



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1565 – Review of immunoglobulin use for Acquired Hypogammaglobulinaemia Secondary to Haematological Malignancies and haemopoietic stem cell transplantation***

**Applicant:** National Blood Authority

**Date of MSAC consideration:** MSAC 77<sup>th</sup> Meeting, 28-29 November 2019

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

This Post-market Review requests MSAC advice on the Government funded supply of replacement human gamma immunoglobulin (Ig) therapy under the National Blood Arrangements for the treatment of acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT). The application (referral) was received by the Department of Health from the National Blood Authority (NBA).

A Post-market Review has been conducted to assess the clinical effectiveness and cost-effectiveness of replacement Ig therapy (with or without antibiotics) versus no Ig (with or without antibiotics) for the treatment of acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).

#### **2. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC advised that immunoglobulin (Ig) is not a cost-effective therapy to manage infections in all patients who have acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haemopoietic stem cell transplantation (HSCT) at the current price. MSAC considered that Ig could be cost-effective in some patients currently eligible for Ig under the Criteria (version 3) for this indication, however the variation in the underlying patient conditions and treatments causing hypogammaglobulinaemia in this population made an overall conclusion about the cost-effectiveness of Ig difficult. The range of incremental cost-effectiveness ratios (ICERs) derived in this review varied greatly and the majority exceed that which MSAC has previously considered acceptable for reimbursement.

MSAC advised that no immediate changes were required to the current eligibility criteria, but considered there should be further research to determine the specific patient groups and best-practice use for Ig to achieve the greatest benefit.

## **Consumer summary**

The National Blood Authority (NBA) sought advice from MSAC on the government-funded supply of human antibodies (immunoglobulin, or Ig) that are used to improve immunity in people with blood cancers or after a stem cell transplant.

Our blood cells make antibodies to help fight infections. People who have cancer in their blood cells (such as leukaemia) or people who have had a stem cell transplant may not be able to make their own antibodies. Instead, they can have an injection of antibodies called Ig that is collected from donated plasma. This application was for people living with acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT). In 2015/16 approximately 4700 people accessed Ig therapy for acquired hypogammaglobulinaemia and this number is expected to increase to around 6500 people in 2019/20.

MSAC considered that Ig use is likely to be safe and effective in these people, but the research evidence base is limited and does not cover all the haematological (blood) malignancies eligible for Ig. Ig may be more effective in some patients than others, but more research needs to be done to check this. MSAC noted some uncertainties with the economic analysis in this application and assessed the cost was very high for the clinical benefit patients receive. Ig is very expensive – the review estimated that Ig will cost the government approximately \$100 million for this indication alone in the 2019-20 financial year. In 2018-19, a total of 6.57 million grams of Ig was supplied nationally for all indications, representing a total cost of \$613.0 million (including the cost of plasma for fractionation). This cost is increasing because more people are using Ig every year and long-term to treat a range of conditions. There is a worldwide shortage of Ig affecting the price and supply. MSAC acknowledged the need to ensure this high-cost and limited resource is targeted to the patients who will get the most health benefit.

### **MSAC's advice to the National Blood Authority**

MSAC advised that at the current price Ig is not cost-effective for all eligible patients under the criteria for acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT). MSAC considered that further research is required to do a full economic assessment of Ig use across the sub-groups of patients treated under this indication. This research should include analysis of Australian data on both the effectiveness and utilisation of Ig in specific patient conditions. MSAC also suggested the NBA consider aspects of eligibility criteria used in Europe and other countries, and further research be undertaken where necessary, to inform decision-making so Ig supply targets the people who will benefit the most.

## **3. Summary of consideration and rationale for MSAC's advice**

MSAC noted that the relevant conditions listed as eligible for treatment under the *Criteria for the clinical use of immunoglobulin in Australia* (version 3) for this indication are:

- acute leukaemia
- chronic lymphocytic leukaemia
- multiple myeloma
- non-Hodgkin lymphoma
- memory B cell deficiency secondary to HSCT.
- other haematological malignancies

Regarding safety, MSAC noted that Ig has inferior safety compared with no Ig due to infusion-related adverse events and a small risk of thromboembolic events. However, antibiotic-related adverse events were not captured, as these were not adequately described in the studies identified.

Regarding clinical effectiveness, comparative analysis favoured Ig treatment for serious and non-serious infections. One trial found that patients who received Ig had fewer days of hospitalisation per year, fewer days of antibiotic treatment per year, and increased quality of life, compared with patients who did not receive Ig. MSAC also noted the feedback from consumers that claimed superior effectiveness compared with no Ig in terms of reduced hospitalisations, reduced exposure to antibiotics, improved quality of life and improved participation in society. However, MSAC noted the limited evidence base, with most studies from the 1990s and not necessarily being reflective of the current Australian context (e.g. many studies used Ig for a short period of six months or less).

In regard to the economic analysis, MSAC noted the high and uncertain incremental cost-effectiveness ratio (ICER) in the base case of \$99,803 per quality-adjusted life year (QALY), based on a cost per gram of Ig of \$60.41. The economic model was highly sensitive to the inclusion of health states for bronchiectasis. The rationale for including bronchiectasis was the higher proportion of patients who develop this condition in the absence of Ig, who continue to have poorer quality of life and higher risk of infection throughout the modelled time horizon. MSAC noted that the aim of treatment would be to prevent bronchiectasis occurring in the first place. However, MSAC noted the lack of data on bronchiectasis incidence in patients with or without Ig. Sensitivity analysis (as requested by ESC) on reducing the probability of transition to bronchiectasis had substantial and non-proportional effects on the ICER (e.g. a 25% reduction in bronchiectasis transition probability led to an ICER of \$117,858; a 95% reduction in bronchiectasis transition probability led to an ICER of \$929,801). Removing bronchiectasis from the model increased the ICER to \$2.9 million per QALY. MSAC acknowledged that bronchiectasis is a clinically important end-point, but noted the lack of data to inform these transition probabilities.

MSAC considered one stakeholder's view that a single health state for 'infection' was inadequate. ESC had suggested that it was not possible to reasonably infer transition probabilities for serious versus non-serious infections from the available evidence in the literature. However, MSAC considered that splitting this health state into serious and non-serious infections could be explored.

The cost per gram of Ig was also a significant driver of the model. MSAC noted that the scope to influence the price of Ig is limited due to the current global shortage and current pricing arrangements.

An additional sensitivity analysis to extend the time horizon from 10 years in the base case, as requested by ESC, had the effect of reducing the ICER (\$65,957 for a time horizon of 15 years; and \$55,303 for 20 years). MSAC considered that due to the range of malignancies and the varying of age of the patients treated, accepting one time horizon for all eligible patients was not possible. In addition, there is likely to be significant variation in the length of time patients remain on treatment and the ongoing level of benefit achieved from Ig, given anticipated changes to the therapeutic options available.

MSAC noted several issues raised by a stakeholder including that disutility associated with intravenous infusion of antibiotics was not accounted for in the model, and that the disutility associated with intravenous Ig infusion was high compared with the disutility associated with

infection. MSAC noted that there is a broad need to consider appropriate population-level antibiotic stewardship in conjunction with any change in Ig usage in these conditions.

Regarding financial and budgetary impacts, MSAC noted that total Ig use comprises more than half of the budget for blood arrangements in Australia and has increased at a rate of 11% per year in recent years. Use of Ig is projected to increase further over the next 5 years, along with projected costs to government (totalling \$550.3 million over 5 years for this indication alone). However, the National Blood Authority (NBA) noted that, with the transition to Version 3 of the Criteria, the rate of growth has slowed as some patients suspend their Ig use to determine their native immunological status. MSAC acknowledged the need to ensure this high-cost and limited resource is targeted to the patients for whom it is most beneficial, based on robust health technology assessment. MSAC noted that the number of therapies available to treat haematological malignancies is increasing, which may also be a driver of increased Ig demand in Australia, and globally.

MSAC noted the pre-MSAC responses from the NBA and stakeholders. One stakeholder response provided a respecified economic model that included: separate states for serious and non-serious infections; a revised (lower) weighted average cost per gram of Ig; and a revised baseline infection rate (based on data from multiple studies, rather than a single small Australian study). The stakeholder also conducted a sensitivity analysis on bronchiectasis transition probabilities in the respecified model, which produced lower ICERs than those presented in the Contracted Assessment (CA). Other model inputs were also questioned and the MSAC agreed that many inputs to the economic model were uncertain; however, the direction of effect of these uncertainties on the ICER could be in either direction. MSAC also noted that the cost of Ig used in the CA was agreed by the Ig Reference Group at the commencement of the review process for consistency across CA's for all Ig Review indications. Acknowledging the cost of Ig quoted by the stakeholder (using 2019 prices) is lower than that used in the base case, MSAC noted the CA presented sensitivity analyses including a range of Ig prices and that this change alone did not reduce the ICER sufficiently.

MSAC noted an ongoing clinical trial by Monash University (ACTRN12616001723471) comparing the efficacy of prophylactic intravenous Ig with prophylactic antibiotics in patients with acquired hypogammaglobulinaemia secondary to haematological malignancies, which will help address the evidence void.

Overall, MSAC considered that Ig was not a cost-effective therapy to manage infections in all people with acquired hypogammaglobulinaemia secondary to haematological malignancies and HSCT, noting the small and incomplete evidence base, the high and uncertain ICER, and the large and expanding budget impact.

MSAC considered whether it would be feasible to explore the heterogeneity of patient groups to assess whether Ig is cost-effective in certain sub-groups. For example, for multiple myeloma, the single included study indicates that Ig is highly effective, but for non-Hodgkin lymphoma (the largest patient group), there are no studies on the effectiveness of Ig. MSAC considered there may be value in using data for individual groups rather than pooled data, and this would require additional research and modelling to identify those who are most likely to benefit. Furthermore, MSAC noted that within disease populations, there is heterogeneity of need for Ig, depending on the therapies a patient is receiving, or has received.

MSAC noted that this is the first assessment of many under the Ig Reviews, and that future assessments of Ig use are likely to have less data and lower-quality data to inform decisions. In addition, not all outcomes reported in other conditions will be measured in costs per QALY. MSAC noted the importance of developing clearly defined parameters in the model

to justify its advice to the NBA, and also developing criteria that inform cost-effectiveness that could be used across the Ig Reviews.

Other evidence to inform and improve the cost-effectiveness of Ig in the Australian context could include further analysis of Ig utilisation data on frequency and dose of Ig treatment (per condition), use of ideal versus actual body weight for dosing, and the length of time patients remain on Ig treatment. Accurate capture of antibiotic use across these patient groups would also be informing.

MSAC advised no immediate changes to the current eligibility criteria, but noted that some aspects of the criteria for Ig use in Europe could be considered. For example, patients should be appropriately immunised against vaccine-preventable diseases, where clinically feasible, and undergo a 3-month trial of antibiotics with monitoring before starting Ig therapy. Consideration should also be given to changing criteria for ongoing treatment such as more frequent assessment of immunological status, and objective response criteria to develop clear review and stopping rules to ensure efficient use of Ig in the patients who are continuing to benefit.

It was noted that the current model was constructed using the Version 2 criteria and is not configured to explore stopping rules. MSAC considered it would be beneficial to reconstruct the model to allow this, and to align the model with the Version 3 Criteria, given the reduction in growth of Ig use since implementation of the Version 3 Criteria (which include continuation rules).

MSAC considered that ongoing review of Ig use would be an appropriate research topic for the Medical Research Future Fund (MRFF), given the current high cost and uncertain effectiveness of Ig treatment. It was noted that any research questions for the MRFF would require careful scoping to ensure that the research answers could inform decisions about cost-effectiveness in a practical way. MSAC considered that the Ig Review Reference Group could progress this issue and scope potential research questions before consulting more widely with consumers and interest groups.

#### **4. Background**

All Australian Governments, through the Jurisdictional Blood Committee (JBC), have agreed to conduct robust Post-market Health Technology Assessments (HTAs) of immunoglobulin use (Ig Reviews) funded under the National Blood Arrangements to ensure government-funded immunoglobulin use is based on strong evidence of clinical 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 Review of Immunoglobulin use in Australia is supported by a bespoke reference group, which oversees and provides advice on evaluation of all immunoglobulin HTA review applications. The PICO Confirmations for the Pilot Ig Reviews have been considered by the Review 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). Application 1565 is the first report from the Pilot Ig Reviews to be progressed to MSAC.

## 5. Prerequisites to implementation of any funding advice

Human normal immunoglobulin is listed on the Australian Register of Therapeutic Goods (ARTG) for replacement IgG therapy in symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment. All IgG products registered on the ARTG, including the sponsor, route(s) of administration, and NBA funding status at the time of the application, are listed in Table 1.

**Table 1 IgG products registered on the ARTG**

Product	Sponsor	Route of Administration	NBA Funded*?
Intragam 10	CSL Behring	IV	Yes
Privigen 10%	CSL Behring	IV	Yes
Hizentra	CSL Behring	SC	Yes
Gamunex 10%	Grifols	IV and SC	No
Flebogamma 10%	Grifols	IV	Yes
Flebogamma 5%	Grifols	IV	Yes
<i>Intragam P</i>	<i>CSL Behring</i>	<i>IV</i>	<i>Yes**</i>
Evogam	CSL Behring	SC	No
Panzyga	Octapharma	IV	No
Hyqvia	Shire	SC	No
Intratect	Pfizer	IV	No
Intratect 5%	Pfizer	IV	No
Octagam	Octapharma	IV	No
Kiovig	Shire	IV and SC	No
Gammanorm	Octapharma	SC (and IM)	No
Cuvitru	Shire	SC	No
<i>CSL Normal Immunoglobulin VF</i>	<i>CSL Behring</i>	<i>IM</i>	<i>Out of scope</i>

\* Indicates that Ig is currently funded for the indication sought in this application. Tendering arrangements may change products funded in the future.

\*\*With the introduction of Intragam 10, Intragam P manufacturing ceased in 2017. Inventories of Intragam P were expected to be exhausted by between mid-March and mid-April 2017 and it is expected to be discontinued by the time this evaluation is completed. The Ig Review Reference Group has indicated it should be out of scope for this application.

IV – intravenous; SC – subcutaneous; IM – intramuscular

Source: Contracted Assessment, Table 10 (from the Therapeutic Goods Administration ([www.ebs.tga.gov.au](http://www.ebs.tga.gov.au)), accessed January 2019)

Abbreviations: ARTG = Australian register of Therapeutic Goods; IV = intravenous; NBA = National Blood Authority; SC = subcutaneous

## 6. Proposal for public funding

Ig replacement therapy, in this indication, is presently funded under the national blood supply arrangements as an “Established Therapeutic Role”, but cost-effectiveness of this use has not previously been established. The products currently funded as at the time of application through the NBA are shown in Table 2 (below).

**Table 2 Ig products funded for this indication (at July 2019)**

Product	Sponsor	Route of Admin.	Strength	NBA price
Intragam 10	CSL Behring	IV	2.5g/25mL	\$145.57
			10g/100mL	\$582.30
			20g/200mL	\$1,164.59
Privigen 10%	CSL Behring	IV	5g/50mL	\$225.00
			10g/100mL	\$450.00
			20g/200mL	\$900.00
			40g/400mL	\$1,800.00
Hizentra	CSL Behring	SC	1g/5mL	\$59.15
			2g/10mL	\$118.31
			4g/20mL	\$236.61
			10g/50mL	\$591.53
Flebogamma 5%	Grifols	IV	0.5g/10mL	\$22.50
			2.5g/50mL	\$112.50
			5g/100mL	\$225.00
			10g/200mL	\$450.00
			20g/400mL	\$900.00
Flebogamma 10%	Grifols	IV	5g/50mL	\$225.00
			10g/100mL	\$450.00
			20g/200mL	\$900.00
Evogam	CSL Behring	SC	16% 0.8g/5mL	\$46.58
			16%3.2g/20mL	\$186.33

**Abbreviations:** IV=intravenous; SC=subcutaneous

**Source:** Contracted Assessment, Table 11.

As noted above, clinical criteria for eligible patients to access subsidised IgG are specified by the NBA's Criteria. The Criteria are periodically updated, and the eligibility criteria may be refined according to recommendations of the relevant NBA working group and subsequent approval by the JBC.

According to the current Criteria (version 3), one of the indications covered is acquired hypogammaglobulinaemia secondary to the following specific conditions (or associated treatment):

- Acute leukaemia (AL)
- Chronic lymphocytic leukaemia (CLL)
- Multiple myeloma (MM)
- Non-Hodgkin lymphoma (NHL)
- Memory B cell deficiency secondary to HSCT.
- Other Haematological malignancy

[Diagnosis of haematological malignancies should be according to the criteria of the current World Health Organization (WHO) classification]

There are different baseline risks of infection (higher in AL and post-HSCT patients) and baseline risk of intensive care admission (greater for post-HSCT) among the above conditions. However, the way in which hypogammaglobulinaemia is diagnosed and treated (with or without access to Ig) is common across the patients in this indication.

The Criteria provide for Ig supply as follows:

- Patients with serum IgG less than 4g/L regardless of episodes of infection or antibiotic use.
- Patients with serum IgG greater than 4g/L, IF serum IgG is less than the lower limit of the age-related reference range, AND the patient has had either (1) at least one life-threatening infection in the last 12 months, or (2) two serious infections in the last six months requiring more than standard courses of antibiotics.  
[Serum IgG refers to values excluding paraprotein]

As advised by the Ig Review Reference Group, the literature search for the Contracted Assessment included a broad definition of the population not constrained by these criteria for access, but limited to the haematological malignancies above.

In order to qualify for supply of Ig, a diagnosis must be made by an immunologist, haematologist, paediatrician, general medicine physician or an oncologist. Management and review of the patient and prescribing of continuing treatment should also be undertaken by one of these specialists. Applications for Ig are made through the BloodSTAR online portal and assessed against the Criteria.

IVIg administration requires a hospital or clinic with IV infusion facilities. For access to SCIg, the patient must be being treated by a clinical specialist within a hospital based SCIg program. The patient/carer must be trained in the procedure by a qualified nurse or technician to deliver SCIg in an out of hospital setting.

## **7. Summary of public consultation feedback/consumer Issues**

Public consultation was undertaken on the Referral and draft Contracted Assessment, and sponsor companies had an additional opportunity to comment on the PICO and provide input to the Contracted Assessment.

Consumer groups agreed with the superior effectiveness of Ig versus no Ig. Claimed benefits to consumers include: reduced exposure to antibiotics and development of antibiotic resistance; less hospitalisations and reduced time in hospital; improved quality of life (QoL); reduced risk of graft-versus-host disease (GVHD) for HSCT patients; reduced risk of death; and mental health benefits. Consumers also claimed societal benefits from access to Ig including greater participation in education and/or work; greater participation in social and community activities; and reduced pressure/anxiety for family/carers. Consumer groups acknowledged the side effects of Ig treatment. Issues with access in rural and remote areas, and access to SCIg were noted.

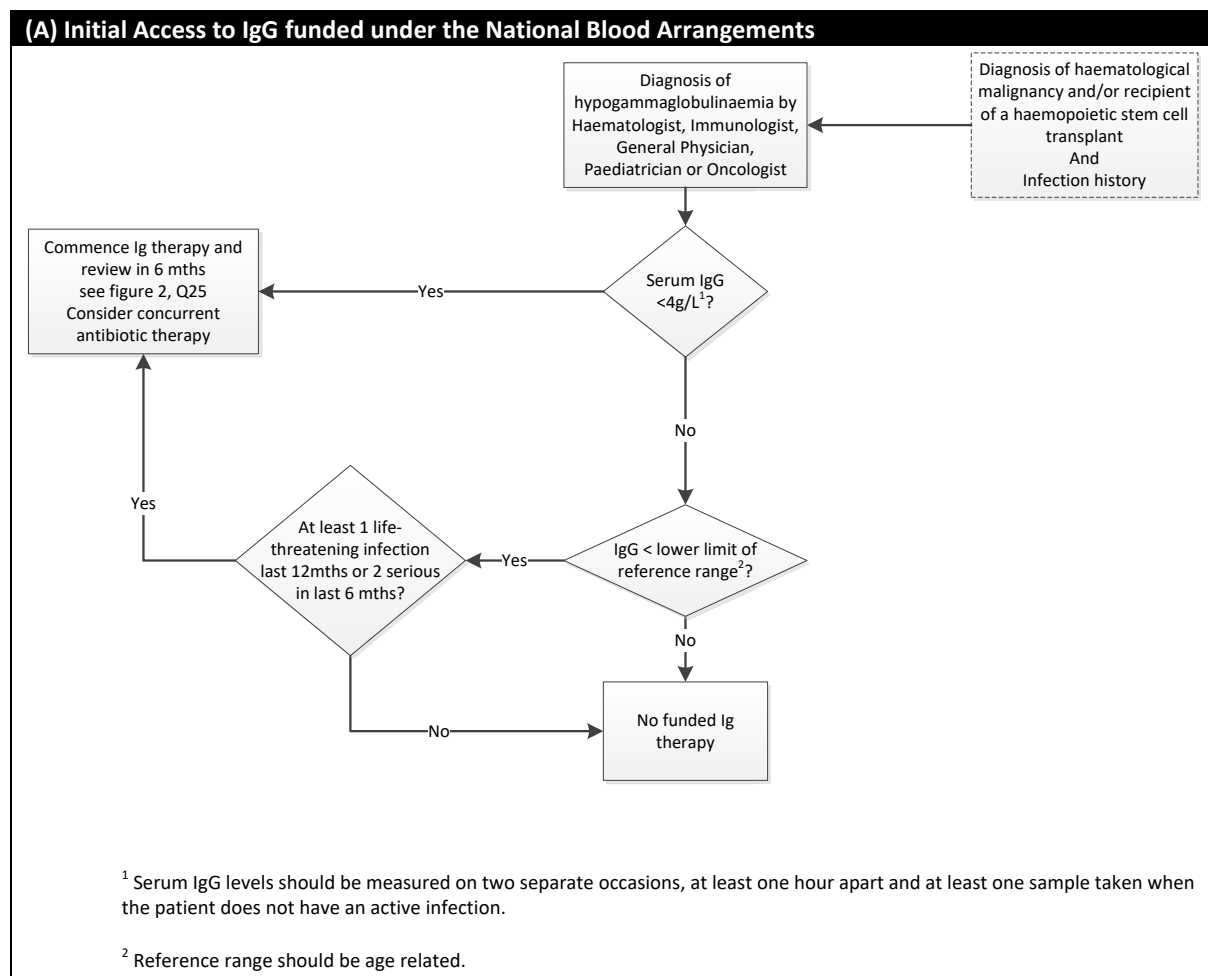
## **8. Proposed intervention's place in clinical management**

Ig replacement therapy is currently funded where no other current active intervention is available for patients in this indication. However, the standard of care includes use of antibiotics as required, which may include antibiotic prophylaxis, and utilisation of antibiotics was expected to be higher in the comparator arm ('No Ig access, with or without antibiotics'). The clinical management algorithm for patients with acquired hypogammaglobulinaemia secondary to haematological malignancy or post-HSCT is provided in Figure 1.

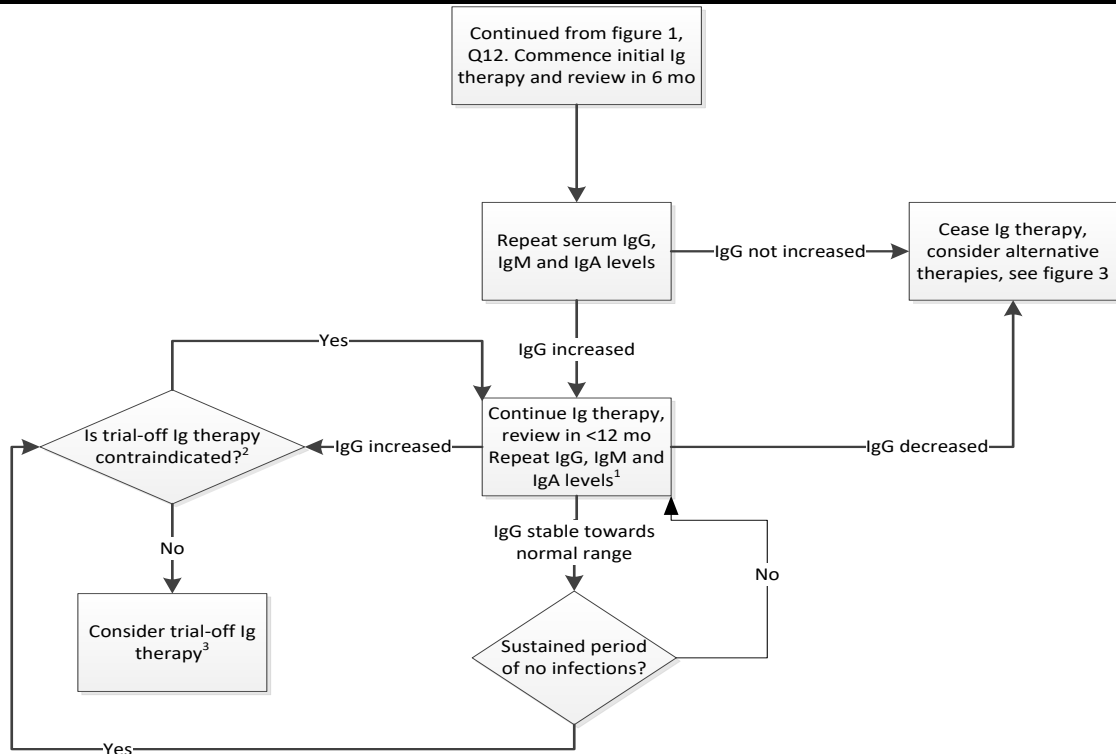
The Contracted Assessment of Ig for acquired hypogammaglobulinaemia addresses all of the PICO elements that were pre-specified in the PICO Confirmation ratified by the Ig Review



Reference Group. However, there was limited clinical evidence available to inform the assessment.



**(B) Monitoring response to IgG therapy**

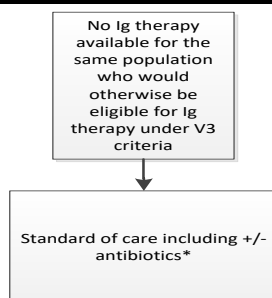


<sup>1</sup> If serum IgM and IgA levels are trending upwards and near normal, IgG is also likely to be normal, this may suggest recovery of the immune system and a trial-off Ig therapy might be considered.

<sup>2</sup> 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.

<sup>3</sup> 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.

**(C) Treatment pathway when IgG is not an option**



**Figure 1 Clinical management algorithm for patients with acquired hypogammaglobulinaemia secondary to haematological malignancy or post-HSCT**

Source: Contracted Assessment Figure 1

## 9. Comparator

The proposed comparator is: No Ig, with or without antibiotics. The comparator is consistent with the PICO Confirmation ratified by the Immunoglobulin Review Reference Group.

## 10. Comparative safety

The studies included in the assessment of safety were: six randomised trials; one cohort study; seven non-comparative case series; one dosing study; and one registry study investigating the risk of thromboembolic events (TEEs) associated with Ig administration during 12 months of follow-up.

Safety data were limited to reports of systemic adverse events (AEs) directly related to the infusion, with the exception of the registry study reporting TEE risk. Otherwise, it was not feasible to consider long term, rare or potentially unknown events. Only two randomised trials reported AEs for both Ig and No Ig (sham injection) arms. One randomised trial did not report AEs associated with Ig, but reported liver AEs due to concurrent antibiotic use.

Overall, the included studies support that Ig has inferior safety to No Ig, due to infusion-related AEs and a small risk of TEEs. It should be noted that safety was assessed in relation to unintended AEs, and the benefits and risks due to infections were considered as part of effectiveness. The included studies did not adequately describe antibiotic use, thus AEs arising from antibiotic use could not be evaluated as specified in the PICO.

AEs associated with Ig infusion were frequent, but generally mild (low grade) and were manageable with adjustments to infusion. Moderate AEs tended to be less frequent and were manageable with dose adjustment, cessation or corticosteroids. None of the included studies reported any AEs greater than Grade 3 severity, nor were there any deaths or anaphylaxis due to Ig. Two randomised trials employed a sham injection of solution such as albumin or saline, which was also associated with infusion-related AEs, but at a lower rate than Ig.

The most common AEs associated with IVIg infusion are chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate lower back pain. Serious AEs such as thromboembolic reactions, myocardial infarctions, stroke, pulmonary embolisms, or deep vein thrombosis are very rare.

## 11. Comparative effectiveness

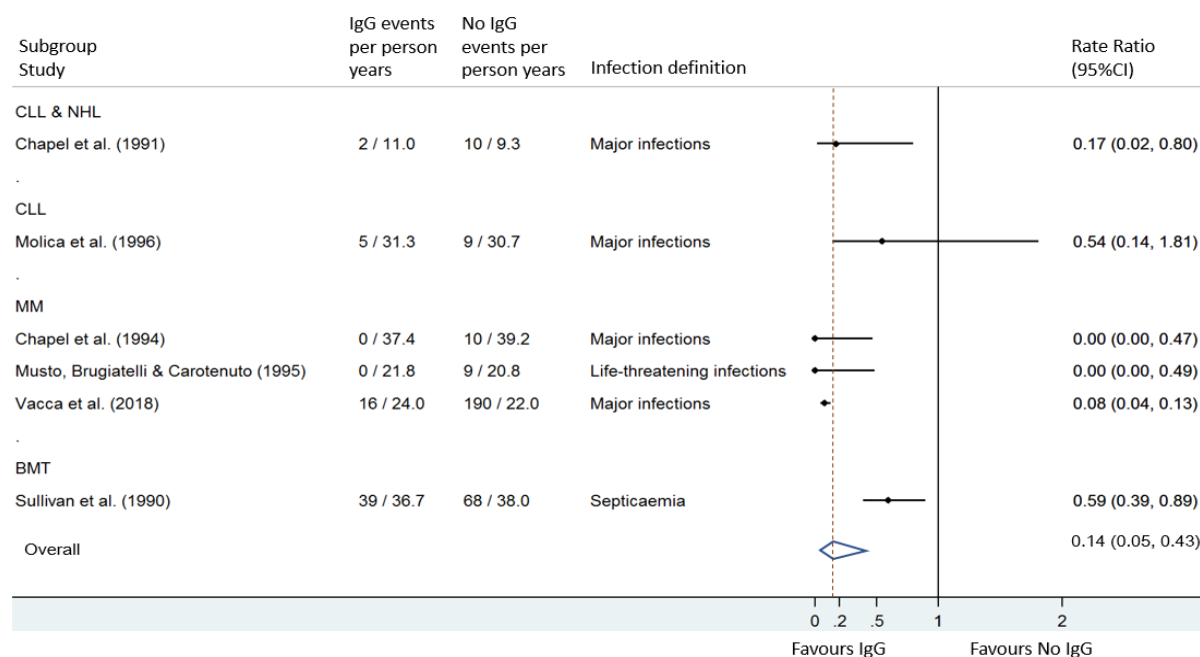
The studies included in the assessment of effectiveness were:

- eight randomised trials (seven with IVIg and one with SCIg)
- four non-randomised cohort studies of IVIg versus no IVIg
- nine case series before and after Ig treatment (four of IVIg, one of SCIg, and four of IVIg and SCIg)
- two dosing studies
- two case series of IVIg versus SCIg.

There is reasonable evidence that Ig is effective at reducing the incidence of infections, despite the highly variable quality of the included studies. The randomised trial evidence showed that the rate of major infections/life-threatening infections/septicaemia was significantly lower in patients with acquired hypogammaglobulinaemia, who received IVIg (k=5), or SCIg (k=1) than those who did not receive Ig (incident rate ratio/IRR=0.14, 95% CI 0.05, 0.43). Those receiving Ig only had one seventh the incidence of serious infections that those being managed without Ig had over the same time period, which is highly clinically

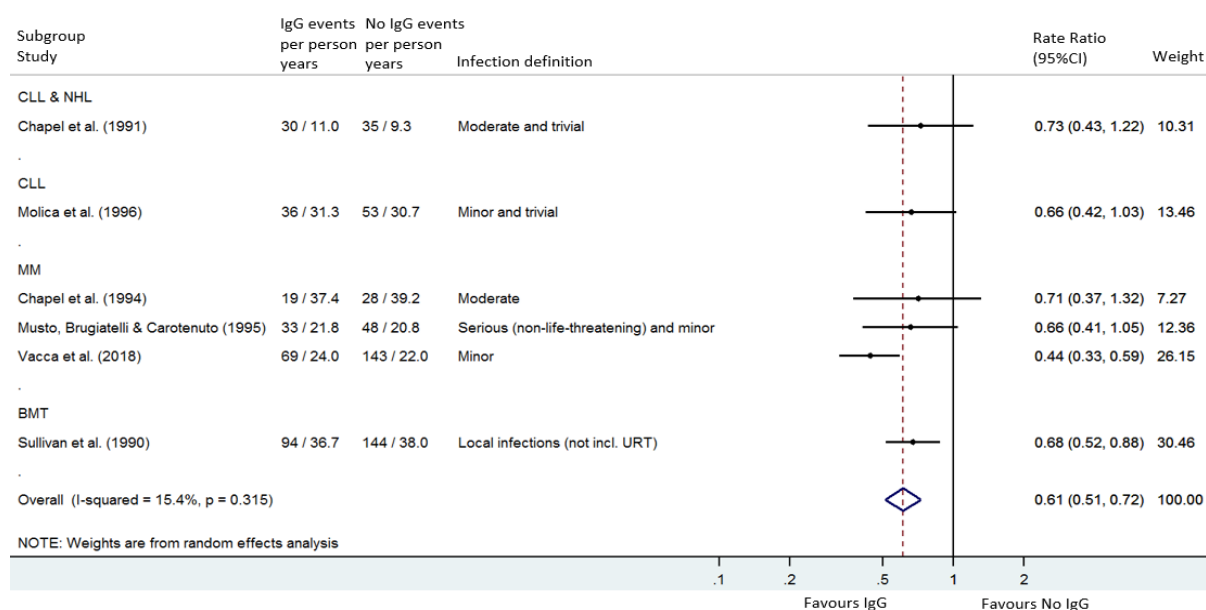
important. The difference in non-serious infections was less marked, but still significant ( $k=6$ ; IRR=0.61, 95% CI 0.51, 0.72). The results from the meta-analyses of the randomised studies are presented as forest plots for serious infections (Figure 2) and for non-serious infections reported in the same studies, where available (Figure 3).

Nine before and after case series compared the rate of infections within patients prior to receiving Ig, and while receiving Ig. The incidence of serious infections/sepsis or pneumonia or infections requiring hospitalisation was only a quarter of the incidence recorded prior to Ig initiation (IRR=0.25, 95% CI 0.15, 0.43). Similar to the randomised trials, the incidence of non-serious infections was also significantly reduced by the use of Ig (IRR=0.64, 95% CI 0.49, 0.84). The limitations of the evidence mean that the risk ratios reported in these meta-analyses are highly uncertain.



**Figure 2 Randomised trials presenting serious infections – Ig vs No Ig groups**

Source: Contracted Assessment, Figure 3



**Figure 3 Randomised trials presenting other infections – Ig vs No Ig groups**

Source: Contracted Assessment, Figure 4

One randomised trial compared transplant-related outcomes in patients who had undergone HSCT, with or without IVIg. In those who received allografts, the rate of GVHD and interstitial pneumonia was significantly less in those who received IVIg than those who did not receive IVIg.

IVIg did not appear to influence overall survival in a single trial and three observational studies identified. However, in the subgroup of patients randomised to IVIg, who were over 20 years old, and had HLA-identical bone marrow transplantation, the cumulative incidence of non-relapse mortality was significantly higher in those who did not receive IVIg (46%) than those who did (30%;  $p=0.023$ ).

One trial randomised MM patients with hypogammaglobulinaemia to receive SCIg or no SCIg. Quality of life on the SF-36 was significantly higher in those receiving SCIg for the domains of general health, physical functioning, role-physical, vitality, social functioning, role-emotional and mental health, but not pain. Patients who received SCIg had far fewer days of antibiotic use (28 vs 217) and hospitalisation (8 vs 121) than those who did not receive SCIg. These differences were considered both statistically significant and clinically important.

Cohort studies were subject to selection bias, i.e. the patients with the highest risk of infections were most likely to receive IgG and hence comparative data from these studies was considered of limited value.

### **Clinical claim**

On the basis of the benefits and harms reported in the evidence base the Contracted Assessment suggests that the use of Ig products with antibiotics as required has superior effectiveness relative to No Ig replacement with antibiotics as required.

## **12. Economic evaluation**

The economic model presented is a cost-utility analysis, where Ig therapy is associated with a reduction in infection rates, but that is traded off against a reduced safety profile (Table 3). One economic analysis was presented across the acquired hypogammaglobulinaemia indications.

**Table 3 Summary of the economic evaluation**

<b>Perspective</b>	Australian healthcare
<b>Comparator</b>	No Ig
<b>Type of economic evaluation</b>	Cost-utility and cost-effectiveness analyses
<b>Sources of evidence</b>	Systematic review
<b>Time horizon</b>	10 years
<b>Outcomes</b>	QALYs Infections avoided
<b>Methods used to generate results</b>	Markov model
<b>Health states</b>	Infection-free Infection Bronchiectasis Bronchiectasis, with infection Bronchiectasis, with chronic <i>Pseudomonas aeruginosa</i> infection Dead
<b>Cycle length</b>	1 week
<b>Discount rate</b>	5%
<b>Software packages used</b>	Microsoft Excel and TreeAge Pro

Abbreviations: Ig = immunoglobulin; QALY = quality-adjusted life year.

Source: Contracted Assessment, Table 6

The results of the stepped economic analysis are presented in Table 4. In Step 1 of the analysis the ICER of Ig is observed to be dominated, with a net reduction in QALYs resulting from the inclusion of a disutility per IVIg infusion. In Step 2, the time horizon is extrapolated to 10 years and allows for the development of bronchiectasis which leads to a substantial improvement in the ICER. Further improvements in the ICER are observed when the best estimates of baseline infection rates, Ig treatment effect and dose are included in the modelling.

In the base case analysis, the cost of Ig was the main driver of the incremental cost, with offsets related to a reduction in the number of infections and costs associated with managing chronic *P. aeruginosa* infections. Incremental QALYs were primarily accrued in the infection-free health state. As Ig was associated with fewer infections of lower severity, less time was spent in the infection health state with Ig and therefore, patients had a lower risk of progressing to subsequent health states.

**Table 4 Results of the stepped economic analysis**

	<b>Inc. cost</b>	<b>Inc. QALYs</b>	<b>ICER</b>
<b>Step 1 – Trial-based analysis.</b> Applies the dose (0.4 g/kg), dose frequency (q4w), infection rates, time horizon (1 year) and Ig treatment duration (1 year) as per the Chapel et al. (1994b) study. This study was chosen on the basis that, of the randomised studies, this study had the most patient years of data and used a dose that was most consistent with those recommended in the Version 3 criteria.	\$22,734	-0.0035	Dominated
<b>Step 2 – Trial-based, extrapolated analysis</b> Applies the dose, dose frequency and infection rates from the Chapel et al. (1994b) study, with the model time horizon extrapolated to 10 years, with the development of bronchiectasis to be modelled. Ig treatment duration is based on Paxton, Hawkins & Crispin (2016) (26 months).	\$66,922	0.2556	\$261,789
<b>Step 3 – Modelled economic evaluation (base case)</b> Applies the pooled IRRs estimated in Section B.6 to the best available source of baseline infection rates in Australia (based on Paxton, Hawkins & Crispin 2016), while assuming the weighted average dose from BloodSTAR data (0.37 g/kg).	<b>\$41,011</b>	<b>0.4109</b>	<b>\$99,803</b>
<b>Sensitivity analyses for the cost per gram of Ig (base case: \$60.41)</b>			
High cost of Ig, \$140.18	\$117,335	0.4109	\$285,543
Low cost of Ig, \$44.94	\$26,209	0.4109	\$63,782
Weighted average cost of Ig, \$94.51	\$73,634	0.4109	\$179,195

**Abbreviations:** ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; QALY = quality-adjusted life years; IRR = incidence rate ratio.

**Source:** Contracted Assessment, Table 7

The model is highly sensitive to the inclusion of the bronchiectasis health states (their removal increases the ICER to just under \$3 million), selection of the time horizon, the relative treatment effect of Ig, and baseline rates of infection (Table 5).

**Table 5 Key sensitivity analyses**

	Inc. cost	Inc. QALYs	ICER	% change
<b>Base case analysis</b>	<b>\$41,011</b>	<b>0.4109</b>	<b>\$99,803</b>	<b>-</b>
Baseline annual infection rates (base case: Paxton, Hawkins & Crispin 2016, serious 0.43, non-serious 1.05)				
Molica et al. (1996): serious 0.29, non-serious 1.73	\$50,160	0.3819	\$131,328	32%
Chapel et al. (1994): serious 0.26, non-serious 1.75	\$51,346	0.3653	\$140,555	41%
Sullivan et al. (1990): serious 1.79, non-serious 3.79	\$48,062	0.7121	\$67,493	-32%
IRR of Ig treatment effect (base case: serious, 0.15; non-serious 0.61)				
Serious infections, 0.43	\$52,526	0.3139	\$167,315	68%
Non-serious infections, 0.72	\$46,236	0.3523	\$131,233	31%
Duration of Ig treatment (base case: 2.2 years)				
5 years	\$84,261	0.5430	\$155,168	55%
10 years	\$125,097	0.5457	\$229,233	130%
Exclude development of bronchiectasis	\$41,213	0.0141	\$2,927,525	2833%
Time horizon (base case: 10 years)				
2.2 years (as per Ig treatment duration)	\$38,869	0.0322	\$1,208,343	1111%
5 years	\$39,552	0.1509	\$262,086	163%
Transition probabilities (base case: adjusted)				
Transitions from infection health state, unadjusted	\$45,309	0.3087	\$146,792	47%
Transitions from infection and bronchiectasis, unadjusted	\$29,927	0.2335	\$128,154	28%
Cost of hospitalisation of serious infections (base case: \$12,775)				
\$52,961, based on AR-DRG R01A	\$19,349	0.4109	\$47,088	-53%

**Abbreviations:** ICER = incremental cost-effectiveness ratio; Ig = immunoglobulin; IRR = incidence rate ratio; QALY = quality-adjusted life year.

Source: Contracted Assessment, Table 8

### 13. Financial/budgetary impacts

A market-based approach has been used to estimate the financial implications of Ig in acquired hypogammaglobulinaemia, based on current utilisation of Ig products in this patient population. As data available on utilisation were only available for use under the Version 2 Criteria, the impact of transitioning to the Version 3 Criteria and recent demand management strategies were not able to be captured in the analysis. There is uncertainty as to whether trends observed in the past would continue to be observed.

It is also acknowledged that rapid technological development is occurring in this therapeutic area and this may also change clinical demand and Ig use in the future. For example, demand may increase if patients using new therapies (such as monoclonal antibodies, chimeric antigen receptor (CAR) T-cell therapy and Bruton's tyrosine kinase (BTK) inhibitors) live longer with suppressed immune systems.

Patient numbers and Ig use were projected using linear extrapolations fitted to the observed data for patient numbers and grams of Ig used per year between 2011-2012 and 2017-2018. The base case financial estimates assume a constant cost per gram of Ig of \$60.41 over the projected period. The average number of treatment episodes per year was derived from NBA data and used to estimate the additional cost associated with Ig administration.



Cost offsets due to a reduction in the number of infections with Ig therapy were included in the financial estimates. Serious infection is associated with one hospitalisation (assumed to be attributable to State budgets) and one follow-up outpatient attendance (attributable to the Commonwealth), while non-serious infections were associated with outpatient attendance(s), and depending on the severity of infection, oral antibiotics and pathology and imaging tests (all assumed to be attributable to the Commonwealth). ESC noted that the inclusion of indirect cost-offsets based on a relative treatment effect of Ig in reducing the incidence of infections in the financial estimates is associated with uncertainty.

The financial implications associated with funding Ig for acquired hypogammaglobulinaemia are summarised in Table 6.

**Table 6 Net financial implications to government associated with Ig for acquired hypogammaglobulinaemia**

	2019-20	2020-21	2021-22	2022-23	2023-24
Total number of patients	6,488	6,894	7,301	7,707	8,114
Total number of Ig grams issued	1,624,506	1,748,903	1,873,301	1,997,698	2,122,096
Total cost of Ig	\$98,136,389	\$105,651,248	\$113,166,107	\$120,680,966	\$128,195,825
Cost of Ig to the Commonwealth	\$61,825,925	\$66,560,286	\$71,294,647	\$76,029,008	\$80,763,370
Cost of Ig to the States	\$36,310,464	\$39,090,962	\$41,871,460	\$44,651,957	\$47,432,455
Cost of Ig administration to the States	\$15,427,172	\$16,394,813	\$17,362,453	\$18,330,093	\$19,297,734
Total cost offsets due to a reduction in the number of infections	-\$18,180,716	-\$19,320,253	-\$20,459,790	-\$21,599,328	-\$22,738,865
Offsets to the Commonwealth	-\$671,936	-\$714,051	-\$756,167	-\$798,283	-\$840,399
Offsets to the States	-\$17,508,780	-\$18,606,202	-\$19,703,623	-\$20,801,045	-\$21,898,466
<b>Net cost</b>	<b>\$95,382,845</b>	<b>\$102,725,807</b>	<b>\$110,068,769</b>	<b>\$117,411,732</b>	<b>\$124,754,694</b>
Net cost to the Commonwealth	\$61,153,989	\$65,846,235	\$70,538,480	\$75,230,725	\$79,922,971
Net cost to States	\$34,228,856	\$36,879,572	\$39,530,289	\$42,181,006	\$44,831,723
Sensitivity analyses for the cost per gram of Ig (base case: \$60.41)					
High cost of Ig \$140.18	\$224,969,664	\$242,235,823	\$259,501,981	\$276,768,140	\$294,034,299
Low cost of Ig, \$44.94	\$70,251,742	\$75,670,273	\$81,088,805	\$86,507,336	\$91,925,867
Weighted average cost of Ig, \$94.51	\$150,773,057	\$162,357,562	\$173,942,066	\$185,526,570	\$197,111,075

**Abbreviations:** Ig = immunoglobulin.

**Source:** Contracted Assessment, Tables 9 and 69.

**Note:** Financial estimates are based on the price of Ig provided by the Applicant that was estimated retrospectively based on costs over 2017/18. Prices may change in the future.

## 14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
High and uncertain ICER which is very sensitive to the inclusion of the bronchiectasis health states	Provide a rationale for the large impact of bronchiectasis health states and factors driving this (Addendum p.1). Add a sensitivity analysis with low, but non-zero, transition probabilities to the bronchiectasis health states (p.1).
Poor reporting of antibiotic use	It was not possible to evaluate the claim that Ig with or without antibiotics is superior to No Ig with or without antibiotics due to poor reporting of antibiotic use. The clinical evidence in the included studies support a claim of superior efficacy, but inferior safety for Ig compared to no Ig (with antibiotic use defined as part of supportive care).
Lack of evidence for some haematological malignancies eligible for Ig	Trials were reported for patients with chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and those who underwent HSCT. No adequate randomised trials were identified in patients with acute leukaemia (AL), non-Hodgkin lymphoma (NHL), or 'other haematological malignancies'. However, it was considered plausible that similar outcomes would be observed in AL, NHL and 'other' haematological malignancies, assuming the patients satisfied the criteria for hypogammaglobulinaemia and history of infections.
Methodological heterogeneity between trials in dosing, frequency, criteria for discontinuation, and assessment of treatment response	<p>This evaluation could not address:</p> <ul style="list-style-type: none"> <li>• Confirmation of a clinically active Ig dose or frequency of dosing from the trials. Most studies included explored Ig doses between 200 and 500 mg/kg given every 3-4 weeks.</li> <li>• A single definition of adequate treatment response: a reduction in incidence or infection rate was usually taken as evidence of a response. Timeframes for assessment were highly variable.</li> <li>• Criteria for discontinuation. An initial patient response in terms of infections seemed to be adequate reason for ongoing Ig replacement, which often lasted for some months or years.</li> <li>• Frequency of serum IgG monitoring as a basis for response assessment or a decision to discontinue.</li> </ul>
Policy question on the maximum price at which Ig is cost-effective in this population	One of the sensitivity analyses in the Contracted Assessment for the 'low cost of Ig' of \$44.94/gram produces an ICER of \$63,782/QALY. The impact of global supply issues and increasing demand for Ig on prices for Ig was acknowledged by ESC .
Very large financial implications coupled with large uncertain ICERs	There is underlying uncertainty associated with the estimates of Ig treatment effectiveness in reducing the incidence of infections, the use of these estimates in the economic model and uncertain indirect cost offsets.

## ESC discussion

Application 1565 requests MSAC advice on the supply of replacement human gamma immunoglobulin (Ig) therapy under the national blood arrangements for the treatment of acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation (HSCT).

ESC noted that the main purpose of treatment is to reduce the risk of infection, and that Ig replacement therapy with antibiotics as necessary is considered the standard of care, with no Ig therapy the comparator. The Contracted Assessment stated that antibiotic use was expected to be higher in the comparator arm and reports trimethoprim/sulfamethoxazole as the relevant first line antibiotic. The ESC noted that this was based on the advice of the Ig Review Reference Group, but considered that this antibiotic combination was generally used for prophylaxis, which was uncommon in this population, and that antibiotics used in the treatment of acute infections would vary according to the clinical presentation. Common oral antibiotics would include amoxicillin with clavulanic acid. However, this was considered unlikely to effect the economic evaluation as the relevant antibiotics are predominantly off-patent and of low cost.

The clinical criteria for subsidised access to Ig for acquired hypogammaglobulinaemia is set out under version 3 of the *Criteria for the clinical use of immunoglobulin in Australia*<sup>1</sup> (the Criteria). ESC noted that there was little evidence to support the requirement for serum IgG levels to be less than 4 g/L, but there was also no evidence to support a different serum IgG requirement.

ESC noted that the Contracted Assessment included 24 studies in the assessment of effectiveness, but the majority were case series. Six randomised studies and five observational studies reported fewer infections with Ig compared to no Ig. One trial of subcutaneous Ig (SCIg) reported improved quality of life compared to no SCIg. No studies demonstrated a survival advantage with Ig.

ESC noted that despite the relatively few studies and low level of evidence, there were consistent findings that the rate of serious infections and infectious complications was reduced in patients who received Ig compared to those who did not. The majority of these studies were in patients with CLL or MM, but ESC noted that the evidence review does not suggest that response to Ig replacement therapy is any more variable in patients with other haematological malignancies. ESC considered that the evidence supported the claim of superior effectiveness in terms of fewer overall infections and serious infections for Ig compared to no Ig (with antibiotic use defined as part of supportive care) in patients with acquired hypogammaglobulinaemia secondary to haematological malignancy or post-HSCT.

ESC noted that the evidence identified in the Contracted Assessment supported that Ig has inferior safety to no Ig. Assessment of safety was often limited to reporting of systemic AEs related to infusion. The comparator was frequent observation and thus had superior safety. The included studies did not adequately describe antibiotic use, so AEs arising from antibiotic use could not be evaluated. The majority of AEs associated with Ig were mild and manageable with adjustment to infusion rate. None of the studies reported AEs greater than grade 3 in severity. ESC noted that the safety profile of Ig products is well understood due to use over many decades, and that safety data within the product information provides a comprehensive assessment of safety.

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<sup>1</sup> National Blood Authority, 2018, [Criteria for the clinical use of immunoglobulin in Australia](#) (version 3).

ESC noted stakeholder comments that disagreed with the claim of inferior safety for Ig compared to no Ig, on the basis that antibiotic use is likely to be higher in the comparator arm and is associated with side effects that could not be evaluated due to the lack of available evidence. The ESC considered that a claim of non-inferior safety for Ig compared to no Ig (with antibiotic use defined as part of supportive care) may also be appropriate in patients with acquired hypogammaglobulinaemia secondary to haematological malignancy or post-HSCT.

The economic model provided in the Contracted Assessment is a cost-utility analysis and cost-effectiveness analysis using a Markov model, with one economic analysis presented across the acquired hypogammaglobulinaemia indications, which ESC considered appropriate. ESC noted that there is uncertainty regarding the estimates of Ig treatment effectiveness and as such, the use of these estimates in the economic model is also associated with uncertainty.

ESC noted that the modelled economic evaluation base case resulted in an incremental cost-effectiveness ratio (ICER) of \$99,803 per quality-adjusted life year (QALY), using a 10-year time horizon and cost per gram of IgG of \$60.41. ESC noted that the cost of Ig was a key driver of the economic model with the ICER ranging from \$63,782 to \$285,543 per QALY, based on 'low cost of Ig' (\$44.94) to 'high cost of Ig' (\$140.18), respectively. The largest driver of the economic model was inclusion of the bronchiectasis health states. Other key drivers of the economic model were the time horizon, the relative treatment effect of Ig, and baseline rates of infection. The disutility associated with infection and infusion were not major drivers of the economic model.

ESC noted that there was no clear data on the incidence of bronchiectasis in patients with or without access to Ig to support the transition probabilities to the bronchiectasis health states in the economic model, and that the removal of these health states increased the ICER to approximately \$3 million per QALY. Therefore, ESC recommended an additional sensitivity analysis be conducted with a lower transition probability of patients entering the bronchiectasis health states. ESC also requested further explanation of the rationale for the inclusion of the bronchiectasis health states and the impact of their inclusion or exclusion on the ICER (See Addendum p.1).

There was no evidence identified during the review on which to determine the duration of immunoglobulin treatment effect, nor time to return of normal Ig levels (and whether this differed with or without Ig treatment). The model assumed that for the duration of treatment, patients received a benefit and that when treatment was stopped, patients had returned to normal Ig levels (if they had not developed bronchiectasis in the meantime). The time to return to normal IgG levels was assumed to be the same with or without Ig.

ESC noted that some patients with acquired hypogammaglobulinaemia secondary to haematological malignancy or post-HSCT may receive treatment with Ig beyond ten years, and therefore it may be appropriate for the Contracted Assessment to include a sensitivity analysis extending the time horizon (See Addendum p.2). It was noted that there is increasing survival of paediatric patients with leukaemia who may require long-term Ig replacement therapy, and that this was likely to be a driver of future use.

In response to stakeholder comments on the appropriateness of the unit price of Ig used for the base case analysis in the Contracted Assessment Review, ESC noted that the unit prices for Ig to be used across all of the Immunoglobulin Reviews were agreed by the Ig Review Reference Group to allow comparison across applications. In addition, a range of unit prices for Ig are presented in sensitivity analyses (Addendum p.2).

ESC noted that one stakeholder recommended the use of a higher cost Australian refined diagnosis-related group (AR-DRG) for the bronchiectasis health state. ESC noted that the cost to treat infections was based on the weighted average cost of relevant AR-DRGs identified by the Ig Review Reference Group. ESC noted that sensitivity analyses were presented in the Contracted Assessment for the cost of each AR-DRG separately, and that the range of costs tested in these sensitivity analyses includes the cost associated with the AR-DRG suggested by the stakeholder.

ESC noted that one stakeholder queried the use of a single 'infection' health state in the economic model, rather than having separate states for non-serious and serious infections. ESC considered that the current model structure was appropriate, as transition probabilities from the infection health state could not be identified from the literature by infection severity.

ESC noted that one stakeholder queried the baseline infection rates used in the economic model. However, ESC considered the rates used in the model appropriate as these were from a contemporary Australian study, which was considered to be most applicable to the population that receives Ig for acquired hypogammaglobulinaemia in Australia.

ESC noted that the net financial costs were estimated to be \$550.3 million over the five years from 2019-20 to 2023-24, with 63% of the cost being borne by the Commonwealth and the remainder by the states and territories. ESC considered that the market-based approach used to estimate the budget impact was appropriate, and noted that the estimates were based on utilisation data for version 2 of the Criteria. This adds uncertainty as the impact of recent demand management strategies through the introduction of the version 3 Criteria was not captured. ESC also noted that the financial estimates include indirect cost-offsets based on a relative treatment effect of Ig in reducing the incidence of infections, which is associated with uncertainty.

In direct response to the policy question posed in the pre-ESC policy document regarding the price at which Ig would be cost-effective, ESC suggested that the Contracted Assessment include a threshold analysis to indicate the cost per gram of Ig associated with a range of ICERs for the base case (see CA Addendum p.2). However, it was noted that global supply issues for Ig, combined with increasing demand for the product, are likely to have an impact on product prices. In addition, the Contracted Assessment presents a range of ICERs according to the highest and lowest and average weighted cost of Ig products currently subsidised in Australia.

ESC noted that although there was no evidence to quantify the extent Ig reduces antibiotic resistance, that there were likely to be broader health system benefits associated with the use of Ig to prevent infections and that this benefit is not captured in the evaluation.

ESC noted general support for access to Ig from a range of groups, including clinical and consumer groups. Issues with equity of access due to partial state funding were noted, as well as the substantial out-of-pocket costs for consumers associated with travel to access Ig replacement therapy.

ESC recommended that MSAC consider whether dispensing approval be reduced to 3-months in length during the first 24 months to trigger more frequent reviews of the appropriateness of continued Ig replacement therapy. Patients, who demonstrate improvement in IgM and IgA levels, could trial a treatment break. This may assist in earlier identification of patients who have recovered native IgG levels and reduce potential wastage. It was noted that after two years, patients who have not recovered native IgG levels are more likely to require long-term use. It was considered that it may be possible to mandate tighter

review requirements in the BloodSTAR system, and to provide additional education on checking for immune system reconstitution and evidence requirements for this. ESC also noted that a requirement to measure IgG levels post replacement therapy could also be added to ensure that treatment results in improved IgG levels.

ESC considered that there was a need for additional data collection on: dose, dosing frequency, antibiotic use (which could be taken from Pharmaceutical Benefits Scheme (PBS) data), rates/types of infections, and health-related quality of life. It was also considered that additional data on patients with NHL would also be useful, as there is very little published evidence for this patient population, which represent a large proportion of use for this indication. ESC also considered that further research into the criteria for continuation/discontinuation of Ig and use of Ig in paediatric cancers would be useful.

ESC noted that there are many novel therapies emerging in haematological malignancies that may affect IgG levels post treatment. It was suggested that relevant clinical trials should be required to monitor long-term IgG levels in order to inform regulatory and reimbursement decisions, and that real-world monitoring data may be able to be used to identify immunosuppressive therapies that place patients at risk of hypogammaglobulinaemia.

### **Addendum**

At its October 2019 meeting, ESC requested the following additional sensitivity analyses:

- Reducing the bronchiectasis transition probabilities from the base case by 25% up to 95%, which resulted in ICERs ranging from \$117,858/QALY to \$929,801/QALY.
- Extending the time horizon of the economic model from 10 years to 15 years or 20 years, which resulted in ICERs of \$65,957/QALY and \$55,303/QALY, respectively.

### **15. Other significant factors**

Nil

### **16. Applicant's comments on MSAC's Public Summary Document**

The National Blood Authority appreciates MSAC's recommendations and agrees that further research is required to differentiate between the specific conditions causing acquired hypogammaglobulinaemia and the benefits and cost effectiveness of Ig therapy for each condition. This review has occurred immediately following the transition from Version 2 to Version 3 of the Criteria for Immunoglobulin Use in Australia. An important addition to Version 3 of the Criteria was to include, where appropriate, review criteria ensuring a clinical response is achieved in order to continue to receive Ig therapy, and greater guidance for prescribers as to when a patient may be ready to trial off Ig therapy. The effect of changes to the Criteria are only now being seen in the data, with a material reduction in the rate of growth of Ig use now becoming apparent. 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, which these recommendations will assist to prioritise.

### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)