resistant demyelinating polyradiculoneuropathy. Muscle and Nerve. 1998;21(4):454-60.

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1. Population, Intervention, Comparator, Outcomes [↑](#footnote-ref-2)
2. The relationship between rituximab and risk of malignancy is not yet fully elucidated in the clinical literature. These patients may have had other predisposing factors to development of lymphoma including monoclonal gammopathies with three different isotypes. [↑](#footnote-ref-3)
3. This scenario is included in the economic model by assuming an annual steroid non-response probability of 99.99% [↑](#footnote-ref-4)
4. The ARTG Public Summary Documents state that the route of administration for Gamunex is intravenous or subcutaneous, whilst the route of administration for Hizentra is subcutaneous only. [↑](#footnote-ref-5)
5. SCIg use for the management of CIDP became funded by the NBA during the process of drafting this report. The report is written from the perspective that SCIg is not funded, but may be funded for CIDP in the future. [↑](#footnote-ref-6)
6. This excludes patients reported by Dyck 1994 and Zinman 2005 as it could not be assumed that other adverse events reported in these studies did not occur. [↑](#footnote-ref-7)
7. One patient died because of cardiac arrest one month after the last course of IVIg and two days after the 6-month visit. The patient had hypertension and cardiovascular risk

   factors and was treated with oral anticoagulants, but a possible relation to the assigned treatment could not be excluded. [↑](#footnote-ref-8)
8. Developed heart failure four weeks after receiving IVIg, relationship to the intervention is uncertain. [↑](#footnote-ref-9)
9. Adverse events occurred after the patient had shifted to the alternative therapy. [↑](#footnote-ref-10)
10. Van Shaik reports events separately for the treatment and the follow-up period. Since patients were counted twice, if they continued to have the event into the follow-up period only the treatment period events are included in the n/N (%) calculation. However, this may underrepresent the true frequency of events. [↑](#footnote-ref-11)
11. This patient also had a severe relapse of symptoms. [↑](#footnote-ref-12)
12. This patient, who had been treated with two infusions of IVIg during the first period and had crossed over (25 days after the last infusion of IGIV-C) to placebo, developed fatal sepsis. Fourteen days after the last placebo infusion during the crossover period, this patient had withdrawn from the study owing to an insufficient therapeutic effect and sepsis developed about six weeks after withdrawal from the study. [↑](#footnote-ref-13)
13. Previously unrecognised and was withdrawn from the trial; did not receive IVIg and died 22 weeks after randomisation. [↑](#footnote-ref-14)
14. This patient received six courses of IVIg after having worsened after one course of IV methylprednisolone. Three months after the last course of IVIg

    and two months after the 6-month visit he died of respiratory failure. This death was not thought to be treatment related. [↑](#footnote-ref-15)
15. In one of the two patients the adverse event occurred after the patient had shifted to the alternative therapy. [↑](#footnote-ref-16)
16. Two studies contributing isolated adverse events are mentioned in the text but not formally included owing to the paucity of data. Dyck, PJ, Litchy, WJ, Kratz, KM, Suarez, GA, Low, PA, Pineda, AA, Windebank, AJ, Karnes, JL & O'Brien, PC 1994, 'A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy', *Ann Neurol*, vol.36, pp. 838-45, Zinman, LH, Sutton, D, Ng, E, Nwe, P, Ngo, M & Bril, V 2005, 'A pilot study to compare the use of the Excorim staphylococcal protein immunoadsorption system and IVIG in chronic inflammatory demyelinating polyneuropathy', *Transfusion and Apheresis Science*, vol.33, pp. 317-24. [↑](#footnote-ref-17)
17. Adverse events will not sum to 38 as some patients experienced > 1 event. [↑](#footnote-ref-18)
18. An emergency coronary angiogram showed an isolated thrombotic occlusion of the left anterior descending coronary artery associated with a mild localised stenosis but no other evidence of coronary artery disease. The coronary circulation was restored by an angioplasty and the patient made a full recovery. While being observed in the coronary care unit, his neurological function deteriorated rapidly and he became quadriplegic, despite prior and ongoing prescription of prednisone 60 mg daily for eight weeks. He then responded favourably to treatment with IVIg. [↑](#footnote-ref-19)
19. Several studies reported that many patients in their series experienced headache, however actual numbers were not reported. Consequently, this outcome is likely to be under-reported in the included studies. [↑](#footnote-ref-20)
20. Includes only patients who experienced this event and where the event continued into, or developed within, the extended follow-up period. [↑](#footnote-ref-21)
21. The relationship between rituximab and risk of malignancy is not yet fully elucidated in the clinical literature, however, this patient may have had other predisposing factors to development of lymphoma including monoclonal gammopathies with three different isotypes. [↑](#footnote-ref-22)
22. Significant disability in upper or lower limb functions (at least arm disability grade 2 or leg disability grade 1), stable or worsening clinical condition (not improving spontaneously) [↑](#footnote-ref-23)
23. Induction as two 1g/kg doses and maintenance as a single 1g/kg dose every 3 weeks (19.3g/kg, or 1,447g in the first year). Assuming an average Australia patient weight of 82.5kg, annual Ig usage would be 1,594g at 19.3g/kg. [↑](#footnote-ref-24)
24. Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [↑](#footnote-ref-25)
25. Fenofibrate Intervention and Event Lowering in Diabetes [↑](#footnote-ref-26)
26. Induction as two 1g/kg doses, and maintenance as a single 1g/kg dose every 3 weeks = 19.3g/kg, or 1,447g in the first year. Assuming an average Australia patient weight of 83kg, annual Ig usage would be 1,601g at 19.3g/kg [↑](#footnote-ref-27)
27. The authors noted (p. 558) that after the end of initial treatment, patients who responded to treatment moved to a remission state and were assumed to switch to corticosteroids alone. Patients not responding to initial treatment were assumed to receive additional IVIg plus corticosteroids for another cycle, then either responded or relapsed. [↑](#footnote-ref-28)
28. Induction as two 1g/kg doses, and maintenance as a single 1g/kg dose every 3 weeks ie 19.3 g/kg or 1,447g in the first year. [↑](#footnote-ref-29)
29. Patients on > 20mg prednisolone for > 2 weeks may also require additional management for prevention of infectious complications. This includes testing for latent infection (e.g. hepatitis B) and prophylactic antibiotics for prevention of opportunistic infection. [↑](#footnote-ref-30)
30. 4364.0.55.001 - National Health Survey: First Results, 2017-18. [↑](#footnote-ref-31)
31. This scenario is included in the economic model by assuming an annual steroid non-response probability of 99.99%. [↑](#footnote-ref-32)
32. ttps://www.abs.gov.au/AUSSTATS/abs@.nsf/mf/3101.0 [↑](#footnote-ref-33)
33. Patients with an IgG or IgM monoclonal gammopathy of undetermined significance (MGUS) were only included when they had a clinical course fully consistent with CIDP. Patients with an IgM MGUS who had antibodies against myelin-associated glycoprotein were excluded [↑](#footnote-ref-34)