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Public Summary Document

Application No. 1592 – Review of immunoglobulin use for primary immunodeficiency diseases with antibody deficiency (PID)

**Applicant: National Blood Authority (NBA)**

**Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

# Purpose of application

This Post-market Review requested MSAC advice on the Government funded supply of replacement human gamma immunoglobulin (IgG) therapy under the National Blood Arrangements for the treatment of primary immunodeficiency diseases with antibody deficiency – hereafter referred to as primary immunodeficiency diseases (PID). The application (referral) was received by the Department of Health from the National Blood Authority (NBA).

# MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to the comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported continued funding of Ig therapy for the treatment of PID. MSAC suggested changes to BloodSTAR are required to improve data collection and reporting, and that further research could be scoped to address data gaps to inform cost-effectiveness. MSAC noted that the available evidence suggests that Ig is safe and is likely to be an effective therapy in this population, however the cost-effectiveness is uncertain. MSAC noted that Ig has been the standard of care in patients with PID since the 1950s, and considered the high clinical need to be important in this population.

The total Ig costs, (including delivery) were estimated to be $50.5 million in 2021, increasing to $53.5 million in 2025. MSAC considered current thresholds to access Ig therapy under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) (the Criteria) for this indication are insufficiently defined.

MSAC considered data collection and reporting could be optimised through BloodSTAR, and proposed further work be done to identify areas for research which may inform any future evaluations of cost-effectiveness. MSAC was of a mind to review the application in 12 months’ time, should additional data become available to inform the cost-effectiveness of Ig in this population.

| **Consumer summary** |
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| The National Blood Authority (NBA) sought advice from MSAC on the government-funded supply of human antibodies (immunoglobulin, or Ig) used to treat primary immunodeficiency diseases (PID) with antibody deficiency. The NBA is the statutory agency within the Australian Government Health portfolio that manages and coordinates arrangements for the supply of blood and blood products and services on behalf of the Australian Government and state and territory governments. This referral to review the use of Ig in PID is included as part of the Ig Reviews, which aim to ensure that government-funded Ig use within Australia is based on evidence of clinical safety, effectiveness and cost-effectiveness.  PID refers to a large group of various conditions in which part of the body's immune system is missing or does not work properly to fight infection. PID is inherited via problems in the genes that control the immune system. PID may present at any age; however, more severe forms, such as severe combined immunodeficiency (SCID), generally become apparent early in life whilst other PID, such as common variable immunodeficiency (CVID), are more commonly diagnosed in adults. People with PID are more likely to get infections and for those infections to be more severe.  MSAC considered that Ig therapy appears to be safe and likely to be clinically effective. Therefore, Ig should continue to be available to treat people with PID, but further research should be done and more information needs to be collected to support Ig use for these conditions.  MSAC noted that continued Ig treatment should only be prescribed to those people with PID who get a demonstrated ongoing benefit. This is important because people should only have treatments that help them – and Ig is very expensive. Over the next five years, the cost to government of supplying Ig is estimated to increase from approximately $50.5 million in 2021 to $53.5 million in 2025. One way to do this is to analyse data collected from BloodSTAR (<https://www.blood.gov.au/bloodstar> ), the online system used across Australia to manage access to the supply of government funded immunoglobulin products. The requirements to access Ig therapy (i.e. the Version 3 Criteria) were revised in October 2018, and aim to limit the use of Ig to people with PID whose symptoms improve on Ig therapy. MSAC proposed that further work be done to identify areas for potential change or further research, which may inform any future evaluations of clinical effectiveness and cost-effectiveness. |

| **MSAC’s advice to the National Blood Authority** |
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| MSAC noted that Ig therapy is standard of care for people living with PID; and the evidence suggests Ig is safe and probably clinically effective.  MSAC discussed how the evidence base for use of Ig could be improved (safety, clinical effectiveness and cost-effectiveness) and concluded by suggesting a scoping exercise to explore the feasibility of conducting further research be undertaken. This could inform a decision whether to make an application to the Medical Research Future Fund (MRFF) or research funding available in other ways, including under the national blood arrangements.  MSAC advised that no immediate changes were required to the Criteria (version 3), but recommended that reviewing the utilisation data collected by the NBA (BloodSTAR) in 12 months would provide a more definitive answer as to whether further changes are required.  After considering the strength of the available evidence in relation to the comparative safety, clinical effectiveness and cost-effectiveness MSAC supported continued funding of immunoglobulin (Ig) therapy for the treatment of PIDs with antibody deficiency. |

# Summary of consideration and rationale for MSAC’s advice

In Australia, Ig for the treatment of PID is funded for subcutaneous (SC) and intravenous (IV) administration and is considered the standard of care for patients with PID, accounting for 12% of Ig used in 2017/18. Version 3 of the Criteria categorises Ig use in this population as a “Condition for which Ig has an established therapeutic role”, with a ‘Level of evidence’ Category 2A (evidence of probable benefit – more research needed).

MSAC noted patients with PID with antibody deficiency may be eligible for treatment under the Criteria for the clinical use of immunoglobulin in Australia (Version 3) under the following specific conditions:

* Severe combined immunodeficiency (SCID)
* Combined immunodeficiency (e.g. thymoma)
* Combined immunodeficiency with associated or syndromic features (e.g. Wiskott Aldrich syndrome; ataxia telangiectasia)
* Possible CVID – below normal serum IgG but normal serum IgA
* Severe reduction in all Ig isotypes with decreases or absent B-cells (e.g. XLA def)
* Severe reduction in at least two Ig isotypes with low/normal B-cells (e.g. CVID)
* Severe reduction in serum IgG and IgA with normal /elevated IgM (e.g. CD40L def)
* Transient hypogammaglobulinaemia of infancy
* Lymphoproliferative syndromes (e.g. XLP1, XLP2, CD27 def).

MSAC noted that PID is a heterogeneous group of rare disorders. These patients have absent or impaired immune function and are prone to infection, inflammatory disorders, cancer and autoimmune diseases. The most common of these is CVID, accounting for over 86% of Ig used and 80% of patients treated with Ig for PID in 2018/19, according to NBA data.

In order to access Ig therapy for PID, a diagnosis must be made by an immunologist and eligible patients may initially receive Ig for a maximum of six months. Review by an immunologist is required after the initial six months of Ig treatment to determine eligibility for a further 12 months of treatment, and ongoing reviews are required at least annually thereafter to assess clinical benefit and to consider cessation of Ig therapy. MSAC noted the threshold requirement to demonstrate treatment response (i.e. serum Ig levels and history of infection) was not currently well defined but considered there may be potential to do so. The Criteria states that cessation of Ig therapy should be considered at least after each 12 months of treatment. MSAC acknowledged advice from the Immunoglobulin Review Reference Group (the Reference Group) that it was unlikely that patients with CVID who start Ig would cease therapy due to absence of effect and Ig treatment was generally lifelong in the absence of curative stem cell transplantation.

Overall, MSAC considered the high clinical need in this population to be extremely important, noting this varies for the range of conditions of differing severity encompassed under this broad indication. In the year 2018-2019, 2,292 patients accessed services for Ig treatment for PID and MSAC noted Ig therapy has been the standard of care in patients with PID since the 1950s. MSAC agreed the comparator to Ig was no Ig (may or may not include supportive care including antibiotic treatment, prophylactic antibiotics and antimicrobials), and considered each component of the PICO Confirmation to be appropriate.

The Contracted Assessment Report included a systematic review of published literature that identified four non-randomised comparative studies (1 with IVIg: n=47), and 17 single-arm case series studies (n=1,010). The studies were of low or very low quality and at high risk of bias, and only included patients with CVID.

With respect to comparative safety, MSAC noted that Ig is inferior to no Ig, but was generally well-tolerated. Reported adverse events (AEs) associated with Ig reported from 10 single-arm studies (n=739) were mostly mild and included chills, flushing, fever, nausea, headache, muscle ache. Moderate AEs associated with IVIg including rash, abdominal pain, joint pain, chest tightness and vomiting were resolved by slowing or stopping the infusions. Severe AE’s associated with IVIg were rare (0-5% of patients/0%-0.2% of infusions). MSAC noted that no comparative safety data were identified, and most studies reported AEs across the entire PID population of the study rather than reporting outcomes for CVID separately (i.e. not disease specific).

With regards to clinical effectiveness of Ig, one retrospective study (Aghamohammadi et al 2009)[[1]](#footnote-1) comparing patients with CVID on Ig (n=23) to patients with CVID not treated with Ig due to delayed diagnosis (n=24) found IVIg treatment was associated with improved patient outcomes (higher IgG levels, lower infection rates, hospitalization, bronchiectasis, mortality). Other studies consisted of 11 single-arm CVID pre-post treatment studies that concluded improved IgG levels, infection/ hospitalisation rates and antibiotic usage. Overall, MSAC noted the available evidence was of poor quality with high risk of bias. Co-interventions   
(e.g. prophylactic antibiotics, chest physiotherapy, steroids, bronchodilators) and confounding factors were generally not reported and it was not clear if any eligible patients were excluded from analysis. The impact these issues have on results of clinical outcomes is uncertain. MSAC noted that the age of patients in the studies was markedly lower than the average age of patients with CVID receiving Ig funded by the NBA (53 years), but considered that data from studies reporting a mean age similar to that of Australian patients receiving NBA-funded Ig were consistent with the overall results of the assessment. Based on the evidence presented, MSAC considered that relative to No Ig, Ig is likely to have superior effectiveness.

Due to limitations with the available evidence, a simplified cost-consequence analysis (CCA) was conducted to estimate the economic impact of Ig for PID patients. The CCA was limited to a one-year time horizon and considered the cost differences between Ig and no Ig in terms of Ig itself, Ig administration costs, and the incremental costs of treating serious infections and managing bronchiectasis. In the base case (Ig cost per gram of $60.41), the overall incremental cost per year per patient was estimated to be $18,282.01, driven largely by the direct cost of Ig product (see Table 4). One-way sensitivity analyses were performed using the lowest cost of $44.94 (imported IVIg), highest cost of $140.18 (domestic IVIg, including plasma collection and fractionation), and weighted average cost of Ig across all indications ($94.51).

Regarding financial and budgetary impacts, MSAC noted the total Ig costs (including delivery) was estimated to be $50.5 million in 2021, increasing to $53.5 million in 2025. The delivery cost of Ig for PID patients accounted for approximately 13.64% of the total costs, and this proportion was stable over the five projected years. Costs for IVIg delivery was estimated to be $5,202 per patient per year, whereas SCIg delivery incurred much lower costs at $1,404.20.

MSAC recommended that Ig therapy should continue to be funded for this population, with potential changes required with respect to improved data collection and further research. MSAC accepted the findings of the review that evidence from studies and systematic reviews suggests that Ig treatment in patients with PID is safe and likely effective, but its cost-effectiveness is uncertain. Stakeholder feedback was highly supportive of Ig, which was seen to improve patients’ quality of life (QoL) and ability to contribute to society.

MSAC noted, and concurred with ESC advice to consider amending the Criteria in patients with CVID or possible CVID for the age of onset from > 4 years to > 2 years. In addition MSAC noted children are currently able to access Ig through the indication ‘Replacement therapy in transient hypogammaglobulinaemia of infancy’ – although this is a separate disease entity to CVID. MSAC considered that the NIGAC or Immunology Specialist Working Group (SWG) was best placed to review and implement changes to the age limit. MSAC noted that new established newborn screening programs in NSW and ACT for the most severe forms of PID are likely to bring forward the age of diagnosis for some children, increasing the clinical need for early treatment.

MSAC noted it is unlikely that higher quality studies would be forthcoming and that due to the low incidence of PID, recruiting enough patients for a large prospective trial may not be feasible or ethical. However, MSAC considered that data collection through BloodSTAR, and reporting of outcomes, could be enhanced noting the current data fields to be completed for continuation of therapy are not very detailed or specific. MSAC proposed that including details of patients’ hospitalisation episodes, duration of hospital/ICU stay; days off work; mortality data; Ig trough levels could also be considered.

MSAC proposed a scoping exercise to explore the feasibility of conducting further research be undertaken. This would identify areas for potential research which may inform any future evaluations of clinical- and cost-effectiveness and inform the decision whether to make an application to the Medical Research Future Fund (MRFF). MSAC considered this could include: better defining eligibility requirements to access Ig therapy (minimum thresholds for effectiveness); research into PID subtypes and Ig usage patterns to identify patients able to stop/reduce Ig usage; evaluating the use of ideal body weight (IBW) to calculate Ig dose. Linkage of BloodSTAR data to hospitalisation records, Medicare, PBS and mortality data may facilitate researchers to study healthcare use, co-interventions and outcomes. MSAC also noted that stakeholders were supportive of SCIg uptake which may improve access and reduce the burden of accessing Ig treatment, and considered that further research could be done to explore dose-equivalence comparisons between SCIg and IVIg. MSAC was of a mind to review the application in 12 months’ time, should additional data become available to inform the cost-effectiveness of Ig in this population.

# Background

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

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

Four reports from the Ig Reviews have been considered by MSAC so far:

* Application 1564 – Immunoglobulin for chronic inflammatory demyelinating polyneuropathy
* Application 1565 – Immunoglobulin for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
* Application 1566 – Immunoglobulin for myasthenia gravis
* Application 1590 – Immunoglobulin for multifocal motor neuropathy

Application 1591 and 1592 are the next two reports from the Ig Reviews to proceed to MSAC.

# Prerequisites to implementation of any funding advice

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). Ig for this indication is already funded by the NBA. The purpose of this application is to consider the clinical effectiveness and cost-effectiveness of these products as currently funded under the Criteria V3. Ig products registered by the TGA for the potential treatment of PID in Australia are summarised in Table 1; those currently funded by the National Blood Authority (7 products) are highlighted in grey. It is important to note that the funded Ig products may change over time, dependent on agreements with suppliers.

**Table 1** **Ig products indicated for PID listed on the ARTG according to the referral form**

| **ARTG no.** | **Product name** | **Product description** | **Sponsor** |
| --- | --- | --- | --- |
| **IVIg** | | | |
| 143803 (20g/400ml); 143802 (10g/200ml); 143801 (5g/100ml); 143800 (2.5g/50ml); 140602 (0.5g/10ml) | Flebogamma 5% | 5% DIF Human normal immunoglobulin intravenous use injection vial | Grifols Australia Pty Ltd |
| 182359 (20g/200ml); 182358 (10g/100ml); 184353 (5g/50ml) | Flebogamma 10% | 10% DIF Human normal immunoglobulin intravenous use injection vial | Grifols Australia Pty Ltd |
| 162489 (20g/200ml); 162488 (10g/100ml); 162487 (5g/50ml); 162486 (2.5g/25ml) | Intragam 10% | Normal immunoglobulin (human) solution for injection vial | CSL Behring Australia Pty Ltd |
| 164549 (10g/200ml); 164551 (5g/100ml); 164548 (2.5g/50ml); 164550 (1g/20ml) | Intratect 5% | 5% human normal immunoglobulin solution for intravenous infusion vial | Pfizer Australia Pty Ltd |
| 232085 (20g/200ml); 232084 (10g/100ml); 232078 (5g/50ml); 232077 (1g/10ml) | Intratect 10% | 10% human normal immunoglobulin solution for intravenous infusion vial | Pfizer Australia Pty Ltd |
| 113928 (10g/200ml); 113927 (5g/100ml); 113926 (2.5g/50ml); 113925 (1g/20ml) | Octagam 5% | Normal immunoglobulin (human) injection bottle | Octapharma Australia Pty Ltd |
| 155604 (20g/200ml); 155603 (10g/100ml); 155602 (5g/50ml); 155601 (2g/20ml) | Octagam 10% | Normal immunoglobulin (human) injection vial | Octapharma Australia Pty Ltd |
| 291644 (30g/300ml); 291646 (20g/200ml); 291648 (10g/100ml); 291647 (5g/50ml); 291740 (1g/10ml); 291645 (2.5g/25ml); | Panzyga 10% | Human normal immunoglobulin solution for intravenous infusion vial | Octapharma Australia Pty Ltd |
| 219160 (40g/400ml); 143368 (20g/200ml); 143337 (10g/100ml); 143273 (5g/50ml) | PriviIgen 10% | Normal immunoglobulin (human) (100g/L, 10%) solution for intravenous infusion | CSL Behring Australia Pty Ltd |
| **SCIg** | | | |
| 282579 | Cuvitru 20% | Normal immunoglobulin (human) infusion 20% for subcutaneous use in glass vial | Shire Australia Pty Ltd |
| AU 173315 (0.8g/5ml); 173323 (1.6g/10ml); 173324 (3.2g/20ml)  NZ 204954 (0.8g/5ml); 204955 (1.6g/10ml); 204956 (3.2g/20ml) | Evogam 16% | Normal immunoglobulin (human) 16% w/v, injection solution vial for subcutaneous use | CSL Behring Australia Pty Ltd |
| 128703 (1.65g/10ml); 128705 (3.3g/20ml) | Gammanorm 16.5% | Normal immunoglobulin (human) solution for intramuscular injection or subcutaneous infusion vial | Octapharma Australia Pty Ltd |
| 285344 (5ml syringe); 285345 (10ml syringe); 207386 (5ml vial); 207385 (10ml vial); 207383 (20ml vial); 207384 (50ml vial) | Hizentra 20% | Human Normal Immunoglobulin 20% Solution for Subcutaneous Injection 5-10ml pre-filled syringe OR 5-50ml vial | CSL Behring Australia Pty Ltd |
| 235178 | Hyqvia 10% | Normal Immunoglobulin Infusion 10% (Human) with Vorhyaluronidase alfa, Injection solution for subcutaneous use | Shire Australia Pty Ltd |
| **IVIg and SCIg** | | | |
| 116689 (1g/10ml); 117237 (2.5g/25ml); 117238 (5g/50ml); 117239 (10g/100ml); 117240 (20g/200ml) | Gamunex 10%\* | Normal immunoglobulin (Human) intravenous solution vial | Grifols Australia Pty Ltd |
| 198488 (30g/300ml); 131973 (20g/200ml); 131969 (10g/100ml); 131968 (5g/50ml); 131966 (2.5g/25ml); 131953 (1g/10ml) | Kiovig 10% | Normal immunoglobulin (human) solution for injection vial | Shire Australia Pty Ltd |

**Source:** Therapeutic Goods Administration, accessed 16 December 2019

**Abbreviations:** ARTG: Australian Register of Therapeutic Goods; IVIg: intravenous immunoglobulin; DIF: dual inactivation and filtration; IV: intravenous; SCIg: subcutaneous immunoglobulin; AU: Australia; NZ: New Zealand; SC: subcutaneous.

**Note:** All products were registered medicines. Those products highlighted in grey are currently funded by the National Blood Authority. It is important to note these may change over time depending on supplier agreements. **\***Gamunex 10% is funded by the National Blood Authority for *IVIg only*.

# Proposal for public funding

Ig therapy for PID is currently funded by the NBA under the national blood supply arrangements. Ig therapy is classified as an established therapeutic role in this population, but the cost-effectiveness of this use has not been evaluated in Australia.

Clinical criteria for eligible patients to access funded Ig are specified in Version 3 of the Criteria. Applications for Ig are made through the BloodSTAR online portal and assessed against the Criteria. The Criteria outlines qualifying criteria for Ig therapy according to age and clinical markers/indication, with the requirement for the initial review by an immunologist, at six months, and ongoing annual review to assess the clinical benefit or effectiveness. The Criteria, including eligibility criteria are periodically updated and may be refined according to recommendations of the relevant NBA working group and subsequent approval by the JBC.

# Summary of public consultation feedback/consumer Issues

The draft Referral Form was released for Targeted Consultation in August 2019 and the PICO Confirmation was released to Sponsor companies in December 2019. Four submissions were received: three from industry and one from a consumer group. Finally, a wider public consultation was undertaken on the Contracted Assessment in August-September 2020. Four responses were received, two from clinical groups, one from a consumer group, and one from a sponsor company.

Overall, stakeholders were highly supportive of the use of Ig to treat PID and considered that Ig significantly improves patients’ quality of life and the ability to contribute to society. Stakeholders were supportive of SCIg use and considered SCIg to be associated with fewer side effects and better patient tolerability.

Noted disadvantages included adverse events, regular attendance at hospital for Ig infusions, time spent travelling to hospital and waiting times for treatment due to delays in day units. However, consumers considered that the advantages of Ig therapy outweigh any potential disadvantages.

Some stakeholders raised concerns about the feasibility of conducting clinical comparisons across a highly heterogeneous population and the Assessment’s ability to draw meaningful conclusions. Stakeholders recognised the challenges of a comprehensive assessment of the effectiveness of Ig to treat patients due to the heterogeneity of the included subpopulations and the scarcity of high-level evidence against a comparator. Stakeholders agreed it is unlikely that there will be further studies in this field as immunoglobulin replacement therapy is an internationally accepted standard for PID and it would be unethical to withhold treatment.

ESC questioned if there were equity issues of Ig access to consider for people with these conditions living in rural or remote areas. It was noted that in regard to gaining further evidence of clinical effectiveness, many international registries exist which, may provide additional data.

# Proposed intervention’s place in clinical management

**Description of Proposed Intervention**

This referral is for Ig used as immunoreplacement therapy. Ig is a plasma-derived product manufactured to treat a range of medical conditions. Access to government-funded Ig is through the national blood arrangements and is determined by the NBA’s *Criteria for Clinical Use of Immunoglobulin in Australia* (the Criteria)[[2]](#footnote-2).

**Description of Medical Condition(s)**

This referral includes patients with PID who are currently eligible for Ig treatment in Australia according to Version 3 of the Criteria. The specific conditions (as diagnosed by an immunologist) for patients with PID with antibody deficiency to be eligible for publicly funded Ig treatment in Australia are:

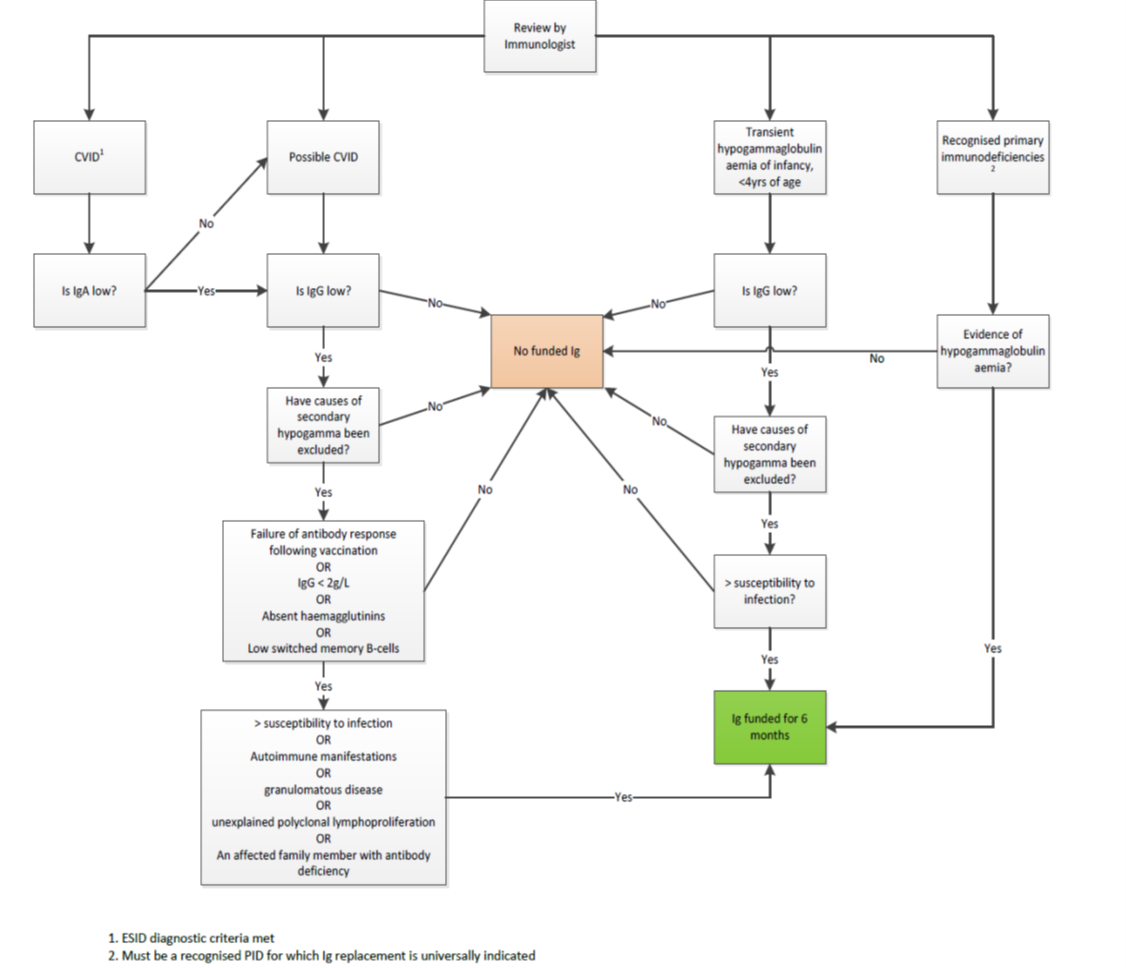
* Severe combined immunodeficiency (SCID)
* Combined immunodeficiency (e.g. thymoma)
* Combined immunodeficiency with associated or syndromic features (e.g. Wiskott Aldrich syndrome; ataxia telangiectasia)
* Possible CVID – below normal serum IgG but normal serum IgA
* Severe reduction in all Ig isotypes with decreases or absent B-cells (e.g. XLA def)
* Severe reduction in at least two Ig isotypes with low/normal B-cells (e.g. CVID)
* Severe reduction in serum IgG and IgA with normal /elevated IgM (e.g. CD40L def)
* Transient hypogammaglobulinaemia of infancy
* Lymphoproliferative syndromes (e.g. XLP1, XLP2, CD27 def).

PID refers to a large heterogeneous group of disorders where one or more components of the immune system are compromised, leading to absent or impaired immune function. Over 350 different PID disorders are recognised by the World Health Organization (WHO), with new ones continually being discovered[[3]](#footnote-3). As such, the presentation of PID is highly variable.

In 2018-19, the majority (86%) of NBA funded Ig usage for PID conditions in Australia was for patients with CVID, according to NBA data.

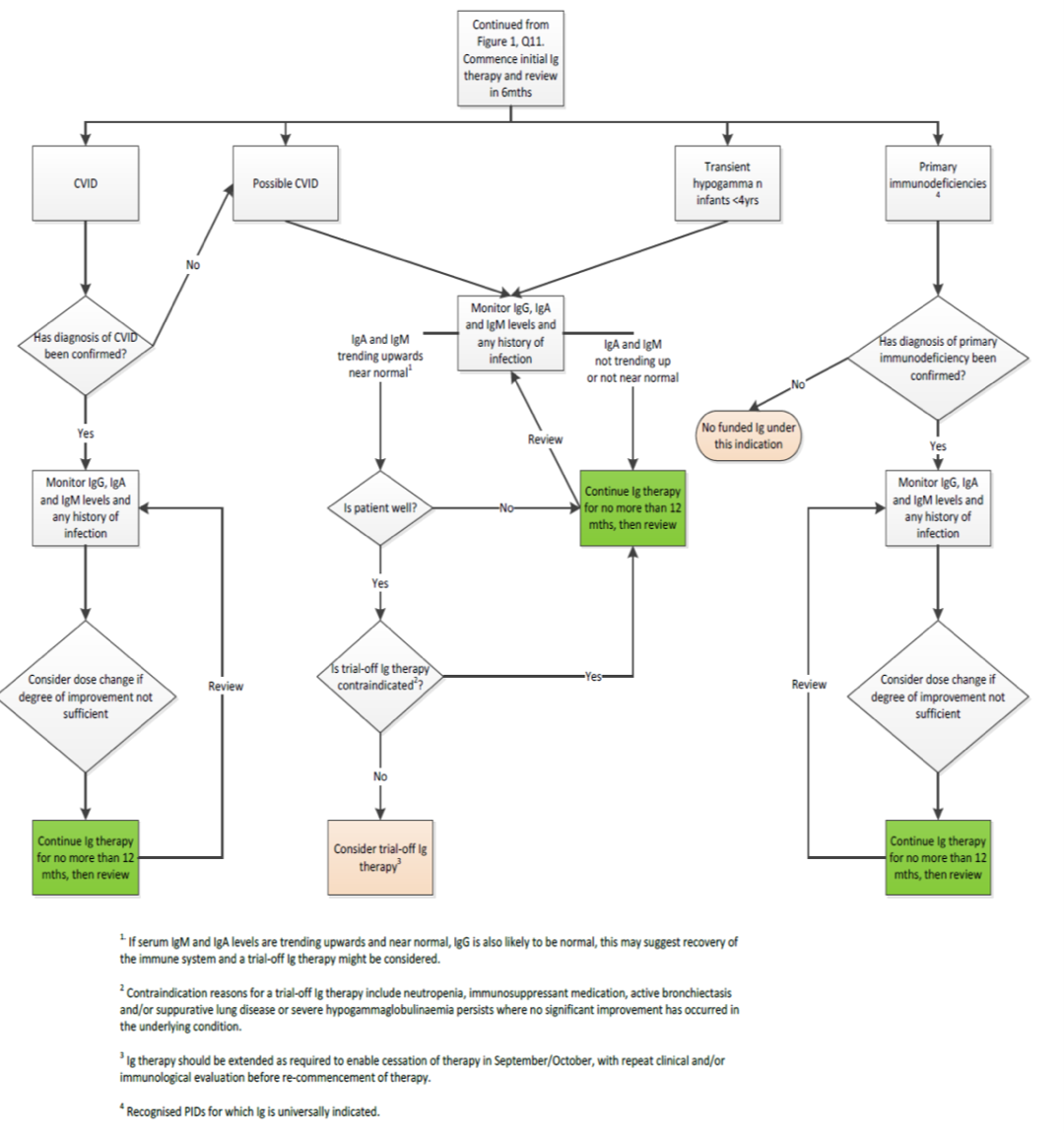
Figure 1 and Figure 2 describe the current management of patients with PID with antibody deficiency using IVIg, funded by the NBA (for initial access to Ig and continued access to Ig, respectively)[[4]](#footnote-4). It is important to note that these clinical management algorithms are a representation only as not all conditions are able to be captured in the flowchart.

**Figure 1 Clinical management algorithm for initial access to Ig for patients with PID with antibody deficiency**

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**Source**: Reproduced from Figure 1, page 15 of the Referral Form. **Abbreviations**: CVID: Common variable immunodeficiency; ESID: European Society for Immunodeficiencies; Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

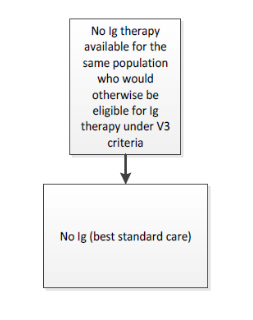
**Figure 2 Clinical management algorithm for continued access to Ig for patients with PID with antibody deficiency**

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**Source:** Reproduced from Figure 2, page 21 of the Referral Form. **Abbreviations**: CVID: Common variable immunodeficiency; ESID: European Society for Immunodeficiencies; Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

Figure 3 describes the current management of patients with PID with antibody deficiency, where IVIg is not a treatment option[[5]](#footnote-5). This is either due to contraindications or ineligibility according to the Criteria Version 3 (including patients who were previously eligible for treatment under the Criteria Version 3 but are no longer, for example, due to treatment failure).

**Figure 3 Clinical management for patients with PID with antibody deficiency in the absence (or failure) of Ig**



**Source:** Reproduced from Figure 3, page 24 of the Referral Form. **Abbreviations**: Ig: Immunoglobulin; PID: Primary Immunodeficiency Diseases

# Comparator

Given the heterogeneous patient group comprising PID with antibody deficiency, the comparator for Ig replacement therapy for the treatment of PID with antibody deficiency is no Ig (no active treatment). This may or may not include supportive care including antibiotic treatment, prophylactic antibiotics and antimicrobials.

# Comparative safety

The DCAR suggested that, relative to no treatment, Ig has inferior safety.

No comparative safety data (Ig versus no Ig) was identified. Given the comparator is ‘no treatment’ there are not expected to be any safety issues relevant to the comparator. The safety of Ig was informed by single arm studies investigating the safety of Ig in patients with CVID. Table 2 summarises adverse events from the ten single-arm studies reporting data on the safety of Ig therapy[[6]](#footnote-6). Most studies reported adverse events across the entire PID population of the study rather than reporting outcomes for CVID separately. When all PID patients have been pooled this is reflected in the table.

Ig use was associated with mostly mild adverse events (chills, flushing, fever, nausea, headache, muscle ache, mild anxiety, pharyngolaryngeal pain, fatigue and hypotension) occurring in 14% to 67% of patients and 2% to 22% of infusions.

Moderate events (rash, severe headache, abdominal pain, joint pain, chest tightness, vomiting, wheezing and mild dyspnoea) occurred in 6.7% to 24% of patients and 0.2% to 1.5% of infusions and were resolved by slowing or stopping the infusions.

Severe events (severe chest pain, severe wheezing/breathlessness, severe headache, severe dizziness, tightness of the throat, pressure in the chest sensation, collapse and moderate events that were persistent and could not be prevented by pre-infusion treatment with steroids and antihistamines) were rare, occurring in 0% to 5% of patients and 0% to 0.2% of infusions. These events required adrenaline, hospitalisation, withdrawal of treatment, or changing to SCIg administration.

**Table 2 Summary of safety data**

| **Author (year)**  **Country** | **Number of patients**  **Duration of follow-up** | **Total AE rate**  **Per patient**  **Per infusion** | **Mild AEs**  **Per Patient**  **Per infusion** | **Moderate AEs**  **Per patient**  **Per infusion** | **Severe AEs**  **Per patient**  **Per infusion** | **Description of AEs and treatment** |
| --- | --- | --- | --- | --- | --- | --- |
| Aghamohammadi et al. (2003)  Iran | 45 (all PID patients pooled)  3 yrs | PP: 25/45 (55.6%)  PI: 50/955 (5.2%) | PP: 22/45 (48.9%)  PI: 40/955 (4.2%) | PP: 3/45 (6.7%)  PI: 10/955 (1%) | PP: 0/45 (0%) | Mild: Chills, flushing, fever, nausea, headache  All subsided with slowed infusion rate  Moderate: Rash, severe headache, abdominal pain, joint pain, chest tightness  Treated with antihistamines and/or hydrocortisone |
| Aghamohammadi et al. (2004)  Iran | 71(all PID patients pooled)  NR data collected over 7 yrs | PP: 35/71 (49.3%)  PI: 152/1231 (12.4%) | PP: 33/71 (46.5%)  PI: 131/1231 (10.6%) | PP: 12/71 (16.9%)  PI: 19/1231 (1.5%) | PP: 2/71 (2.8%)  PI: 2/1231 (0.2%) | Mild: chills, fever, flushing, muscle aches, nausea, headache, anxiety  All subsided with slowed infusion rate  Moderate: vomiting, chest pain, wheezing  Treated with antihistamines and/or hydrocortisone  Severe: severe chest pain, severe wheezing, severe headache.  Treatment NR  Note: AE rate for CVID per infusion was higher than for the rate of all PID infusions pooled (23% vs 12.4%) |
| Bayrakci et al. (2005)  TurkeyB | 46 (all PID patients pooled)  Median 4.25 yrs (range 1.25-12.25 | PP: 3/46 (6.5%)  PI: NR | PP: NR  PI: NR  39 events total | PP: NR  PI: NR  12 events total | PP: NR  PI: NR  2 events total | Mild/Moderate: type NR, resolved by changing infusion rate or switching Ig brand  Severe: hospitalisation required for 2 patients  Note: no patient required therapy discontinuation  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (5.5% vs 5.8%) |
| Berger et al. (2007)  USA/Canada | 42 (ITT, all PID patients pooled)  0.5 yrs | PP: 25/42 (60%)  PI: 100/314 (32%) | PP: 23/42 (54.8%)  PI: 69/42 (21.7%) | NR | PP: 0/42 (0%) | Mild: headache (59.5%), pharyngolaryngeal pain (38.1%), sinusitis (28.8%), diarrhoea (23.8%), fatigue (23.8%), nausea (23.8%), pyrexia (23.8%)  Moderate: mild dyspnoea resolved by stopping infusion  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (62% vs 60%).  AE rates were higher for first infusion compared to subsequent ones (47.6% vs 22.2-37.5%)  AE rates higher with higher doses of Ig |
| Bichuetti-Silva et al. (2014)  Brazil | 117 (all PID patients pooled)  2 yrs | PP: 28/117 (23.9%)  PI: 38 /1765 (2.2%) | PP: NR  PI: 31/1765 (1.8%) | PP: NR  PI: 4/1765 (0.2%) | PP: NR  PI: 3/1765 (0.2%) | Mild: headache, fever, chills, nausea, emesis, hypotension, muscle cramps  Moderate: reactions necessitating discontinuation of infusion  Severe: moderate reactions that were persistent, tightness of throat, severe shaking, severe breathlessness or wheezing, severe dizziness, sensation of pressure in the chest, collapse. Severe reactions required adrenaline treatment.  Note: AE rate for CVID patients was similar to the rate of all PID infusions pooled (2.3% vs 2.2%) |
| Dashti-Khavidaki et al. (2009)  Iran | 99 (all PID patients pooled)  NR data collected over 13 years | PP: 66/99 (66.7%)  PI: 216/3004 (7.1%) | PP: 66/99 (66.7%)  PI: 172/3004 (5.7%) | PP: 24/99 (24%)  PI: 41/3004 (1.4%) | PP: 3/99 (3%)  PI: 3/3004 (0.1%) | Mild: chills, fever, cold feeling, backache, headache  Moderate: vomiting, chest pain, wheezing  Treatment: infusion stopped or rate reduced, antihistamines, anti-inflammatory agents and/or corticosteroids administered  Severe: severe chest pain, severe wheezing, severe headache  Note: AE rates per infusion varied depending on PID: e.g. CVID = 8.5%, XLA = 3.35%, Ataxia-telangiectasia = 3.8%, IgG subclass deficiency = 17.4% |
| De Garcia et al. (2004)  Spain | 24  24 months | PP: NR  PI: 61/888 (6.8%) | NR | NR | NR | Type of AE NR  No AE required infusions to be discontinued |
| Martinez Garcia et al. (2001)  Spain | 19  Mean 7.5 yrs | NR | NR | NR | NR | Note: 1 patient withdrawn due to anaphylactic reaction |
| Quinti et al. (2008)  Italy | 262  Mean 7 years  1,982 patient years | NR | NR | NR | PP: 13/262 (5.0%)  PI: NR | Severe: Ig treatment withdrawn due to AE that could not be prevented with premedication (steroids, antihistamines) or switching Ig brand. Patients were started on SCIg which was well tolerated by most patients. |
| Singh et al. (1994)  India | 14  NR | PP: 2/14 (14%)  PI: NR | PP: 2/14 (14%)  PI: NR | None | None | Mild: nausea, joint pain, chills |

**Source**: Table 15: Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT

# Comparative effectiveness

The DCAR suggested that, relative to no treatment, Ig may have superior effectiveness.

One comparative study (Aghamohammadi et al 2009)[[7]](#footnote-7) was identified which retrospectively compared a group of patients with CVID on Ig treatment (n=23) to a group of patients with CVID not treated with Ig due to delayed diagnosis (n=24). IVIg treatment was associated with improved patient outcomes (including lower infection rates, hospital admissions, bronchiectasis and mortality).

Data from single arm studies of patients with CVID comparing pre- and post-treatment outcomes reported consistent findings. The post-Ig outcomes (infection rates, IgG levels and hospitalisation rates) were improved compared to those measured pre-Ig treatment.

Data from three studies (Busse et al., 2002, De Garcia et al., 2004, Martinez Garcia et al., 2001) reporting a mean age similar to that of Australian patients receiving NBA-funded Ig were consistent with the overall results of the Assessment. All three studies reported that Ig use was associated with reductions in infection rate compared to pre-treatment rates.

Key issues with the evidence base were identified which may have a substantial effect on effectiveness results. Confounding factors and co-interventions were generally not reported and not investigated; therefore, it is not clear how these influence results. Unadjusted co-intervention use may bias results in favour of Ig. Most studies were retrospective and it was not clear that all patient information was captured consistently and comprehensively. Further, it was not clear if any eligible patients were excluded from analysis. The magnitude of impact these issues may have on results is uncertain.

Despite the significant limitations associated with the evidence base, it is unlikely that higher quality studies will be forthcoming to investigate the comparative effectiveness of Ig therapy in patients with PID due to Ig being an established part of patient management. No relevant upcoming clinical trials were identified. Due to the collective low incidence of PIDs, recruiting enough patients for a large prospective trial may not be feasible and/or ethical.

The summary of findings is shown in Table 3[[8]](#footnote-8)

**Table 3 Balance of clinical benefits and harms of intervention, relative to comparator, and as measured by the critical patient-relevant outcomes in the key studies**

| Outcome  (units, follow-up) | No. of studies and study design | Risk of bias | Effect Ig | Effect no treatment | Quality | Importance |
| --- | --- | --- | --- | --- | --- | --- |
| Adverse events  follow up: range 1 years to 12 years (count) | 8 observational studies | Serious | 184/434 (42.4%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Serious adverse events (count) | 5 observational studies | Serious | 20/519 (3.9%) | NA | ⨁⨁⨁⨀  **Moderate quality** | Critical |
| Lower respiratory infection rates (per patient per year) | 8 observational studies | Very serious | Range of means  0.16-0.34 | Range of means  0.28-2.04 | ⨁⨀⨀⨀  **Very low quality** | Critical |
| IgG trough levels (mg/dl) | 7 observational studies | Serious | Range of means  455-891 | Range of means  195-416 | ⨁⨁⨀⨀  **Low quality** | Critical |
| Hospitalisations (per patient per year) | 4 observational studies | Very serious | Range of means  0.13-0.7 | Range of means  1.35-3.4 | ⨁⨀⨀⨀  **Very low quality** | Critical |

**Abbreviations**: Ig: immunoglobulin, IgG: immunoglobulin G, NA: not applicable. 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. On the basis of the benefits and harms reported in the evidence base (summarised above)**, it is suggested that, relative to no treatment, Ig has inferior safety and may have superior effectiveness noting that there is only low- to very low-quality evidence available to support these conclusions.**

**Source**: Table 20 Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT

# Economic evaluation

Given the limitations with the available evidence, it was determined that conducting a modelled economic evaluation comparing Ig and non-Ig standard of care would not be feasible or meaningful for decision-making. Furthermore, as Ig use for patients with PID is considered to be the standard clinical management strategy (particularly for patients with common subtypes of PID including common variable immunodeficiency (CVID) and X-linked agammaglobulinemia (XLA)), further evidence for ‘no Ig’ use (required to populate an economic model) is unlikely to be forthcoming.

A simplified cost-consequence (CCA) analysis was conducted to estimate the economic impact of Ig for PID patients, as show in Table 4[[9]](#footnote-9). The CCA was limited to a one-year time horizon and considered the cost differences between Ig and no Ig in terms of Ig itself, Ig administration costs, and the incremental costs of treating serious infections and managing bronchiectasis. The overall incremental cost was estimated at $18,281.01 per year per patient, driven largely by the direct cost of Ig (with some cost offsets associated with avoidance of hospitalisations due to serious infections).

**Table 4 Result of the cost consequence analysis (base case)**

| **PID outcomes** | **The intervention arm**  **Ig therapy** | **The comparator arm**  **No Ig treatment** | **Incremental effectiveness or costs** |
| --- | --- | --- | --- |
| **Effectiveness** |  |  |  |
| Annual probability of serious infections and the number of patients estimated\* | 0.259  637 per year | 0.336  828 per year | 190 avoided |
| Annual probability of bronchiectasis and the number of patients estimated\* | 0.324  796 per year | 0.417  1,026 per year | 230 avoided |
| **Costs** |  |  |  |
| Cost of product (Ig cost alone) | $18,327.88 | - | $18,327.88 |
| Cost of Ig administration | $2,896.21 | - | $2,896.21 |
| Hospitalisation due to infection | $9,282.47 | $12,066.59 | -$2,784.11 |
| Treatment and management of bronchiectasis | $549.44 | $708.41 | -$158.97 |
| **Total annual incremental cost** |  |  | **$18,281.01** |

**Abbreviations**: PID = primary immunodeficiency;

**Note**: The calculation of the number of patients avoiding associated illnesses was based on the estimate annual PID patient number of **2,460** . However, these numbers have NOT been directly used as the basis of calculating Ig product cost

**Source**: Table D3.1 Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT

# Financial/budgetary impacts

Financial estimates are primarily based on the Ig usage figures from the past two financial years (2017 to 2019) provided by the NBA, as well as externally sourced epidemiological studies conducted in Australia. Four methods were explored to estimate the PID population treated with Ig over the forward estimates. The Method 2 (using NBA patient counts according to each of the six patient subgroups) and Method 4 (based on epidemiological approach) were considered the most accurate estimates. The base case (Method 4) relies on the population prevalence for PID of 9.09 per 100,000 Australians, projected over five years assuming annual population growth of 1.5%. The estimates using Method 2 are presented in a sensitivity analysis in Table 6 below.

The total Ig cost, including delivery, was estimated at $50.5 million in 2021 and increasing to $53.5 million in 2025. The delivery cost of Ig for patients with PID accounted for approximately 13.64% of the total costs, and this proportion was stable over the five projected years.

The total Ig costs, including delivery costs, are summarised in Table 5[[10]](#footnote-10).

**Table 5 Total Ig costs including delivery**

| FY | 2021 | 2022 | 2023 | 2024 | 2025 | Source | Calculation reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| IVIg number | 1805 | 1832 | 1860 | 1888 | 1916 | Table 25 | A |
| SCIg number | 570 | 579 | 587 | 596 | 605 | Table 25 | B |
| **Total cost of Ig delivery** | $6,879,371 | $6,982,561 | $7,087,300 | $7,193,609 | $7,301,513 | **Calculated** | **C** |
| Ig product costs | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 | Table 30 | D |
| **Grand total of Ig for PID patients** | **$50,445,780** | **$51,202,467** | **$51,970,504** | **$52,750,061** | **$53,541,312** | **Calculated** | **E = C + D** |
| *% of delivery from the total* | 13.64% | 13.64% | 13.64% | 13.64% | 13.64% | *Calculated* | *F = C ÷ E* |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

**Source**: Table 32 Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT

Sensitivity analyses were conducted in Section E.3 of the DCAR to test assumptions in patient number estimates, the price of Ig and Ig dosage. These are summarised in the table below.

**Table 6 Sensitivity analyses considering only Ig costs (not delivery)**

| Year | 2021 | 2022 | 2023 | 2024 | 2025 |
| --- | --- | --- | --- | --- | --- |
| Base case  Ig cost alone | $43,566,409 | $44,219,905 | $44,883,204 | $45,556,452 | $46,239,799 |
| ***Ig cost alone***  ***Sensitivity analysis*** |  |  |  |  |  |
| PID patients via Method 2  *Uncertainty range by Method 1 and Method 3* | $41,896,385  ($40.5m, $47.9m) | $41,849,003  ($40.0m, $49.9m) | $41,801,621  ($39.5m, $51.9m) | $41,754,239  ($39.1m, $53.8m) | $41,706,857  ($38.5m, $55.8m) |
| Price of Ig at lowest cost ($44.94) | $32,409,774 | $32,895,920 | $33,389,359 | $33,890,200 | $34,398,553 |
| Price of Ig at highest ($140.18) | $101,094,839 | $102,611,262 | $104,150,431 | $105,712,687 | $107,298,378 |
| Price of Ig at weighted average ($94.51) | $68,158,605 | $69,180,984 | $70,218,699 | $71,271,980 | $72,341,059 |
| 10% increase in dosage | $47,923,050 | $48,641,896 | $49,371,524 | $50,112,097 | $50,863,779 |
| 10% decrease in dosage | $39,209,768 | $39,797,915 | $40,394,884 | $41,000,807 | $41,615,819 |

**Abbreviations:** PID = primary immunodeficiency diseases; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin; FY = financial year

**Source**: Table 33 Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT

# Key issues from ESC for MSAC

| **ESC key issue** | **ESC advise to MSAC** |
| --- | --- |
| Potential changes required to the Criteria Version 3 | MSAC should consider if the age of onset in the Criteria should be amended from > 4 years to e.g. >2 years to improve access for paediatric patients.  Documentation of clinical effectiveness at review periods is necessary for continuation of Ig therapy; however, ESC considered that a clearer definition to determine the minimum threshold for “effectiveness” is warranted. |
| Evidence presented in the review was focussed on patients with common variable immunodeficiency (CVID), and not representative of the heterogeneous PID population. | Ig use for CVID accounted for 86% of total Ig usage for PID in 2018-19. However, the results are not generalizable to all PID which may be associated with different severity and rates of infection. CVID is more common in adulthood, while paediatric patients typically have rarer conditions than CVID. |
| The unit price of Ig had a large impact on the financial estimates. | A sensitivity analysis was presented using the highest (domestic), lowest (imported) and weighted average price of Ig. ESC considered that a price reduction for domestic Ig would have significant cost savings. ESC considered that greater transparency on how the cost of Ig is derived, may be of interest to MSAC. |
| Available evidence was of low quality and it was unlikely high quality studies will be forthcoming, Focus should be on areas for potential future research. | ESC agreed there should be a focus on further research reporting on PID subgroups separately (considering subgroups of children and adults, disorder type and severity, and patterns of use), noting that this may be difficult in some rare conditions. Linking patient level data on Ig use (from BloodSTAR): to hospitalisation, Medicare, PBS and mortality data would allow a better understanding of the healthcare use, co-interventions and outcomes for patients with PID.  ESC considered the establishment or enhancement of existing structures such as a registry or data base or the National Blood Sector Research and Development Program (NBA) may be possible pathways.  ESC noted that international registries (e.g. the European Society for Immunodeficiencies (ESID)) could also be reviewed for information on larger cohorts. |
| Ideal body weight (IBW) as a means to calculate Ig dose | ESC considered that the use of IBW may result in an appropriately lower dose given to a patient if they are above their ‘ideal’ weight, thereby optimising Ig use. The option to dose according to IBW is already available on the BloodSTAR website, but adherence to this dosing calculation is not monitored, and outcomes are not reported separately based on the bodyweight used. |

**ESC discussion**

Application 1592 requests MSAC advice on the supply of Ig therapy under the national blood arrangements for the treatment of PID with antibody deficiency. In line with the PICO confirmation, the DCAR reviews the available evidence on safety and effectiveness of Ig replacement therapy for patients with PID. MSAC is asked to consider the evidence presented, and provide advice on a range of strategies to manage the cost-effectiveness of Ig use in this population.

As described in the PICO, immunodeficiencies are a group of disorders characterised by a defect in the immune system. The term PID encompasses a group of more than 400 disorders. They may present at any age; however, more severe forms, such as SCID, generally become apparent early in life whilst other PID, such as CVID are more commonly diagnosed in adults.

The clinical criteria for funded access to Ig for PID is set out under *version 3 of the Criteria for the clinical use of immunoglobulin in Australia*[[11]](#footnote-11) (the Criteria). The current indications under which patients with PID may be eligible for replacement therapy with intravenous Ig (IVIg) or subcutaneous Ig (SCIg) therapy are: CVID; possible CVID; transient hypogammaglobulinaemia of infancy; and primary immunodeficiencies for which immunoglobulin replacement is universally indicated (e.g. SCID, Wiskott-Aldrich syndrome, etc.). Initial review by an immunologist is required within six months of starting Ig therapy, and annually thereafter. ESC noted that documentation of clinical effectiveness is necessary for continuation of Ig therapy, however the minimum threshold for “effectiveness” is not clearly defined in the Criteria. Overall, ESC considered the current Criteria V3 and treatment algorithms to be broadly consistent with other guidelines used in the evidence base (WHO 1999 and PAGID/ESID 1999). However, the Criteria V3 limits Ig use in CVID or possible CVID to patients over the age of 4 years compared to the age of onset of > 2 years defined in the studies. ESC considered that amending the age of onset in the Criteria V3 to > 2 years would improve access for paediatric patients.

ESC noted that Ig may be prescribed for a variety of PID although the cost-effectiveness of this use has not been established. The true prevalence of PID are not known, however, based on a 2007 study (Kirkpatrick and Riminton), the DCAR reported an estimated prevalence of 5.6 cases of PID per 100,000 population in Australia. By comparison, the prevalence of PID in Australia was calculated from 2018-19 NBA data to be approximately 9.1/100,000 population. Ig product used for patients within the CVID subgroup accounted for 86% of total Ig usage in patients with PID. The DCAR states that the differences between these prevalence estimates over the past 20 years may be due to one or more reasons such as: increasing diagnostic capabilities; changes in disease definitions; or improved access to treatments.

The clinical evidence presented in the DCAR consisted of four non-randomised comparative studies and seventeen single arm studies. With respect to the evidence base, ESC agreed that several issues identified in the review may limit the applicability of these results to the Australian context. These included; the evidence base only included patients with CVID (and not other PID), the age of patients in the studies was markedly lower than the average age of CVID patients receiving Ig funded by the NBA (53 years), and studies did not adequately describe or investigate confounding factors and co-interventions that may be indicated as part of standard of care for these patients. The outcomes of interest included IgG trough levels, infection rates, antibiotic usage and PID-related hospitalisations. Overall, ESC agreed that Ig may have superior effectiveness to No Ig; however, the available evidence was of very poor quality and with a high risk of bias.

No comparative safety data were identified comparing Ig to no Ig in this population, and ten single-arm studies were used to assess the safety of Ig in patients with CVID. ESC agreed that the safety of Ig is inferior to No Ig because infusion events associated with Ig therapy would not be experienced with the comparator. Ig therapy was generally well tolerated and adverse events (AEs) were mostly mild and reversible.

ESC noted that a literature review on published economic evaluations identified no studies comparing Ig use to non-Ig standard of care for patients with PID. Instead, existing literature compared clinical and economic outcomes of SCIg versus IVIg, which was considered to be outside the scope of this review. ESC noted pre-ESC advice suggesting there is a move towards a higher use of SCIg, which may influence the overall financial impact due to a reduction in administration costs. However, this would also be dependent on patients’ personal preferences or ability to switch from IVIg to SCIg.

A cost-consequence analysis (CCA) was presented in the DCAR to estimate the economic impact of Ig for patients with CVID. This approach was supported by the Ig Review Reference Group and ESC considered this to be appropriate, given the low quality evidence from which to establish causality (clinical effectiveness). The CCA considered the cost differences between Ig treatment and no Ig treatment in terms of Ig itself, Ig administration costs, and the incremental costs of treating serious infections and managing bronchiectasis. The incremental cost between Ig treatment versus no Ig treatment is estimated to be $18,281.01 per patient per year, and the greatest contributor of this cost difference is the Ig product cost, at $18,327.88 per patient per year (see Table 4). ESC noted that for consistency with other Ig Reviews, the economic and financial estimates use the Ig base unit cost of $60.41 as provided by the NBA. Sensitivity analyses were performed using the lowest cost of $44.94 (imported IVIg), highest cost of $140.18 (domestic IVIg, including plasma collection and fractionation), and weighted average cost of Ig across all indications ($94.51). ESC noted that a price reduction for domestic Ig would have significant cost savings. ESC heard that pricing for domestically manufactured Ig is determined through the National Fractionation Agreement for Australia with monopoly fractionator CSL Behring. ESC considered that greater transparency on how this cost is derived may be of interest to MSAC.

ESC noted consultation feedback indicated that consumers were supportive of Ig therapy and considered Ig therapy to be superior to No Ig. For people living with PID, perceived benefits included prevention of infections, significant improvements in the quality of life and the ability to contribute to society. Noted disadvantages of Ig therapy included the burden of travelling to and attending appointments for infusions, and adverse events such as headache, nausea, fever, chills, flushing, malaise, rash, and itching. SCIg was seen to reduce inconvenience for patients, compared with IVIg. Overall, the advantages of Ig therapy were considered to outweigh any disadvantages.

ESC was supportive of the areas identified for potential future research of PID in Australia as identified in the review. ESC agreed that it is unlikely that higher quality studies to investigate the comparative effectiveness of Ig therapy in patients with PID will be forthcoming. However, the collection of more granular information should be considered, such as: variance in Ig usage patterns depending on the PID subtype, if usage patterns differ for children compared to adults, and identifying those patients able to successfully stop or reduce Ig usage. International registries could also be reviewed for information on larger cohorts. Further, linking of patient level data on Ig use (from BloodSTAR) to hospitalisation, PBS, Medicare and mortality data could allow a better understanding of the healthcare use, co-interventions and outcomes for patients with PID.

# Other significant factors

Nil

# Applicant comments on MSAC’s Public Summary Document

The National Blood Authority appreciates MSAC’s recommendations and will consider and discuss with experts the suggestion of undertaking a scoping exercise to explore the feasibility of conducting further research. The NBA has previously been in contact with the MRFF to discuss the possibility of further funding for Ig research. The ability of BloodSTAR, or other sources, to capture more detailed outcomes in this group will be considered, with a view to providing a balance between the capture of enough information to inform future criteria and burden on prescribers. The NBA agrees with MSAC’s recommendation to review utilisation data in 12 months to best inform any changes required to data collection. Prescriber compliance to the V3 Criteria will continue to be monitored through the Ig Governance Program. This review followed the transition from Version 2 to Version 3 of the Criteria for Clinical Use of Immunoglobulin in Australia. The Criteria will continue to be reviewed on both a reactive and proactive basis, based on available evidence and clinical expert advice, to ensure the supply of Ig continues for those patients who benefit from it the most. Furthermore, the NBA plans to continue to undertake and support research into the effectiveness and utilisation of Ig, of which these recommendations will assist to prioritise. The NBA negotiates prices of Ig through tendering processes and will continue to strive to achieve the best prices for governments within existing limitations.

# Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:   
[visit the MSAC website](http://www.msac.gov.au/)

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9. Duncan, J., Forel, D., Gaget, V., Vandepeer, M., Tivey, D. Wendy, B. (2020). Immunoglobulin (Ig) for Primary Immunodeficiency Diseases (PID). MSAC Application 1592, Assessment Report. Commonwealth of Australia, Canberra, ACT [↑](#footnote-ref-9)
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11. National Blood Authority, 2018, Criteria for the clinical use of immunoglobulin in Australia (version 3) [↑](#footnote-ref-11)