Australian Government

Department of Health

Referral Form

Immunoglobulin use referred for HTA through MSAC

Review of Immunoglobulin use funded under the National Blood Agreement for

1591 SHG - Secondary Hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)

Disclaimer: There is a limit on the extent of research undertaken for this referral. Some elements are an expression of the NBA's general understanding which may or may not be fully comprehensive and accurate.

REFERRER DETAILS AND SPECIFICATION OF THE SCOPE OF THE REFERRAL

Referrer details (primary and alternative contacts)

Corporation / partnership details (where relevant): Statutory Authority

Corporation name: National Blood Authority (a statutory authority forming part of the Commonwealth of Australia, established under the *National Blood Authority Act 2003 ('NBA Act')*)

ABN: 87 361 602 478

Business trading name: National Blood Authority

Primary contact name: REDACTED

Primary contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: REDACTED

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

Overview of supply arrangements for publicly funded Immunoglobulin (Ig) in Australia

There are three frameworks which define the availability of publicly funded Ig products under the national blood arrangements. These arrangements are established under the National Blood Agreement and the *NBA Act:*

a) TGA regulation
b) policy decisions of all Australian Governments comprised in the *Criteria for the clinical use of immunoglobulin in Australia* (the Criteria), currently in force as Version 3, and
c) supply arrangements implemented under national contracts established by the National Blood Authority.

Ig products are available as intravenous (IVIg) or subcutaneous (SCIg) formulations. Intramuscular (IMIg) formulations are also available but are treated as equivalent to SCIg formations for the purpose of these referrals. The potential use and availability of Ig differs for IVIg and SCIg, and these differences are identified where relevant throughout these referral.

Each of these frameworks is described briefly below.

a) TGA regulation

Ig products for therapeutic use in Australia are regulated as prescription medicines under the *Therapeutic Goods Act 1989* and associated statutory instruments.

IVIg products are assessed for registration against the European Medicines Agency (EMA) EMA/CHMP/BPWP/94033/2007 rev.2 *Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)* 22 July 2010, adopted by TGA effective 1 June 2014 (available from http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines#products). This Guideline replaced CPMP/BPWG/388/95 Rev 1 (adopted by TGA 19 April 2001). (See Attachment A). This version has been included as some Ig products were registered on the Australian Register of Therapeutic Goods (ARTG) prior to the adoption of the updated Guideline and therefore assessed against this earlier version.

Under this regulatory guideline, IVIg products are considered to be registered indications in the following two categories: 'replacement therapy' and 'immunomodulatory effect'. The Guideline describes a range of conditions within each of these categories which are considered to be 'established', and others for which confirmatory data is required. Within this background, the Guideline describes a regulatory approach where certain lead indications are used as the proxy basis for establishment of efficacy for a range of other indications. The EMA approach is based on the regulatory approach adopted by the Federal Drug Administration in the USA.

In relation to hypogammaglobulinaemia, paragraph 7.3.2 provides as follows:

1. Hypogammaglobulinaemia and recurrent bacterial infections in patients with CLL, in whom prophylactic antibiotics have failed.
2. Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase MM patients who have failed to respond to pneumococcal immunisation.
3. Children and adolescents with congenital AIDS and recurrent bacterial infections.
4. Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT)

The above indications would be granted as long as efficacy has been proven in primary immunodeficiency syndromes (see 7.3.1). Standard doses are 0.2-0.4 g/kg every three to four weeks. If other dosage regimens are requested, they should be supported by clinical data. Please note that of the above listed indications, only children and adolescents with congenital AIDS and recurrent bacterial infections are funded under Secondary hypogammaglobulinaemia in V3 of the Criteria. The remaining indications above can be found under Acquired hypogammaglobulinaemia.

SCIg products are registered against the EMA document CHMP/BPWP/410415/2011 Rev.1 *Guideline on the clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg)* 23 July 2015 adopted by TGA effective 2 February 2016 (available from http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines#products). This Guideline replaced EMEA/CPMP/BPWG/283/00 *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular Use* (adopted by TGA 12 March 2003), any SCIg products registered prior to the TGA adoption of the updated guidelines would have been assessed under this previous version.

The SCIg Guideline is read together with the IVIg Guideline above. Under the SCIg Guideline, SCIg products can be registered on an established basis for four replacement therapy indications, and any additional indications including CIDP are subject to a requirement for specific clinical data under para 5.3.4

b) *Criteria for the clinical use of immunoglobulin in Australia*

Under the National Blood Agreement, Australian Governments have determined that the basis for access to publicly funded Ig products under the National Blood Arrangements will be as specified in the Criteria for Clinical Use of Immunoglobulin in Australia (Criteria) available at https://www.criteria.blood.gov.au/MedicalCondition/View/2577. This is confirmed in the *National Policy: Access to Government Funded Immunoglobulin Products in Australia* https://www.blood.gov.au/national-policy-to-ig .

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 supported by some other source of funding.

Version 1 of the Criteria was issued in 2008, and partial review lead to Version 2 issued in 2012. Version 2.1 was included in the national online system BloodSTAR from the time it was initially launched in 2016.

Version 3 of the Criteria has been developed through a comprehensive process of review managed by the NBA based on advice from Specialist Working Groups for Neurology, Immunology, Transplantation and the National Immunoglobulin Governance Advisory Group, and endorsed by all Governments through the Jurisdictional Blood Committee. The work on Version 3 commenced in 2014 and was completed in 2018. Version 3 of the Criteria more clearly articulates and standardises the diagnostic, qualifying and review criteria, initial and continuing authorisation periods, dosing controls and supporting evidence for access to Ig under the National Blood Agreement. These changes enhance consistency in access and further support the use of Ig products for clinically appropriate purposes, and for the treatment of patients whose health is most likely to be improved with Ig therapy.

Version 3 of the Criteria came into effect on 22 October 2018 and is available only in electronic form. It is primarily used for transactional authorisation of product access through the BloodSTAR system, and is available at https://www.criteria.blood.gov.au/.

In general, the Criteria follow the approach of TGA regulation and do not differentiate between individual brands of Ig products in relation to funded access under the National Blood Arrangements.

In relation to the availability of SCIg products under the National Blood Arrangements, governments have made a further policy decision that, in addition to access requirements applying generally under the Criteria, SCIg products are only approved for patients with a medical condition:

1. Where there is support for use cited in the Criteria, namely:

- primary immunodeficiency diseases with antibody deficiency
- specific antibody deficiency
- acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)
- secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT), and

2. Being treated by a clinical specialist within a hospital based SCIg program, where the hospital provides access to all resources and takes full accountability for the management and use of the SCIg product, at no additional cost to patients.

Further details on the requirements for access to SCIg products are available at https://www.blood.gov.au/SCIg. Note however, that the above hospital SCIg access model is scheduled for review in 2019 which may extend the range of ways in which patients can access SCIg. The policy decision of governments to fund access to SCIg products was supported by advice from the Medical Services Advisory Committee which can be found at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1334-public

A detailed statement of the basis on which Ig is available under Version 3 of the Criteria for the condition in this referral is provided in Attachment B, which includes all evidence items which form part of the basis for access through the implementation of Version 3 of the Criteria in BloodSTAR. A summary of these criteria is provided at Attachment C. Evolution of the Criteria is expected to be a continuing process. For this reason any changes made to the Criteria V3 for the condition under this review, that occur during the assessment process that could potentially affect outcomes, will be communicated as an adjustment to this referral if and when the changes occur.

There could be differences in response rates between IVIg and SCIg for some of the selected outcomes (adverse events, disability, venous damage), and differences in health service consumption (e.g. outpatient, day- admission, hospital care v self-care). However, the product for both IVIg and SCIg is immunoglobulin (Ig) and for this reason it is recommended that Ig is the intervention and IVIg and SCIg are considered as different routes of administration.

c) *NBA supply arrangements*

The NBA has provided national supply of immunoglobulin products from Australian domestic arrangements for collection of plasma by the Australian Red Cross Blood Service and plasma fractionation by CSL Behring Pty Ltd and through imported product arrangements from a range of possible suppliers, since 2003.

NBA supply arrangements have evolved over that period with increasing demand for publicly funded Ig, with increasing numbers of Ig products registered for use in Australia on the ARTG, and with the addition of SCIg in addition to IVIg products under the National Blood Arrangements.

NBA supply arrangements do not simply fund all Ig products registered in Australia from time to time. To support supply security, good contract performance and value for money through competitive tendering, NBA arrangements currently include supply of multiple products from different sources and with some differing characteristics.

However, in general, NBA arrangements follow the approach of TGA regulation and the Criteria and do not differentiate between individual brands of Ig products in relation to funded access under the National Blood Arrangements. The most recent tender process for imported Ig products conducted by the NBA for supply from 1 January 2016 allowed for tenderers to put forward substantiated claims supporting the clinical fitness for purpose and utility of particular Ig products, which were then taken into account as one factor in the qualitative tender assessment process.

Currently Ig products supplied under the National Blood arrangements are manufactured by the suppliers listed on the National Product List found at https://www.blood.gov.au/national-product-list.

Under NBA supply arrangements, all Ig product suppliers deliver products to the Australian Red Cross Blood Service (the Blood Service). The Blood Service operates as a secondary distributor of Ig products to hospitals and other health care facilities under a separate contract with the NBA.

1. Provide a list of the medical condition/s and indications for which Immunoglobulin is funded under the National Blood Arrangements within the scope of this referral. Please indicate the specific Ig product(s) within the scope of this referral and the manner of administration (eg intravenous or subcutaneous)?

This referral relates to the medical condition "Secondary hypogammaglobulinaemia unrelated to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT)".

Ig is used as immunoreplacement therapy in Secondary hypogammaglobulinaemia.

The indication for use under Version 3 (V3) of the Criteria is "Replacement therapy for recurrent or severe bacterial infections or disseminated enterovirus infection associated with hypogammaglobulinaemia caused by a recognised disease process or B cell depletion therapy and/or immunosuppressant therapy".

The specific conditions within this medical condition include:

- Hypogammaglobulinaemia following Solid organ transplantation
- Hypogammaglobulinaemia following B cell depletion therapy
- Thymoma-associated hypogammaglobulinaemia (Goods Syndrome)
- Other Hypogammaglobulinaemia unrelated to haematological malignancies or haemopoietic stem cell transplantation (HSCT)

This particular referral is for Ig as a whole, as SCIg is currently funded under the National Blood Arrangements for this condition. As above, it is recommended that immunoglobulin is the intervention for this medical condition and IVIg and SCIg are considered as different routes of administration.

INFORMATION ABOUT REGULATORY REQUIREMENTS

2. Has Ig been registered in the Australian Register of Therapeutic Goods (ARTG), for any of the medical condition/s and indications within the scope of this Referral?

TGA registered Ig products relevant to this referral

Table 1. Ig products registered on the ARTG for use in Australia

Product name and company	**Route of Administration**	**TGA indication for *Secondary hypogamma-globulinaemia****	****NBA Funded for *Secondary hypogamma-globulinaemia****
Privigen 10% – CSL Behring Australia P/L (5g/50mL to 40g/400mL)	IV	Yes	Yes
Hizentra – CSL Behring Australia P/L (1g/5mL to 10g/50mL)	SC	Yes	Yes
Flebogamma 10% – Grifols Australia P/L (5g/50mL up to 40g/400mL)	IV	Yes	Yes
Evogam 16% – CSL Behring Australia P/L (0.8g/5mL or 3.2g/20mL)	SC	Yes	Yes
Intragam 10 – CSL Behring Australia P/L (2.5g/25mL to 20g/200mL)	IV	No	Yes
Flebogamma 5% - Grifols Australia P/L (0.5g/10mL to 20g/400mL)	IV	No	Yes
Cuvitru 20% - Shire Australia P/L	SC	Yes	No
Panzyga – Octaphama Australia P/L	IV	Yes	No
Gamunex 10% – Grifols Australia P/L	IV and SC	Yes	No
Hyqvia – Shira Australia P/L	SC	Yes	No
Intratect – Pfizer Australia P/L	IV	Yes	No
Intratect 5% – Pfizer Australia P/L	IV	Yes	No
Kiovig – Shira Australia P/L	IV and SC	Yes	No

* Secondary hypogammaglobulinaemia unrelated to haematological malignancies or HSCT

** Indicates that Ig is *currently* funded for secondary hypogammaglobulinaemia under the National Blood Arrangements. Note that tendering arrangements may change products funded in the future. The current National Product List with suppliers and prices can be found at https://www.blood.gov.au/national-product-list. *Please note that in the event of any discrepancy between Table 1 and the National Product List, the material from the National Product List should take precedence over any information in Table 1*

IV – intravenous

SC – subcutaneous

IM – intramuscular

An overview of the listings can be found at Attachment D1 and the full listing of all indications for Ig products listed can be found at Attachment D2.

SUMMARY OF EVIDENCE

3. Provide an overview of all key published journal articles or research related to Ig for any of the medical condition/s and indications within the scope of this review. Please do not attach full text articles; this is just intended to be a summary.

Table 2. Overview of key published journal articles or research related to Secondary hypogammaglobulinaemia

Study No.	*Type of study design*	*Title of journal article/research project (include trial identifier/study lead)*	*Short description of research (max 50 words)*	*Website link to journal article or research (or citation details if link not available)*	*Date of publication*
1.	Guidelines	Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline	Guidelines for managing chronic suppurative lung disease (CSLD) and bronchiectasis in Australian and New Zealand children and adults updated (latest search date Oct 2013) based on systematic reviews, multi-disciplinary meetings and a modified Delphi process.	https://www.thoracic.org.au/journal-publishing/command/download_file/id/36/filename/TSANZ-ChronicSuppurativeLungDisease-Guidelines-2016-web.pdf Chang AB, Bell SC, Torzillo PJ, et al 2014, Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline.	2014
2.	Meta-analysis	Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation	Meta-analysis of 18 studies incorporating 1756 patients to evaluate prevalence of hypogammaglobulinaemia after solid organ transplantation and its impact on the rate of opportunistic infections during the first year	https://onlinelibrary.wiley.com/doi/10.1111/cei.12510 Florescu, DF, 2014, 'Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation', *Clinical and*	2014

Study No.	*Type of study design*	*Title of journal article/research project (include trial identifier/study lead)*	*Short description of research (max 50 words)*	*Website link to journal article or research (or citation details if link not available)*	*Date of publication*
			post-transplantation. Included both adult and paediatric studies.	*Experimental Immunology,* ; no. 178, suppl. 54-6	
3.	Systematic review	Good's syndrome remains a mystery after 55 years: A systemic review of the scientific evidence	A systematic review of the clinical, laboratory and immunologic finding from 152 patients with Good syndrome.	https://www.sciencedirect.com/journal/clinical-immunology/vol/135 Kelesidis, T, Yang, O, 2010,'Good's syndrome remains a mystery after 55 years: A systemic review of the scientific evidence', *Clinical Immunology,* vol. 135, pp. 347–363.	2010
4.	Review of evidence	Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology	Reviews the basis for the FDA-approved indications for IGIV and will discuss other disease states in which IGIV has been used. Includes the review of 357 citations. Primary literature review on each subject was derived from searching the National Center for Biotechnology Information Pubmed database using the words 'IVIG', 'IGIV' and 'intravenous immunoglobulin'.	https://www.ncbi.nlm.nih.gov/pubmed/16580469 Orange, JS, Hossny, EM, Weiler, CR, et al 2006, 'Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology', *Journal of Allergy and Clinical Immunology,* vol. 117, no. 4, pp. S525–53.	2006
5.	*Guidelines	Update on the use of immunoglobulin in human disease: A review of evidence	An update of the 2006 review guideline.	https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/IVIG-March-2017.pdf Perez EE, Orange JS, Bonilla F et al 2016. Update on the use of immunoglobulin in human disease:	2016

Study No.	*Type of study design*	*Title of journal article/research project (include trial identifier/study lead)*	*Short description of research (max 50 words)*	*Website link to journal article or research (or citation details if link not available)*	*Date of publication*
				A review of evidence. *Work Group Report of the American Academy of Allergy, Asthma and Immunology*.	
6.	Retrospective analysis	Subcutaneous IgG replacement therapy is safe and well tolerated in lung transplant recipients	A retrospective analysis of the efficacy and tolerability of subcutaneous Ig replacement on 10 lung-transplant recipients.	https://www.ncbi.nlm.nih.gov/pubmed/23499641 Shankar, T, Gribowicz, J, Crespo, M, et al 2013, 'Subcutaneous IgG replacement therapy is safe and well tolerated in lung transplant recipients', *Int Immunopharmacology*, vol. 15, issue. 4, pp. 752–755.	2013

** Not included in citation list for V3 of the Criteria*

4. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration by MSAC Please do not attach full text articles; this is just intended to be a summary.

The NBA is not currently associated with any research projects relating to Secondary hypogammaglobulinaemia.

Table 3. Overview of yet to be published research related to Secondary hypogammaglobulinaemia

Study No.	*Type of study design**	*Title of journal article/research project (include trial identifier/study lead)*	*Short description of research (max 50 words)***	*Website link to journal article or research (or citation details if link not available)*	*Relevant dates of research****

** Categorise study design, for example meta-analysis, randomised trial, non-randomised trial or observational study, etc.*

*** Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** For example, research start date, expected research completion date, and expected publication date.*

CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

5. List all appropriate professional bodies / organisations representing the groups of health professionals who are <u>allowed to request</u> Ig for the medical condition/s and indications within the scope of this referral:

Any specialist is allowed to request Ig for Secondary hypogammaglobulinaemia in the Criteria. The specialists listed in BloodSTAR as prescribing Ig for Secondary hypogammaglobulinaemia from September 2016 to August 2018 include:

- Haematologists
- Paediatricians
- Immunologists
- Intensivists
- Transplantation specialists
- General Medicine Physicians
- Dermatologists
- Neurologists
- Rheumatologists

Some professional bodies/organisations known to the NBA representing specialists above are listed below:

- Australian Society for Clinical Immunology and Allergy
- ANZ Society of Blood Transfusion
- Haematology Society of ANZ
- Australian Paediatric Society
- Royal Australasian College of Physicians
- ANZ Association of Neurologists
- Australian and New Zealand Intensive Care Society
- Australian and New Zealand Society for Geriatric Medicine
- Australian Association of Gerontology
- Australian College of Rural and Remote Medicine
- Australian Medical Association
- Australian Rheumatology Association
- Australian Specialist Practitioners of Transfusion
- Australasian Society for Immunology
- Cardiac Society of ANZ
- College of Intensive Care Medicine of ANZ
- Rural Doctors Association
- The Australasian College of Dermatologists
- The Thoracic Society of Australia and New Zealand
- Thrombosis and Haemostasis Society of Australia and NZ
- Transplantation Society of Australia and New Zealand
- Australian Society of Infectious Diseases

Please note that this may not be a comprehensive list and that further research may need to be undertaken.

6. List professional bodies / organisations that may be impacted by the use of Ig (i.e. those who provide a comparable product / device / service) within the scope of this Referral

The comparable product listed for this condition is prophylaxis antibiotics. The providers of these products may be impacted.

Suppliers of Ig may also be impacted:

- CSL Behring

- Grifols
- Shire (Takeda)
- Octapharma
- Pfizer

7. List the consumer organisations relevant to the use of Ig within the scope of this Referral

- Australian Federation of AIDS Organisation
- Cancer Australia
- AusPIPS
- Brain Foundation
- HeartKids Australia
- Immune Deficiencies Foundation Australia
- Transplant Australia
- Rare Voices Australia (RVA)
- Multiple Sclerosis Australia (because some have transplants)
- Australian Rheumatology Association

8. Nominate the clinical experts who will be advising on the use of Ig within the scope of this Referral:

Clinicians nominated by the Reference Group have been sent the targeted survey on the draft referral, however no prior agreement from specialist clinicians to provide advice was able to be obtained.

Please note that the Department may also consult other referrers, procedural lists and disease specialists to obtain their insight.

POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)
INFORMATION ABOUT THE PROPOSED POPULATION

9. Summarise the natural history of the medical condition/s within the scope of this referral, and a high level summary of associated burden of disease in terms of morbidity and mortality:

Hypogammaglobulinaemia is defined as a serum immunoglobulin G (IgG) level <700mg/dl[1]. An abnormal susceptibility to bacterial infections may arise from acquired hypogammaglobulinaemia that has diverse causes, including haematological malignancies and complications of its treatment (considered in acquired hypogammaglobulinaemia related to haematological malignancy and post haemopoietic stem cell transplantation); protein losing states; malnutrition; thymoma, immunosuppressant therapy; and repeated cycles of B-cell depletion therapy (e.g. rituximab), especially when used with immunosuppressant therapy and in children. In many cases, successful management of the underlying condition will reverse the hypogammaglobulinaemia. However, in some cases, hypogammaglobulinaemia persists and is complicated by recurrent or severe bacterial infections. Secondary hypogammaglobulinaemia may occasionally be complicated by a disseminated enterovirus infection, particularly in patients who have received B cell depletion therapy for a B cell lymphoproliferative disorder[2]. Approximately 15 percent of patients who have received a solid organ (heart, lung, kidney) transplant experience secondary hypogammaglobulinaemia with severe IgG deficiency (<4g/L) during the first year after transplantation. These patients experience a 3·73-fold increased risk of infection when compared with patients who have normal IgG levels and several studies have shown that IVIg therapy reduces the risk of infection in heart and lung transplant patients[1].

Chronic suppurative lung disease/bronchiectasis should be diagnosed early and appropriate investigation and treatment instigated. This includes planned coordination of care among healthcare providers, and specialist evaluation to confirm diagnosis, investigate aetiology, assess baseline severity and to develop individualised management plans, including self-management when appropriate. All exacerbations require treatment. Intensive treatment seeks to improve symptom control, reduce exacerbation frequency, preserve lung function, optimise quality of life and enhance survival. Long-term antibiotics, inhaled corticosteroids, bronchodilators and mucoactive agents may be individualised, but are not recommended routine therapy[3].

10. Specify characteristics of patients with the medical condition/s within the scope of this referral who would be considered eligible for Ig therapy under the National Blood Arrangements, including details of how a patient is investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for Ig therapy:

How a patient with Secondary hypogammaglobulinaemia is investigated, managed and referred in the lead up to being considered eligible for Ig therapy is outside of the NBA's expertise. Clinical experts on the Ig Reference Group[4] advised that this patient group includes a wide range of rare conditions including both paediatric and adult patients. Patients often present with atypical features, have an autoimmune disease as their primary presentation and are therefore on multiple therapies. Overall, given that this patient group is so heterogeneous, the full work up of the patient and diagnostic tests varies for each patient group.

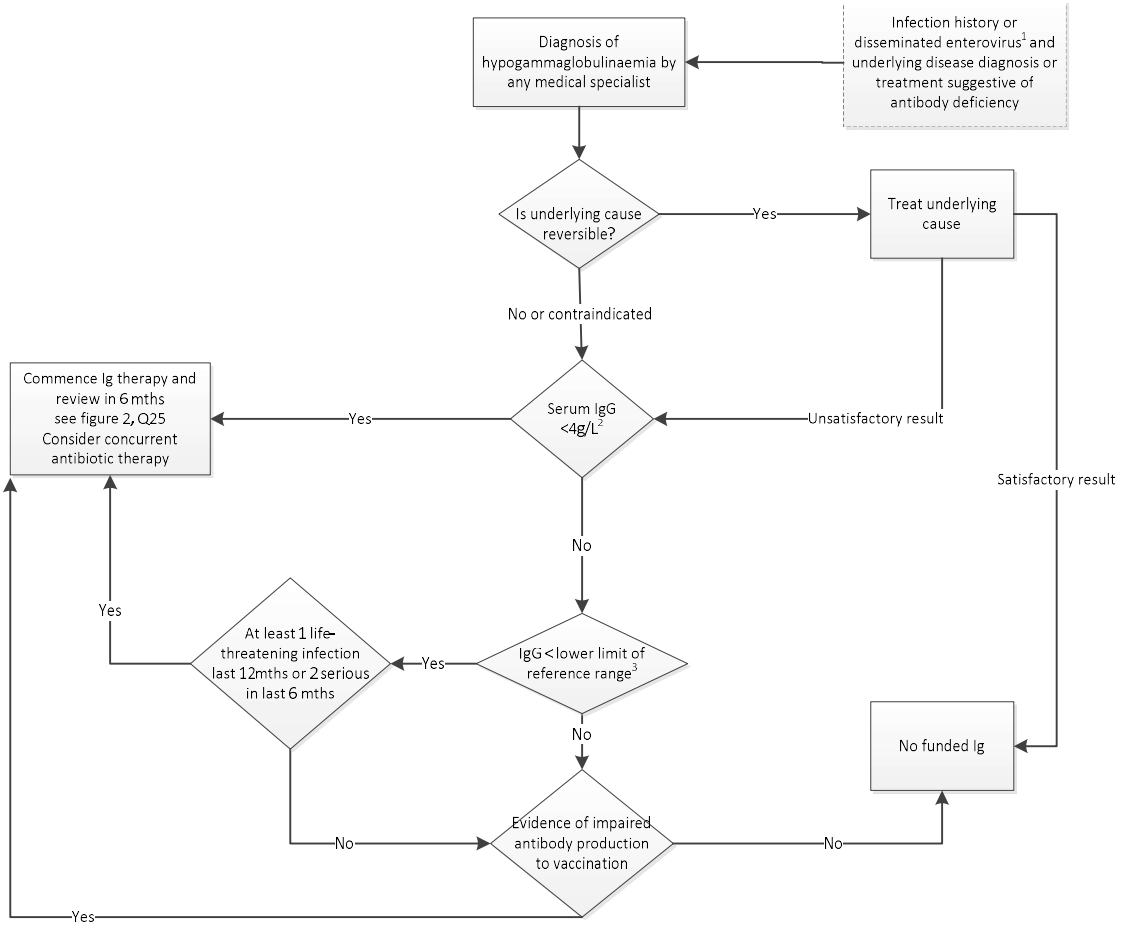
[1] Florescu, DF, 2014, 'Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation', *Clinical and Experimental Immunology,* ; no. 178, suppl. 54-6
[2] V3 Criteria for Clinical Use of Immunoglobulin in Australia
[3] Chang AB, Bell SC, Torzillo PJ, et al 2014, Thoracic Society of Australia and New Zealand Chronic Suppurative Lung Disease and Bronchiectasis in children and adults in Australia and New Zealand – Clinical Practice Guideline.
[4] Ig Reference Group Meeting 3, July 2019

An outline of the qualifying criteria for Ig funded under the National Blood Arrangements for Secondary hypogammaglobulinaemia can be found at Attachment C or https://www.criteria.blood.gov.au/MedicalCondition/View/2577. For more detailed criteria refer to Attachment B.

11. Define and summarise the current clinical management pathways (algorithm) for patients who are eligible for Ig therapy (supplement this summary with an easy to follow flowchart depicting the current clinical management pathways leading up to being considered eligible for Ig therapy):

Please note that in the event of any discrepancy between Figure 1 and Q10, the material from the Criteria provided in Q10 should take precedence over any interpretation taken in Figure 1.

FIGURE 1 –Initial access to Ig funded under the National Blood Arrangements as per this Referral – Algorithm



[1] Diagnosis of bronchiectasis and/or suppurative lung disease must be consistent with the Thoracic Society of Australia and New Zealand (Chang et al 2014)

[2] Serum IgG levels should be measured on two separate occasions, at least one hour apart and at least one sample taken when the patient does not have an active infection.

[3] Reference range should be age related.

12. If applicable, advise which health professionals primarily manage the patient receiving the Ig product within the scope of this referral:

Under V3 of the Criteria, any specialist may diagnose and review a patient with Secondary hypogammaglobulinaemia. However the majority of specialists who have prescribed Ig for patients with

Secondary hypogammaglobulinaemia previously include transplantation specialists, immunologists, haematologists and paediatricians. Note however that this data has been obtained prior to the implementation of V3 of the Criteria, in which hypogammaglobulinaemia related to haemopoetic stem cell transplant (HSCT) has now been excluded from this medical condition and can be found under Acquired hypogammaglobulinaemia. Some of these patients may not yet have transitioned to the new criteria. This change is likely to reduce the amount of requests for Ig from haematologists under Secondary hypogammaglobulinaemia.

INFORMATION ABOUT THE INTERVENTION

13. Describe the key components (including administering health professionals) and clinical steps involved in delivering Ig therapy to eligible patients within the scope of this referral:

If the Ig therapy is delivered by intravenous infusion, patients will attend hospital for a day procedure to be infused. Depending on the dose, which may be split over several days, they may (or may not) be required to attend for a 'day procedure' on a number of days (usually consecutive) each month.

Intravenous infusion involves:

- identification check to ensure the right patient is receiving the right product at the right dose and at the right time. This check is done by two health professionals – usually one must be a doctor or a registered nurse and the other can be either a doctor, registered nurse or an enrolled nurse.
- Preparation of equipment (Ig vial/bottle, vented line, aseptic dressing pack, cannula)
- The procedure is explained to the patient and consent is obtained
- Cannula is inserted using aseptic technique by a credentialed nurse or doctor
- The IV line is inserted directly into the Ig vial/bottle and the IV line is primed with Ig product (without dilution) and hung in accordance with the local hospital's protocol.
- The patient is monitored for any reactions and the infusion is slowed or stopped depending on the patient's response.

If the Ig therapy is delivered subcutaneously, the patient or carer will be educated about how to administer the product at home. They will undertake more frequent subcutaneous infusions (usually twice weekly) at home. This requires:

- Storing the product in accordance with the manufacturer's advice
- insertion of a butterfly subcutaneous cannula using aseptic techniques into subcutaneous layer just under the skin of the abdomen or thigh;
- drawing up the required dose into a syringe
- connection of the syringe to the subcutaneous line
- pushing the dose into the abdomen at the required rate which will vary depending on the dose size and the patient's response.

14. Specify how long the delivery of Ig therapy typically takes to perform within the scope of this referral:

The timeframe to administer an Ig infusion is dependent on the:

- dose required;
- the patient's weight (as dosing is in grams/kg);
- the product's advised infusion rate and hospital's protocol which determines the infusion rate used at that location (which may differ from the product's Product Information Sheet);
- the patient's response during the infusion. If the patient experiences a reaction such as a headache, the rate of infusion will be slowed or stopped depending on the severity of the reaction.

Typical IVIg delivery time for Secondary hypogammaglobulinaemia

The dose could be administered over the course of a few hours for an 80 Kg person (including day admission, identification, cannulation and set-up, infusion, post infusion monitoring) (e.g. 0.4g/kg for an 80Kg person = 32g) . Applying the infusion rate provided

in the Product Information sheet provided for Intragam 10 is set out below. This table indicates a minimum total infusion time of 100 minutes for a patient of 80kg. The infusion rate could reduce for various reasons, e.g. adverse events. Please note that this is only one of the products funded for PID and that other products may have different infusion rates.

Table 4: 80Kg person @ 0.4g/Kg = 32grams of a 10% Ig product

Minutes	Rate ml/min	grams	Mls	Mls remaining
Starting	0	0	0	320
15	1	1.5	15	305
15	3	4.5	45	260
15	3	4.5	45	215
15	4	6	60	155
15	4	6	60	95
15	4	6	60	35
10	4	4	40	-5

Typical SCIg delivery time for Secondary hypogammaglobulinaemia

The Product Information sheet for Hizentra[1] states that the recommended initial infusion rate should not exceed 15 mL/hour/site. If well-tolerated, the infusion rate can then gradually increase to 25 mL/hour/site. Applying this infusion rate and assuming only one site is used at a time, the minimum administration time for a patient of 80kg on a dose of 0.1g/kg (0.5mL/kg) per week would be approximately 1 hour and 48 minutes (note that the 'gradual increase' of rate may be interpreted and implemented differently, see table 5 for interpretation in this example). It is advised that if the dose is above 25mL that multiple injection sites be used. The infusion rate could reduce for various reasons, e.g. adverse events. Please note that this is only one of the products funded for Secondary hypogammaglobulinaemia and that other products may have different infusion rates. There are also likely to be multiple infusion devices available for SCIg which may increase or decrease the rate of infusion.

[1] Product information for AusPAR Hizentra Normal Human Immunoglobulin CSL Behring Ltd 2013-00301-2-2 Final 25 June 2014. Accessed 7 August 2019 from https://www.tga.gov.au/sites/default/files/auspar-normal-human-immunoglobulin-140625-pi.pdf

Table 5: 80Kg person @ 0.1g/Kg = 8grams = 40mL Hizentra

Minutes	Rate ml/min	Mls	Mls remaining
Starting	0	0	40
15	0.25	3.75	36.25
15	0.3	4.5	31.75
15	0.35	5.25	26.5
15	0.42	6.3	20.2
15	0.42	6.3	13.9
15	0.42	6.3	7.6
18	0.42	6.3	0

15. If applicable, are there any limitations on provision of the various Ig product to the relevant patient groups within the scope of this referral (i.e. accessibility, dosage, quantity, duration or frequency):

In addition to the 'Criteria' outlined above:

- Patients receiving (or carers administering) subcutaneous immunoglobulin will require training and sufficient aptitude and capability to administer the product at home. SCIg also requires the appropriate infusion equipment as appropriate for the particular product. SCIg programs are not available at all hospitals. This varies depending on the local jurisdiction's policy, and the local hospital's capacity.
- IV administration of Ig requires good venous access and availability of a day hospital with IV infusion facilities.
- The following dosing parameters are set in the Criteria V3:
    - Maximum dose
    - Minimum dose
    - Dose frequency
    - Whether divisions are allowed

While higher doses can be accessed, doctors must provide a rationale for requiring a higher dose. The Criteria V3 encourages dosing at the lowest effective dose by defaulting to the minimum dose and frequency.

- Duration of access to Ig is determined by the 'authorisation period' determined in the Criteria V3. Access to Ig cannot exceed the 'authorisation period'. To access further treatment the doctor must reapply and demonstrate the patient meets the 'criteria'. (see Attachment B: V3 Proforma for *Secondary hypogammaglobulinaemia*).

16. If applicable, identify any healthcare resources or other medical services that need to be delivered at the same time as the Ig products within the scope of this referral):

The patient's vital signs will be monitored during the course of the infusion (blood pressure, pulse, temperature) by a nurse or enrolled nurse. Patients may require analgesia or antihistamine to manage a reaction e.g. headaches, flushes, rash.

As an example; in all patients receiving Flebogamma, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg;
- monitoring of urine output;
- monitoring of serum creatinine levels;

- avoidance of concomitant use of loop diuretics[5].

17. If applicable, advise whether delivering Ig therapy could be delegated or referred by the health professional primarily responsible for managing the patient to another professional for delivery including any limitations on who might deliver it:

The diagnosis and management of the patient cannot be delegated. Intravenous administration of Ig requires a treating doctor to determine the dose. However, the doctor who diagnoses the condition may not be the same doctor who reviews treatment. The administration of Ig intravenously delivered Ig is undertaken by nursing staff or possibly a junior doctor and cannot be delegated. The intravenous infusion is overseen by the hospital medical staff with overarching responsibility held by the treating clinician. The NBA understands that in very rare circumstances, IVIg has been administered by the patient or by a 'hospital in the home' nurse.

If Ig is administered at home via subcutaneous administration, the administration of the product can be delegated to the patient or their carer. A nurse or technician has responsibility for ensuring the patient or carer is trained in subcutaneous administration. Ongoing support is generally provided by a registered nurse. Access to, and protocols and processes for, SCIg programs vary across the country.

18. If applicable, advise what type of training or qualifications are required to deliver Ig therapy as well as any accreditation requirements to support its delivery:

BloodSTAR requires any medical officer registered as a specialist with the Australian Health Practitioner Regulation Agency (AHPRA) to diagnose and review a patient with Secondary hypogammaglobulinaemia.

Local hospital policies will vary. Nursing qualifications are required to commence and monitor an IVIg infusion.

As this procedure requires cannulation, training should be provided and competence determined and monitored for this procedure which may be done by a doctor or a nurse depending on the institution.

For subcutaneous administration, the patient/carer must be trained in the procedure by a qualified nurse or technician.

All sites that administer blood or blood products should be accredited under the National Safety and Quality Health Service Standard for Blood Management.

19. Indicate the proposed settings in which Ig therapy is delivered (select all relevant settings):

☒ Inpatient private hospital
☒ Inpatient public hospital (as a private patient)
☒ Inpatient public hospital (as a public patient)
☒ Outpatient clinic
☐ Consulting rooms
☐ Day surgery centre (as an admitted private patient)
☐ Day surgery centre (as an outpatient)
☐ Residential aged care facility
☒ Patient's home
☐ Laboratory
☒ Other – please specify below 'Private same day infusion facility unattached to a hospital'

[5] Therapeutic Goods Administration 2019. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion. Found at https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01254-1&d=201905201016933

20. Please describe the rationale for and proportion of delivery in each setting (to enable a judgement about the settings that are important enough to fall within the scope of the clinical and economic evaluations in the review):

Inpatient – private hospital. Patient requires admission due to dose required over multiple days, comorbidities/advanced age, has private medical insurance and a preference to be in a private facility and is managed by a neurologist who is able to support the patient's preference.

Inpatient - public hospital (as a private patient). Patient requires admission due to dose required over multiple days, comorbidities/advanced age, has private medical insurance and a preference to be admitted as a private patient and is managed by a neurologist who is able to support the patient's preference.

Inpatient - public hospital (as a public patient) - Patient requires admission due to dose required over multiple days, comorbidities/advanced age, and does not have medical insurance or has a preference to be admitted as a public patient.

Outpatient clinic (as an outpatient) - Patient has regular maintenance infusions and does not require admission to hospital.

Patient's home – SCIg is available under the National Blood Arrangements for Secondary hypogammaglobulinaemia and may be available to be administered in the patient's home where: the patient or carer has a preference for SCIg, the patient has access to a hospital participating in a suitable SCIg program, the doctor prescribes SCIg, SCIg service/training is available, the patient/carer has received training.

Private same day infusion facility (e.g. private infusion facility where chemotherapy or other infusion/venesection procedures are conducted). These would be pre-arranged infusions.

Clinical expert advice[6] indicates that patients are more likely to be initiated IVIg by presenting to the hospital with an acute infection. The majority of ongoing doses are given in the outpatient setting. For this reason the vast majority of public hospital patients receiving Ig for this condition would be outpatients.

NBA advises that in 2017-18, around 8.3 percent of *treatment episodes* of Ig therapy used SCIg of which around 4.9 percent was for Secondary hypogammaglobulinaemia. In the same year, approximately 3.3 percent of *total Ig* grams were for SCIg of which 6.3 percent was for secondary hypogammaglobulinaemia. While the initial infusions are administered in the public hospital outpatient setting to train the patient or the carer, SCIg is subsequently administered in the patient's home. SCIg use at home is expected to increase.

Table 6: 2017-18 breakdown of public and private patients receiving Ig for Secondary hypogammaglobulinaemia: sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) (publication forthcoming, date to be confirmed)

	Public n (%)	Private n (%)	Total N (%)
Patients	628 (62%)	383 (38%)	1011 (100%)
Grams	131,953 (59%)	90,184 (41%)	222,137 (100%)

21. Define and summarise the current clinical management pathways (algorithm) from the point of initiating Ig therapy within the scope of this referral, including provision of health care resources (supplement this summary with an easy to follow flow chart, including health care resources):

The current basis for ongoing access to Ig products for Secondary hypogammaglobulinaemia unrelated to haematological malignancy or HSCT under Version 3 of the *Criteria* under the National Blood Arrangements is described in BloodSTAR at https://www.criteria.blood.gov.au/MedicalCondition/View/2577 and in detail at

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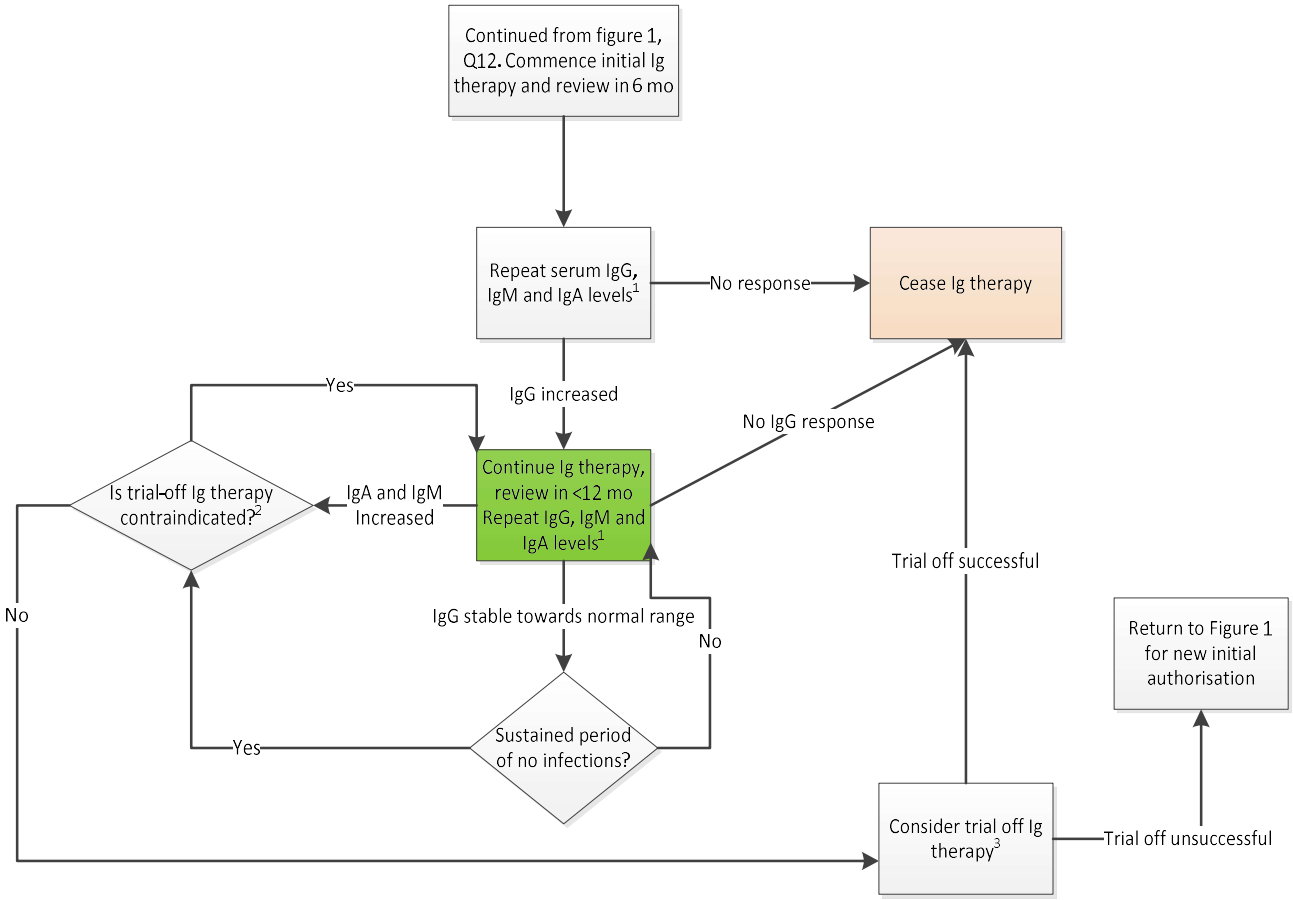
Attachment B (V3 Condition Proforma) . If there is a discrepancy between the information available from the BloodSTAR weblink and the detailed proforma at Attachment B, the web-link should take precedence.

A schematic summary of the basis for ongoing access to Ig therapy for Secondary hypogammaglobulinaemia, is provided at Figure 2.

Please note that in the event of any discrepancy between the BloodSTAR weblink and Figure 2, the material from the BloodSTAR weblink should take precedence over any interpretation taken in Figure 2.

FIGURE 2 –Continuing access to Ig funded under the National Blood Arrangements as per this Referral – Algorithm



[1] If serum IgM and IgA levels are trending upwards and near normal, IgG is also likely to be normal, this may suggest recovery of the immune system and a trial-off Ig therapy might be considered.

[2] Contraindication reasons for a trial-off Ig therapy include neutropenia, immunosuppressant medication, active bronchiectasis and/or suppurative lung disease or severe hypogammaglobulinaemia persists where no significant improvement has occurred in the underlying condition.

[3] Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy.

INFORMATION ABOUT THE COMPARATOR(S)

22. Nominate the appropriate comparators for Ig therapy, i.e. how would the eligible populations be managed if they cannot receive Ig therapy (including identifying health care resources that are delivered at the same time as the comparator product or service):

The Ig Reference Group[7] agreed that, given the heterogeneous patient group, 'no Ig' should be the comparator to Ig therapy for Secondary hypogammaglobulinaemia. Best practice standard of care for certain specific conditions may or may not include antibiotic treatment, prophylactic antibiotics and thymectomy.

Patients may require different concurrent therapies for Secondary hypogammaglobulinaemia depending on the initial cause. For example, a patient with Good's syndrome is likely to require a thymectomy to treat a thymoma.

23. Do the products or alternative service that are nominated as the comparator have existing MBS items or PBS listings?

☒ Yes (please provide all relevant MBS items or PBS listings)
☐ No

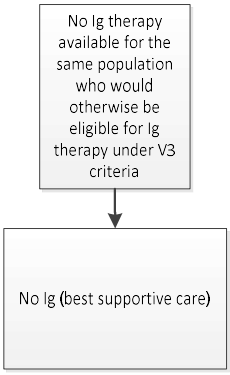
Table 7: PBS listing for comparator products

Generic Name	PBS subsidised for *insert condition name*	PBS unrestricted or Authority required	PBS item numbers and presentations if available

24. Define and summarise the comparator clinical management pathways (algorithm) that patients would follow after they first receive the products or alternative services nominated as the comparator (supplement this summary with an easy to follow flow chart, including health care resources):

In circumstances where Ig is not an option, a schematic summary of the treatment pathway is suggested for the purpose of this review as follows:

Figure 3 – Treatment pathway when Ig is not an option.



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25. (a) Are there additional products or services used with the nominated comparators

☐ Yes
☐ No

(b) If yes, please identify these products or services and outline the extent to which each additional product / device is used with the nominated comparators:

INFORMATION ABOUT THE CLINICAL OUTCOMES

26. Summarise the clinical claims of Ig therapy, against the nominated comparators, in terms of consequences for health outcomes (comparative benefits and harm):

Administration of immunoglobulins has been shown to reduce the overall rate of infections in patients with Secondary hypogammaglobulinaemia following solid organ transplantation, suggesting that IVIg administration might be associated with some reconstitution of the immune system. As the main cause of mortality in this subset of patients is infection, it can be expected that if the rate of infection is reduced, then mortality rates should also decrease[8].

Lyophilized products that are hyperosmolar should not be given in patients after transplantation, as they are likely to cause osmotic nephropathy and renal failure. Newer, chromatographically derived IVIg products are iso-osmolar but may contain higher concentrations of anti-blood group antibodies (anti-A, anti-B). These products appear to pose an increased risk of haemolysis following high-dose (2g/kg) IVIg infusions while patients are on dialysis. Patients with blood type A, B, or AB should be monitored carefully for haemolysis after high-dose IVIg therapy[9].

Hypogammaglobulinaemia may also be a complication of a thymoma (often known as Good's syndrome). This is usually associated with B cell deficiency. The hypogammaglobulinaemia often increases susceptibility to respiratory tract infections. Ig replacement therapy has been reported to increase infection control, reduce hospitalisation, and decrease the use of antibiotics for these patients. Other therapies that have been trialled to treat Good's syndrome include immunosuppressive therapy, plasmapheresis, splenectomy and transfer factor from human leukocytes with moderate results[10] .

The Therapeutic Goods Administration (TGA) maintains a reporting service for adverse events or defects in medicines in Australia.

The Product Information for Flebogamma in Australia[11] advises: Certain severe adverse reactions to the medicinal product may be related to the rate of infusion. The recommended infusion rate and method of administration must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency
- in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction. Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses have been observed with human normal immunoglobulin.

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

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[8] Florescu, DF, 2014, 'Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation', *Clinical and Experimental Immunology,* ; no. 178, suppl. 54-6

[9] Perez EE, Orange JS, Bonilla F et al 2016. Update on the use of immunoglobulin in human disease: A review of evidence. *Work Group Report of the American Academy of Allergy, Asthma and Immunology*.

[10] Kelesidis T, Yang O. Clinical Immunology 2010; 135: 347–363

[11] Therapeutic Goods Administration. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion. Accessed May 2019 from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01254-1&d=201905201016933

Other risks include:

- Haemolytic anaemia
- Transfusion-related acute lung injury (TRALI)
- Transmission of infectious agents[12]

27. Please advise if the overall clinical claim is:

☒ Superiority
☐ Non-inferiority

28. Please list the health outcome types that need to be specifically measured in assessing the clinical claim of Ig therapy versus the comparator within the scope of this referral, prioritising the major health outcomes first:

Outcomes	***The outcomes identified pre assessment and considered in scope are:***
	Safety Outcomes:
	• Serious adverse events (e.g. antibiotic allergy, anaphylaxis, veno-occlusive events)
	• Antibiotic resistance
	
	Clinical effectiveness outcomes:
	• Infections (decrease in infection rate)
	• Mortality
	• Morbidity
	• Hospitalisations
	• Quality of Life
	
	Healthcare system resources utilisation:
	• Changes in health system resource utilisation associated with the intervention
	  ○ Ig products
	  ○ Infusion equipment
	  ○ Administrative and clinician time (e.g. resources associated with requesting, and authorising, access to Ig)
	  ○ Nursing time (for initiation and monitoring if IVIg)
	  ○ Hospitalisation (including use of hospital resources)
	  ○ Medication to treat adverse events (e.g. analgesia or antihistamines)
	  ○ Product dispensing and disposal of any unused product
	  ○ Follow-up and/or monitoring visits, including regular immunologist visits
	
	• Change in health system resource utilisation associated with the comparator(s)

[12] Therapeutic Goods Administration. Australian Product Information, Flebogamma 10% DIF (Human Normal Immunoglobulin [IVIg] 100mg/ml) solution for infusion. Accessed May 2019 from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01254-1&d=201905201016933

INFORMATION ABOUT ESTIMATED UTILISATION

29. Estimate the prevalence and/or incidence of the proposed populations within the overall medical condition:

The prevalence of hypogammaglobulinaemia in the overall underlying medical conditions would likely vary significantly dependent on the cause.

The continued development of newer biologic agents targeting the immune system, and their increased clinical use, will require further study of secondary immunodeficiencies in patients treated with these agents[13].

The incidence of hypogammaglobulinaemia in patients with thymoma is 6-11 percent[14].

Approximately 15 percent of patients who have received a solid organ (heart, lung, kidney) transplant experience secondary hypogammaglobulinaemia with severe IgG deficiency (<4g/L) during the first year after transplantation[15].

30. Provide data on the use of Ig therapy over recent years for the medical condition/s within the scope of this referral:

Table 8: Data on the use of Ig therapy over recent years for Secondary hypogammaglobulinaemia (NBA internal data)

	2013-14	2014-15	2015-16	2016-17	2017-18
New patients	182	215	249	302	304
Total patients	516	580	652	781	953
Grams	110,024	126,561	145,497	180,831	222,136
Average grams per patient	213	218	223	232	233

** These data are from V2 of the criteria which included post HSCT patients. In V3, access under Secondary hypogammaglobulinaemia excludes post HSCT patients (V3 criteria – see Attachment B).*

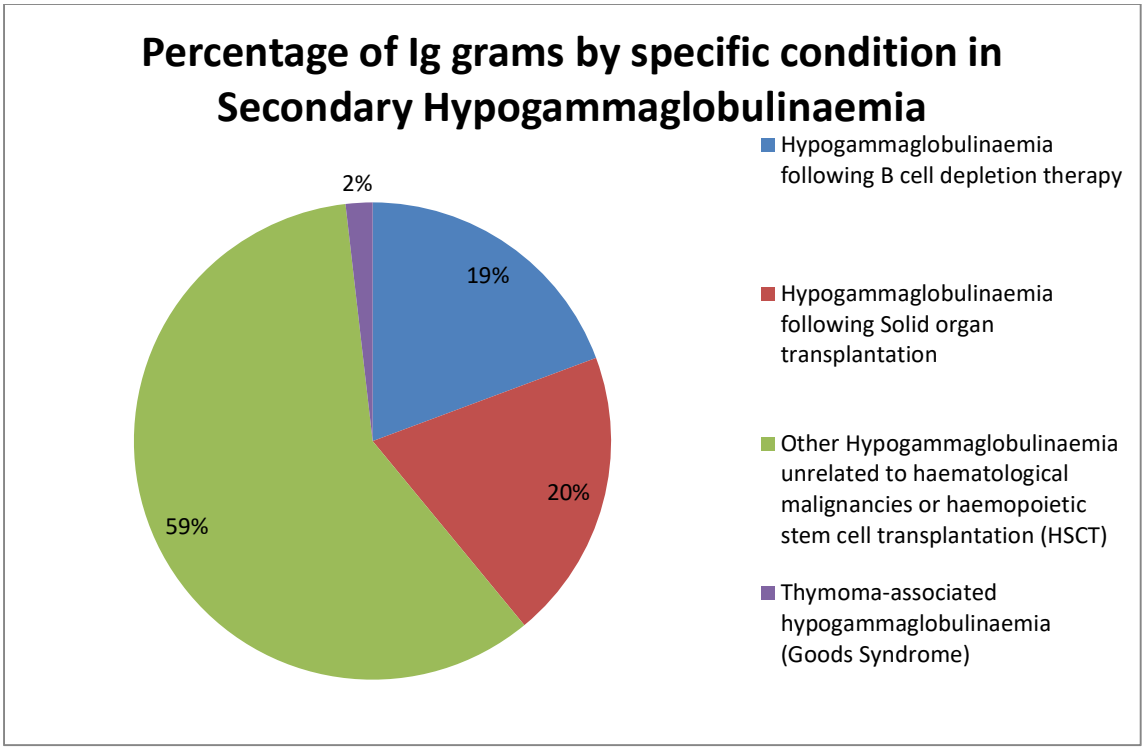
[13] Perez EE, Orange JS, Bonilla F et al 2016. Update on the use of immunoglobulin in human disease: A review of evidence. *Work Group Report of the American Academy of Allergy, Asthma and Immunology*.

[14] Kelesidis, T, Yang, O, 2010,'Good's syndrome remains a mystery after 55 years: A systemic review of the scientific evidence', Clinical Immunology, vol. 135, pp. 347–363.

[15] Florescu, DF, 2014, 'Solid organ transplantation: hypogammaglobulinaemia and infectious complications after solid organ transplantation', *Clinical and Experimental Immunology,* ; no. 178, suppl. 54-6

Distribution of the four specific conditions under V3 of the Criteria can be seen in the chart below. Note that the data obtained for this chart is limited to a short time-frame - from the implementation of V3 (22 October 2018) to 31 December 2018.

Figure 4: Distribution of grams of Ig by specific condition (NBA internal data)



31. Estimate the dose of Ig and the number of times Ig is delivered to a patient per year for the medical condition/s within the scope of this referral:

Table 9: Ig dosing and frequency for Secondary hypogammaglobulinaemia (NBA internal data).

Secondary hypogamma	2016-17	2017-18
Treatment episodes	7719	9487
Average treatment episodes per year	10	10
Average Gms/Kg/Episode	0.40	0.38
Grams/patient IVIg	230	228
Grams/patient SCIg	207	228

Note: The meaning of term 'episode' has evolved over the course of the development of this administrative dataset. The definition of the term is more closely related to a 'dispensing episode or event'. As there may be more than one 'dispense episode or event' in a single course of treatment, the true number of courses of treatment during any period is highly likely to be fewer than the number of 'episodes' recorded in BloodSTAR and STARS.

32. How many years is Ig required for the patient with the medical condition/s within the scope of the referral?

This condition can be acute, chronic or transient. The usual length of an authorisation for maintenance therapy is one year. Continuing therapy is allowed so can exceed one year and can be ongoing. The majority of patients have more than one authorisation. However, authorisations can be shorter (e.g. one month). The average duration of Ig therapy for Secondary hypogammaglobulinaemia is unknown and is likely to vary between specific conditions due to varying specific conditions and underlying causes.

Clinical experts[16] advised that patients with Secondary hypogammaglobulinaemia are usually treated for 12-24 months while their immune system recovers. However, this recovery time doesn't apply to all patients as the underlying conditions of this group are heterogenous and the treatments used to manage the conditions have varying durations. Whilst most patients are likely to improve from Ig therapy, there are patients that do not respond to Ig therapy who would continue to be treated with Ig therapy under another condition, or would die.

33. Provide commentary on risk of 'leakage' to populations with the medical condition/s not targeted by Ig therapy (outside the population indicated in V3 Criteria):

The most significant leakage risk is associated with patients receiving ongoing Ig therapy after recovery of the immune system.

To manage this risk, Criteria V3 encourage cessation of Ig therapy to be considered at least after each 12 months of treatment, unless contraindicated. If serum IgM and IgA levels are trending upwards and near normal, this may suggest recovery of the immune system and a trial might be considered if the patient is well. Once the patient has normal IgA and IgM levels, the IgG is also likely to be normal and a trial off Ig therapy may be undertaken. Ig therapy should be extended as required to enable cessation of therapy in September/October, with repeat clinical and/or immunological evaluation before re-commencement of therapy. If patients do require further Ig therapy after trialling off, a new request may be made[17].

There is a small risk of patients receiving Ig therapy for Secondary hypogammaglobulinaemia when the severity of disease has not been reached. Criteria V3 mitigate this risk to a degree by requiring IgG levels, IgM and IgA levels and detailed information about the severity of infections.

Jurisdictional data for 2015-16 on number of patients, grams, grams/episode and grams/1,000 population in the relevant state or territory and nationally are provided below. These data indicate substantial variation in practice between jurisdictions.

Table 10: Jurisdictional differences in Ig prescribing (NBA Annual Report 2015-16)

Secondary hypogamma	NSW	VIC	QLD	WA	SA	TAS	ACT	NT	National	Fold Vari*
Patients	269	125	197	34	14	15	8	<5	652	
Grams	57,591	22,351	51,562	5,405	2,456	5,260	834	39	145,497	
Grams/Episode	26	25	23	16	18	33	22	39	24	
Grams/1,000 population	8	4	11	2	1	10	2	<1	6	11

* Fold vari = Fold variation calculated by dividing the largest grams/1000 population by the smallest g/1000 population using only data from the five largest states (NSW, VIC, QLD, WA and SA).

[16] Ig Reference Group Meeting 3, July 2019

[17] V3 Criteria for Clinical Use of Immunoglobulin in Australia

COST INFORMATION

34. Indicate the current cost of providing Ig therapy within the medical condition/s. Where possible, please provide overall and breakdown costs:

The cost of Ig for Secondary hypogammaglobulinaemia funded under the National Blood Arrangements for domestic Ig products was $26,693,824 ($25,681,558 IVIg and $1,012,266 SCIg) in 2017-18, this equates to an average cost per patient of $28,010.30.

Table 11: Breakdown of product costs (excluding GST) for Secondary hypogammaglobulinaemia (NBA internal data)

Ig Product category	Cost (ex GST)
*Domestic IVIg cost	$23,821,133
Imported IVIg cost	$1,860,425
*Domestic SCIg	$651,539
Imported SCIg	$360,727

*Domestic costs include the cost of plasma collection and fractionation.

Costs associated with the following have not been included in the above estimate:

- MBS costs: i.e. doctor visits
- Costs associated with requesting access to Ig product
- Hospital costs: nursing time, infusion centre administration, patient/carer training costs
- IV and SCIg infusion equipment costs
- Authorisation costs: cost to contract Blood Service to conduct authorisations
- Product dispensing costs
- Product wastage (e.g. discarding unused portion of product)
- Criteria review and update costs

Table 12: Ig product use 2017-18: sourced from the National Report on the Issue and Use of Immunoglobulin (Ig) (publication forthcoming, date to be confirmed)

	IVIg					SCIg		
Secondary hypogammaglobulinaemia	**Flebogamma 5 percent**	**Flebogamma 10 prcent**	***Intragam P**	**Intragam 10**	**Privigen 10 per cent**	**SCIg Evogam**	**SCIg Hizentra**	**Total**
Ig product issued in grams	7,729	57,250	573	41,681	110,950	0	0	218,183
NBA current price per gram in $	45	45	58.49	58.49	45	58.49	59.15	
**Total cost by product in $	347,805	2,576,250	33,515	2,437,922	4,992,750	0	0	

*Intragam P no longer available

**Note that product issued data is from 2017-18 and the price listed is current as at 20 June 2019. Prices and allocation of products change over time. Costs are for product only and domestic costs do not include plasma collection or fractionation.