

# REVIEW OF THE USE AND SUPPLY OF INTRAVENOUS IMMUNOGLOBULINS IN AUSTRALIA.

A report by  
the  
Blood and Blood Products  
Committee

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Executive Officer  
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C/- Department of Human Services, Victoria  
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# REPORT ON THE USE AND SUPPLY OF INTRAVENOUS IMMUNOGLOBULINS IN AUSTRALIA

## STATEMENT FROM THE AUSTRALIAN HEALTH MINISTERS' ADVISORY COUNCIL - BLOOD AND BLOOD PRODUCTS COMMITTEE

The Australian Health Ministers' Advisory Council (AHMAC) has considered the final Report of the Working Party and has agreed to accept the report with qualification as outlined below.

AHMAC accepts the Report and the recommendations relating to:

- The new categorisation model for the uses of IVIG;
- The distribution of IVIG on a national basis;
- The monitoring of the use of IVIG by the ARCBS; and
- The national review of the use of IMIG.

AHMAC also endorse the target levels of:

- 810 kg per annum of IVIG for category 1 indications, ie, where there is now convincing evidence of [clinical] benefit;
- 90 kg per annum for category 2 indications, ie, where there is currently inconclusive evidence of [clinical] benefit, when product becomes available; and
- that these targets be reviewed regularly.

AHMAC does **not** endorse the recommendations relating to

- the strategies to increase IVIG supply;
- matters of funding; and
- the timeframe to reach the recommended targets.

These recommendations are to be considered in line with other major strategic policy and funding priorities for the Australian blood supply as a whole.

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## **WORKING PARTY**

Professor Ron Penny, Centre for Immunology, St Vincent's Hospital and University of NSW. Chairman.

Dr Bill Beresford, Royal Perth Hospital, Western Australia

Dr Mark Dean, Australian Red Cross Blood Service -NSW

Ms Jane Evans, Department of Human Services, Acute Health Division, Victoria.

Dr Albert Farrugia, Therapeutic Goods Administration (TGA)

Mr John Haines, Commonwealth Department of Health and Aged Care

Mr Bill Heiler, NSW Department of Health

Professor David Henry, University of Newcastle, Newcastle

Dr John Rowell, Royal Brisbane Hospital, Queensland

Dr Peter Schiff, CSL Limited, Victoria

Dr Marie-Louise Stokes, NSW Department of Health

Dr Jill Carstairs, NSW Department of Health

---

## **CLINICAL REFERENCE GROUP**

Professor Ron Penny, Centre for Immunology, St Vincent's Hospital and the University of NSW. Chairman.

Professor Warwick Britton, Department of Medicine, University of Sydney. Nominated by the Australasian Society of Clinical Immunology and Allergy.

Dr Stephen Flecknoe-Brown. Nominated by the Australian Medical Association, NSW Branch.

Associate Professor John Gibson, Institute of Haematology, Royal Prince Alfred Hospital, Sydney. Nominated by the Haematology Society of Australia and New Zealand.

Associate Professor Andrew Lloyd, Department of Infectious Diseases, Prince of Wales Hospital, Sydney and School of Pathology, University of NSW. Nominated by the Australasian Society of Infectious Diseases.

Professor John Pollard, Department of Medicine, University of Sydney. Nominated by the Australian Association of Neurologists.

Dr Boyd Webster, Haematology Department, The Royal Alexandra Hospital for Children, Paramatta. Nominated by the Australasian Society of Blood Transfusion.

Associate Professor Graham Young, Kanematsu Laboratories, Royal Prince Alfred Hospital, Sydney. Nominated by the Royal Australasian College of Physicians – Adults.

Associate Professor John Zeigler, Sydney Children's Hospital, Sydney. Nominated by the Royal Australasian College of Physicians – Paediatrics.



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**AHMAC BLOOD AND BLOOD PRODUCTS COMMITTEE**

**REVIEW OF USE OF INTRAVENOUS IMMUNOGLOBULINS  
(IVIG)**

**TERMS OF REFERENCE**

1. Report on the current demand for, and supply of, intravenous immunoglobulin (IVIG) across Australia.
2. Identify current clinical and cost effective indications for IVIG and review the impact of the recently revised ASBT guidelines on the usage of IVIG.
3. In the event that current guidelines for the use of IVIG are not evidence based, make recommendations in relation to a process for developing guidelines which reflect:
  - Clinical effectiveness
  - Cost effectiveness
  - Priority of use of product where demand exceeds supply.
4. Review the current Red Cross Intragam allocation policy and make recommendations, where appropriate, to improve distribution on a national basis so that patients receive product in order of clinical priority.
5. Using the ASBT guidelines, determine how much IVIG Australia needs in the short to medium term to treat patients where the use of IVIG has been shown to be clinically and cost effective.
6. In the event that the Working Party establishes that a chronic shortage of IVIG exists in Australia, recommend strategies to increase supply to the required level. Such strategies as might be recommended should take account of the impact of the national approach to the supply of blood and plasma products currently being implemented by the Australian Red Cross Blood Service.
7. Submit a draft report to and recommendations for consideration by the AHMAC Blood and Blood Products Committee six months after the appointment of the Research Officer.
8. Determine a time frame and process for a review of the recommendations contained in the report.



## EXECUTIVE SUMMARY

Immunoglobulins were initially used for treating immunodeficiencies in the 1950s. This continues to be their main use. However, since the 1980s they have been used to treat an increasing number of different conditions. As a consequence the demand for them has greatly increased in Australia, as in other countries in the world.

Growing concern on the part of clinicians, patients, and other interested parties over a perceived chronic shortage of IVIG in Australia led to the current AHMAC Blood and Blood Products Committee national review of the use and supply of IVIG.

Australia has a long-standing policy of self-sufficiency in relation to blood and plasma products. Nevertheless, in recent years the Commonwealth government has recognised that this might not always be practical.

In Australia intravenous immunoglobulins (IVIG) are produced exclusively by CSL Limited. They are manufactured from voluntarily donated plasma collected around Australia by the Australian Red Cross Blood Service (ARCBS). Funding for the manufacture of IVIG is provided by the Commonwealth government and the product is issued free of charge to patients in Australia.

The Australian-produced IVIG is supplemented by an overseas product, *Sandoglobulin*, which is imported and sold by the Pharmaceutical Company, Novartis Pharmaceuticals Australia Pty Ltd. Funding for this product comes from individual hospital budgets and/or patients. It should be noted that there are other IVIG products available on the world market; however, these are currently unregistered with the TGA.

### USES OF IVIG

The Working Party established that Guidelines for the clinical use of IVIG in Australia had been drawn up in 1992 but that there were no national data to show which indications were currently being treated or to show the proportion of IVIG used to treat these indications. Furthermore, there were no data relating to the cost effectiveness of IVIG treatment in Australia. Audits were carried out on behalf of the Working Party. These showed that:

- the number of people treated in Australia with IVIG is small;
- the major indications treated with IVIG are primary immunodeficiencies;
- of the States audited, not all adhered to the 1992 Guidelines; and
- differences exist in the clinical usage of IVIG between the States audited.

The Working Party recognised that in the light of current knowledge, the 1992 Guidelines were outdated. The Clinical Reference Group reviewed current reported evidence for the efficacy of IVIG for various indications/conditions and, based on this information, drew up a new set of guidelines for the clinical use of IVIG to be used nationally. Indications/conditions were assigned to one of three new categories. Certain conditions, particularly the neuropathies and myopathies, for which there was previously insufficient evidence of IVIG efficacy, now have ample supporting evidence for its use.

The Working Party acknowledged that even if the quantity of IVIG for use in Australia were increased, future acute shortages could not be ruled out. In order to cover this contingency they developed a system for prioritising the use of IVIG. The scheme adopted was not that of ranking named indications. It was felt that this approach could lead to inequitable treatment. Instead, the approach adopted for prioritisation is based on clinical need as determined by consensus criteria.

In relation to the uses of IVIG the Working Party recommends:

- **The adoption of a national policy for the clinical use of IVIG based on a new categorisation of clinical indications i.e.**

**Category 1: Indications for which there is now convincing evidence of benefit.**

**Category 2: Indications for which currently there is inconclusive evidence of benefit.**

**Category 3: Conditions for which there is convincing evidence that IVIG has no benefit.**

- **The indications in these categories undergo regular review (on an annual basis) by a Clinical Reference Group to ensure that the therapeutic use of IVIG is kept current.**
- **During times of acute shortage, prioritisation of the use of IVIG should be based on clinical need as determined by the following consensus criteria:**
  - **clinical significance using the level of therapeutic effect as judged by improvement of quality of life and /or survival;**
  - **availability of other forms of treatment including a consideration of cost-effectiveness; and**
  - **risks involved with IVIG treatment.**

In order to monitor the impact of the new categorisation and to provide data on indications treated, the Working Party recommends that:

- **All requests for IVIG, including requests not approved, be recorded by the ARCBS and reported to the AHMAC Blood and Blood Products Committee on an annual basis and that the records include the following information:**
  - Date**
  - The requesting Medical Officer's name**
  - The requesting institution**
  - Clinical Indication**
  - Patient's age/sex**
  - Amount of IVIG requested**
  - The amount of IVIG issued (in grams, number of bottles and bottle volume)**
  - Response to alternative treatments where appropriate**

The Working Party recognised that further research needs to be undertaken in order to determine cost-effectiveness issues and evaluations of the efficacy of IVIG. The Working Party recommends that:

- **Funding be provided from the Intragam Program to support the necessary staff (secretarial support and a co-ordinating Research Officer) to carry out this research which could be part of a broader Blood and Blood Products Committee program for plasma.**

### **SUPPLY OF IVIG**

Data relating to supplies of IVIG from CSL Limited and IVIG issues by the ARCBS indicates that there is a chronic shortage of IVIG at the national level and that usage is determined largely by IVIG availability. The extent of the IVIG shortage could not be determined accurately because of the lack of data relating to unmet requests for IVIG. At the State/Territory level the quantities of IVIG received by ACT, the Northern Territory and Tasmania during the years 1996/97 and 1997/98 were sufficient for their needs.

The Working Party established that under the current IVIG allocation policy the quantity of IVIG allocated to a State/Territory may bear no relation to that State/Territory's clinical requirements since the quantity allocated to it is determined by the quantity of plasma collected by that State/Territory. This in turn is largely determined by the funding provided for plasma collection by the State/Territory government although other factors, such as donor availability and geographical factors, also influence the quantity of plasma collected. The Working Party acknowledged that the current IVIG allocation policy does not provide for the equitable treatment of patients throughout Australia but they considered that this situation will be rectified by the recent AHMAC-endorsed new method of funding blood and blood products. As a result of the new funding arrangements, the State/Territory-based IVIG allocation policy will be

replaced with a national allocation policy based on a State/Territory's clinical requirements.

In relation to the chronic under-supply of IVIG in Australia, the Working Party recommended that the annual quantity of IVIG produced in Australia should be increased by an amount that will take into account the new requirements for the product. The Working Party recommends that:

- **The amount of IVIG be increased to 900Kg (i.e. 5.03 kg/100,000 population) in the first year and that this figure be reviewed annually.**
- **AHMAC endorse 900 kg (5.03 kg/100,000 population) as a national target figure.**
- **The usage of IVIG be reviewed annually to assess the adequacy of the figures.**

Although the Working Party recognized that IVIG should be made available for clinical trials it conceded that this was not a top priority in the first instance and it recommends that:

- **The quantity of IVIG required for research purposes (clinical trials for new indications where there is currently insufficient evidence of efficacy of IVIG) be considered in one year's time.**

The Working Party established that the chronic shortage of IVIG in Australia is exacerbated from time to time by acute shortages of IVIG resulting from factors such as seasonal variations in plasma donations, CSL's production scheduling, manufacturing problems etc. These acute shortages have the greatest impact on States holding low stock reserves since they have little buffering capacity. Acute shortages of IVIG experienced by particular States may be met by using stock in hand, supplementing the Australian product with imported IVIG and ad hoc loans from other States/Territories, although this is not always possible. The Working Party acknowledged that these acute shortages have a marked effect on the treatment and lives of patients requiring IVIG and in relation to the acute shortages the Working Party recommends that:

- **ARCBS and CSL continue to work together to ensure optimisation of production of IVIG in relation to demand, to monitor the production schedules and to improve reliability of the data provided.**
- **There is a contingency stock of IVIG ( 225 kg) equal to one quarter the new annual IVIG requirement to maintain the consistency of**

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**supply of IVIG.**

The Working Party considered a number of options for increasing the supply of IVIG:

- Increasing the Australian plasma supply by increasing funding required for plasma collection;
- Importing additional IVIG from commercial sources into Australia;
- Importing plasma for local manufacture in Australia; and
- Altering the current ratio of IVIG produced in relation to the production of normal immunoglobulins produced for intramuscular injection (IMIG). Both products are produced from plasma with the intramuscular preparation being produced at the expense of the intravenous preparation.

The Working Party felt that it could not recommend the latter option until it had been ascertained what Australia's need for IMIG was in relation to Public Health needs and emergency elective travel. The Working Party recommends that:

- **A national review be carried out to investigate the of use and supply of normal IMIG:**
  - **to establish the national requirements for normal IMIG, particularly for emergency foreign travel and Public Health indications; and**
  - **to develop Guidelines for the usage of normal IMIG.**

The Working Party thought that the best option available, particularly in light of Australia's policy of self-sufficiency in relation to blood and blood products, was to increase the supply of IVIG by increasing plasma collected in Australia. The Working Party was advised by the ARCBS and CSL that it would take at least two years before the target IVIG figure could be achieved and therefore it recommended that in the meantime the shortfall between the amount of IVIG produced in Australia and that required to meet the new national target should be supplemented with overseas product. The Working Party recommends that:

- **The supply of IVIG be increased through a combination of :**
  - **Option 1: Increasing the amount of plasma collected within Australia; and**
  - **Option 2: Increasing the amount of IVIG obtained from overseas sources.**
- **In relation to Option 1, a proposal be developed by the ARCBS and CSL Limited and the Commonwealth government to implement the production of the additional IVIG.**

- **In relation to Option 1, the extra plasma collected should be used for IVIG production. In this way the IVIG: IMIG ratio can be increased without impacting on the current supply of IMIG.**
- **In relation to Option 2, suppliers of IVIG on the Australian market are required to submit clinical data or bibliographic submissions in support of their application to register the product for as wide a range of Category 1 indications as possible. This should include, as a minimum, the following indications:**
  - **Primary Immunodeficiencies**
  - **Immune thrombocytopenic purpura**
  - **Chronic inflammatory demyelinating polyneuropathy**
  - **Guillain-Barre syndrome**
  - **Inflammatory myopathies**

Suppliers should note that the Working Party's strategy for achieving the levels of IVIG described in this report requires that Category 1 indications be supported by the appropriate registration procedure. Suppliers should contact the Therapeutic Goods Administration for information about the Orphan Drug Program and relevant submissions.

- **Even if the ultimate aim is to increase the amount of IVIG by increasing the amount of plasma collected in Australia, the difference between the projected target figure and the quantity of IVIG produced in Australia should in the short term be made up with IVIG obtained from overseas sources.**
- **The cost of any imported IVIG during the financial year 1999/2000 be borne by the Commonwealth and State/Territory governments on a 50:50 cost-share basis. From the beginning of 2000/2001 the cost is to be borne solely by the Commonwealth government.**

The Working Party considered the funding for the preferred options for increasing IVIG. CSL's IVIG production figure for 1998/1999 was 661 kg. In order to meet the projected demand for 900 kg IVIG, an extra 239 kg of IVIG is required. The cost for collecting the requisite quantity of plasma (68,286 kg) to produce this amount of IVIG is \$ 13,657,200. Until 2000/01, the additional costs for plasma collection will be borne by the Commonwealth and States/Territories under the existing funding arrangements. The cost of an equivalent quantity of imported IVIG is \$23,900,000; this figure is based on the current quoted cost of \$100 per gram for *Sandoglobulin*.

If imported IVIG is used to fill the shortfall between the quantity of IVIG produced by CSL and the new national target, the cost based on CSL's production figure of 661 kg for 1998/99 will be \$23,900,000; this will fall over time as the ARCBS provides additional plasma.

The cost for funding the collection of plasma (64,286 kg) to produce 225 kg IVIG for the contingency stock is estimated to be \$12,857,200. This is a 'one-off' cost. Funding for the collection of additional plasma is to be borne between the States/Territories and Commonwealth on a 50:50 cost-share basis. The cost of an equivalent quantity of imported IVIG (*Sandoglobulin*) is \$22,500,000.

The Working Party noted that any agreement to purchase overseas IVIG during the financial year 1999/2000 will be borne jointly by the Commonwealth and the States/Territories on a 50:50 cost-share basis. From the beginning of the financial year 2000/2001, when the new funding arrangement commences, the Commonwealth government will be responsible for the full cost.

In relation to the future collection of plasma and the production of IVIG and IMIG, the Working Party recommends that:

- **CSL and the ARCBS provide the AHMAC Blood and Blood Products Committee with annual reports which detail on both a national and State/Territory basis:**
- **The amount of plasma (kg) collected and sent to CSL each year;**
- **The amount of plasma pooled (kg) and used to make immunoglobulins;**
- **The quantities of IMIG and IVIG produced each year (kg);**
- **The IMIG:IVIG production ratio;**
- **The production yield; and**
- **Stock in hand held by the ARCBS and CSL on behalf of the ARCBS at the beginning and end of each year.**

The Working Party recognised the importance of the future management of issues relating to the use and supply of IVIG in Australia. In view of the new funding arrangements, it considered that the Commonwealth should be responsible for the overall continuing management of IVIG and that AHMAC's Blood and Blood Products Committee should continue to monitor supply on an ongoing basis. This Committee will also be responsible for any relevant policy decisions. The Working Party recommends that:

- **The AHMAC Blood and Blood Products Committee be advised and assisted by a Clinical Reference Group.**
- **The Clinical Reference Group be supported by a secretariat with expertise in research and analysis.**



## INTRODUCTION

Immunoglobulins consist of a mixture of different classes of antibodies (proteins) present in blood plasma. The antibodies present in the plasma reflect the pathogens encountered in the local community.

Therapeutic preparations of immunoglobulins, mainly of the IgG class, were initially used in the 1950s to treat patients with primary immunodeficiency disorders affecting the production of immunoglobulins. These disorders result from abnormalities in the development and maturation of cells of the immune system with the result that people with these conditions are very susceptible to infections which, unless treated, can prove fatal. Early recipients of the treatment were found to respond well and immunoglobulin replacement therapy soon became standard treatment for these disorders. However, the presence of IgG aggregates in the early preparations restricted their use to intramuscular or subcutaneous administration and this had its limitations. The injections were painful which meant that doses had to be limited in size and frequency. In addition, muscle proteases degraded much of the infused immune globulins and the remaining protein reached the circulation only after significant delay.

In the late 1970s highly purified monomeric suspensions of IgG that exhibited normal pharmacokinetics became available; most importantly they could be tolerated intravenously. Use of these intravenous preparations (IVIG) rapidly subsumed the use of the intramuscular preparations as replacement therapy for primary and secondary immunodeficiencies.

The chance discovery by Imbach et al in 1981<sup>1</sup> that IVIG reversed the autoimmune thrombocytopenia in a young patient with severe chronic idiopathic thrombocytopenic purpura and secondary hypogammaglobulinemia created increased interest in the therapy. This resulted in numerous new applications for the product being reported. Current indications treated with IVIG include a variety of autoimmune disorders, haematological conditions and neurological diseases.

As the list of potential new indications expanded, so did demand for the product, both locally and worldwide.

The mechanism(s) of action responsible for the beneficial effect of immunoglobulins in many of the reported indications is still unclear and treatment is by no means totally safe. Adverse effects have been reported in 1-15% (but usually less than 5%) of patients receiving commercial preparations of IVIG<sup>2</sup>. Such reactions include pyrogenic reactions marked by

high temperature and systemic symptoms; minor systemic reactions with headache, myalgia, fever, chills, light-headedness, nausea and/or vomiting;

vasomotor and/or cardiovascular manifestations marked by changes in blood pressure and tachycardia. These latter symptoms may be associated with shortness of breath and chest tightness. Other reported effects associated with IVIG administration include aseptic meningitis syndrome (infrequent), positive direct antiglobin tests and red cell haemolysis, thrombophlebitis (associated with prolonged administration), hypersensitivity reactions (very rare), neutropenia and impaired renal function.

Australia has a long standing commitment to a policy of self-sufficiency in relation to blood products. In keeping with this policy, the increased demand for IVIG was met mainly by increasing supplies of IVIG manufactured in Australia.\* Nevertheless, supplies of IVIG still proved inadequate for the nation's needs. In an attempt to address the issue, the Australasian Society of Blood Transfusion (ASBT) convened a consensus symposium in 1992 to discuss the indications for the use of IVIG and to formulate a list of recommendations for its use. Evidence for the efficacy of IVIG for each reported indication was assessed on the basis of the reported study type, the findings and the number of people in each particular study. The outcome of the symposium was a set of consensus guidelines (referred to as the 1992 Guidelines) which grouped indications for the use of IVIG into three categories: -

- **Category A:** Diseases and situations where the use of IVIG is indicated;
- **Category B:** Potentially severe diseases or situations where IVIG may have a role; and
- **Category C:** Clinical conditions where the evidence for benefits derived from the use of IVIG was either conflicting or anecdotal such that the use of IVIG in those conditions could not be justified.

In spite of these measures the demand for IVIG became more pressing.

In 1994-95 an annual \$8m plasma funding initiative was launched in order to meet national Factor VIII targets. A spin-off of this initiative was that it enabled more IVIG to be produced since Factor VIII and IVIG are derived from different fractions of the plasma.

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\* Supplies of Australian-produced IVIG were, and still are, supplemented by supplies of imported IVIG purchased from NOVARTIS. This Pharmaceutical Company is the only importer of the product in Australia. The product was registered in Australia in 1987 on the basis of its quality and efficacy relative to the product that produced in Australia at that time.

A further attempt was made to rationalise the use of IVIG in 1996 when a second ASBT Review was carried out. Revised Guidelines were drawn up and indications were classified into four categories:

- **Category A:** Proven benefit
- **Category B:** Probable benefit
- **Category C:** Possible benefit
- **Category D:** Unproven benefit

The 1996 Guidelines were not adopted and as a consequence, allocation of IVIG is still largely determined by the 1992 Guidelines.

In the past two/three years increasing concern has been expressed by clinicians, patients and other interested parties over a perceived chronic shortage of IVIG in Australia. Evidence for the shortage was largely anecdotal. As a result the Australian Health Ministers' Advisory Council (AHMAC) and their Blood and Blood Products Committee initiated the current national review of the use and supply of IVIG in Australia.

The review was carried out by a Working Party whose members represented different States, the Commonwealth, CSL Limited, the Australian Red Cross Blood Service, AHMAC, the NSW Department of Health and the Therapeutic Goods Administration (TGA). The Working Party was advised and assisted by a Clinical Reference Group whose members represented the main clinical areas and specialties in which IVIG is used.

## IVIG - INTERNATIONAL PERSPECTIVE

### Usage

Since the 1980s the demand for IVIG has increased in both Australia and other countries of the world. International comparisons for 1996 show that Australia was the second highest user of IVIG, with the United States of America ranking first (see Table 1). The reasons for the discrepancies in IVIG usage between the different countries are not known but it is likely that factors such as different disease prevalence rates as well as differences in clinical practice and IVIG funding policy may play a role. The high usage in the United States has been attributed to a number of factors including the fact that IVIG has been available in the United States longer than in most other countries and the fact that health insurance companies cover it more readily than in many other countries.

Whatever the reasons for the differences in IVIG usage by different countries, the increased demand for IVIG is likely to continue within the foreseeable future. Current estimates from the United States indicate that demand is growing by 10% per annum due to better diagnosis of IVIG-treatable diseases and the continued increase in demand, particularly for treating 'off-label' or non-approved conditions ie. treatment of conditions for which IVIG is not licensed.

**Table 1: Comparison of the per capita usage of IVIG in different countries of the world**

Country	IVIG used kg/100,000 population
United States	6.14
Australia	3.39
Germany	3.35
Israel	3.05
Sweden	2.87
Italy	2.84
Japan	2.37
United Kingdom	1.50

IVIG usage in 1996. Data for countries other than Australia were obtained from the Marketing Research Bureau Ltd. Data for Australia based on data obtained from the 1996 Sales and Marketing Data produced by CSL. *Sandoglobulin* usage is not included. The Population figures were the 1996 Census figures obtained from the Australian Bureau of Statistics.

## Other relevant matters

Unlike the situation in Australia, the international plasma products industry is dominated by a number of commercial manufacturers, based mainly in the USA. These companies are able to access large amounts of plasma from paid US donors. In addition, they purchase plasma and intermediates produced by “non-commercial blood agencies” worldwide and manufacture it into the final product.

Historically, the USA has enjoyed a long period as a net exporter of plasma products because of its large capacity to produce plasma. The relatively liberal guidelines in the USA allow a donor to donate up to a maximum of two litres of plasma weekly by plasmapheresis. Guidelines in other countries are considerably stricter; they limit the quantity of plasma donated to 15 litres per donor per year. These two factors – access to a large plasma supply and the large manufacturing capacity of the manufacturers – have, until recently, enabled the USA to consistently meet its own needs and export products worldwide.

This situation has changed since late 1997 and product shortages are being experienced in the USA and countries supplied with IVIG produced by the American-based companies.

The current shortage has been caused by a number of factors:

- Production disruption caused by the requirement to comply with Food and Drug Administration (FDA) compliance measures. Following observations by the US Auditor General's Office and some major GMP-type incidents, the FDA has considerably tightened its compliance program over the plasma fractionation industry. This has resulted in practically all the major US fractionators coming under consent decree\* and in the closure of some plants. This has had a very significant effect on the overall amount of IVIG produced.
- Product withdrawals due to the industry's and the FDA's conservative and prudent approach to reducing the theoretical risk of CJD transmission through blood products. Withdrawals have tended to involve products usually no longer in inventory, and have thus not affected supply as much as might have been expected. In addition, the products involved are manufactured from plasma recovered mainly from whole blood voluntary donations, rather than commercial plasmapheresis material.
- Better diagnosis of IVIG-treatable conditions.

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\* An agreement entered into by the FDA and the manufacturing company to address issues identified by the FDA in a pre-determined, defined time frame.

- Continued increase in demand, in particular for treating non-approved indications; and
- Inaccurate projections of product demand, leading to insufficient manufacturing capacity.

In the USA, the shortage of IVIG has led to the adoption of various approaches to reduce current usage and at a congressional sub-committee hearing in May 1998 the Surgeon General recommended that the FDA extend its enforcement charter to prevent 'off-label' (non-authorised) use of the product.

As a result of the problems experienced by the manufacturing sector, as opposed to the plasma collection industry, the USA now produces an excess of plasma which is available on the international market for use by non-USA fractionators. For example, the English fractionator, Bio Products Laboratory, purchases plasma from the USA collection agencies for manufacture into products. This arrangement commenced when the CJD problem led British authorities to ban the use of UK plasma for manufacturing plasma products.

Although the world supply of IVIG is currently compromised, largely because of the FDA's compliance program and growing demand, the situation is improving as the problems experienced by the USA manufacturers are gradually overcome.

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## PRODUCTION OF IMMUNOGLOBULINS

Australia has a long-standing commitment to a policy of self-sufficiency in relation to the production of blood products. This is enshrined in Appendix 19 of the Australian Guidelines for the Registration of Drugs:

.....Australia favours national self-sufficiency in products derived from human blood or plasma, believing that a policy of not being reliant on donors in other countries is not only in the national interest but an international responsibility.

In keeping with this policy, the Commonwealth government entered into a ten-year contract with CSL Limited in 1994 to manufacture and supply a range of plasma-derived products (including IVIG) for Australia. These products are produced from plasma collected by the Australian Red Cross Blood Service (ARCBS) from volunteer non-remunerated donors throughout each of the States and Territories of Australia.

Plasma is obtained either by fractionation of whole blood or by plasmapheresis which is a process whereby only the plasma is collected and the blood cells are returned to the donor. This method has the advantage of permitting more frequent donations to be made since the blood cells do not have to be replaced by the body between consecutive donations. However, the process is expensive; considerable capital outlay is required for the necessary machines and the associated running costs are high.

The amount of plasma collected throughout the year is not uniform; in general, less tends to be collected during the winter months because of the higher incidence of sickness amongst donors.

### **Funding for the collection of plasma**

Australia's blood banking system is funded primarily by governments with a contribution from the ARCBS. The States/Territories and the Commonwealth share the operating costs of the ARCBS on a 60:40 basis and capital costs on a 50:50 basis. In 1997-98 combined government funding amounted to \$135 million.

A State/Territory government is responsible for determining its budget for the collection of plasma within that State/Territory. The funding provided by the State/Territory amounts to 60% of the total cost. Once this figure has been determined the Commonwealth government provides an additional 40%. As a consequence, the amount of plasma collected by each State/Territory is largely determined by the funding made available for this purpose by the State/Territory government.

Other factors which impact on the amount of plasma collected by the different States and Territories include:

- donor availability
- geographical factors and
- efficiency of the collection method used.

The volume of plasma collected by the different States and Territories during the period 1990/91–97/98 is shown in Figure 1. On a State/Territory basis, NSW provides the greatest volume of plasma and the Northern Territory the least. However on a per capita basis, NSW provides the least amount of plasma while the Northern Territory is one of the higher suppliers (Fig 2).

Figure 3 shows the total amount of plasma collected in Australia from 1989/90-1997/98. The marked increase in plasma collected since 1994/95 reflects the Factor VIII plasma-enhancement funding.

### Method of production of immunoglobulins

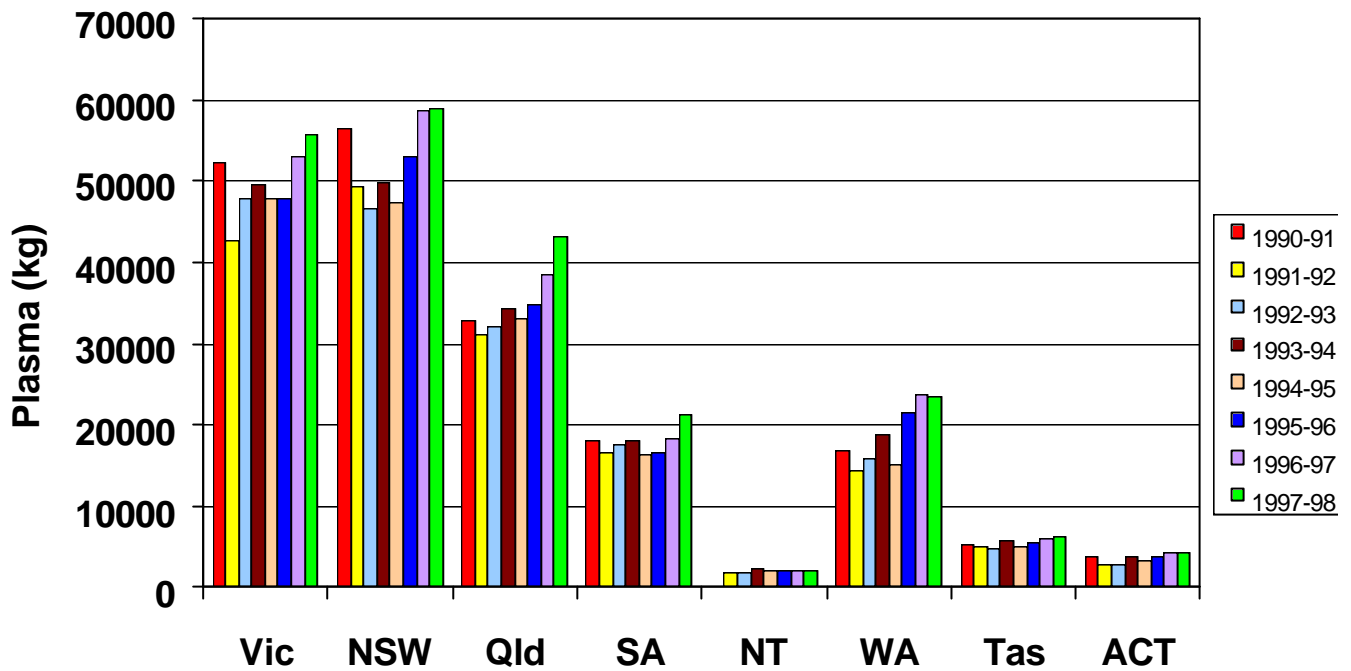
Two preparations of immunoglobulins are made by CSL. One preparation is suitable for intravenous administration (intravenous immunoglobulin, IVIG, Trade name: Intragam). The other preparation is suitable for intramuscular or subcutaneous administration and includes normal (IMIG) and specific Immunoglobulins. Specific immunoglobulins are made from plasma that has particularly high antibody titres for specific antigens. A comparison of IVIG and IMIG is given in Table 2.

**Table 2 : Comparison of composition of IVIG (*Intragam*) and normal IMIG**

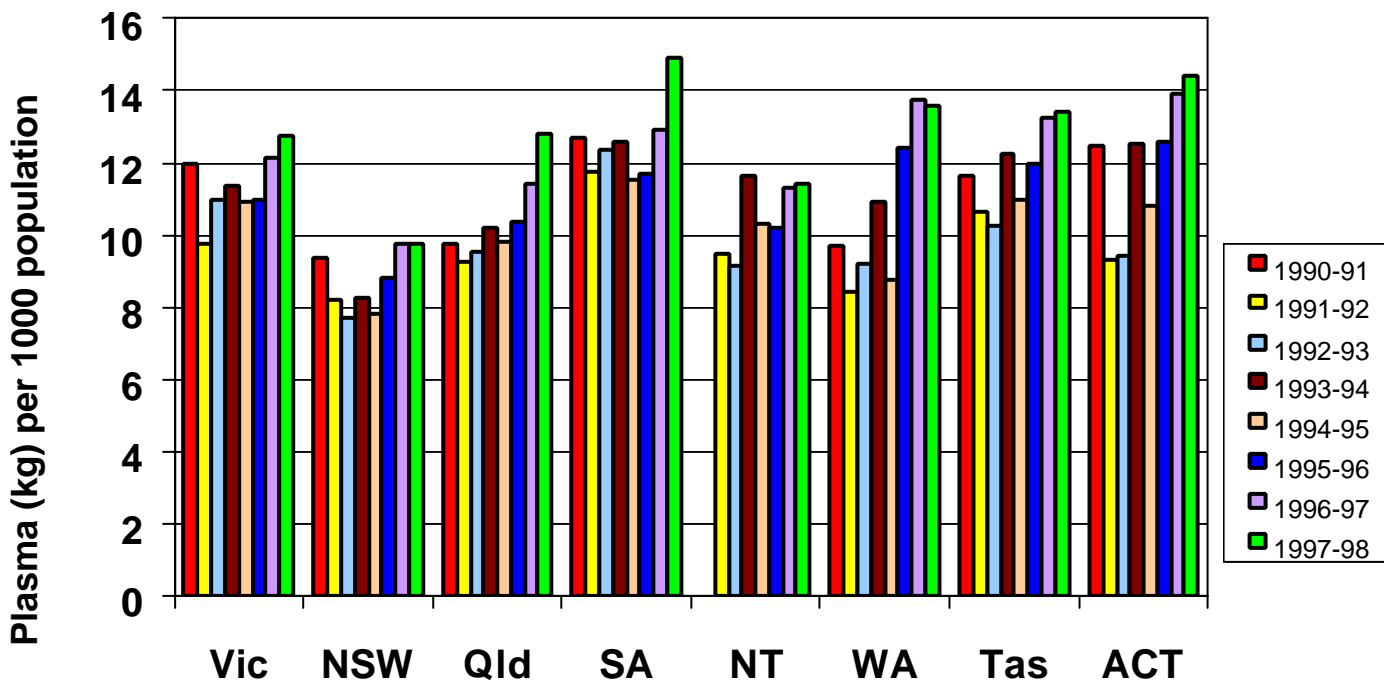
IVIG	IMIG
6% Immunoglobulins	16% Immunoglobulins
At least 98% IgG - 95% in monomeric form	Approximately 90% IgG
Traces of IgA	Traces of IgA
Traces of IgM	Traces of IgM
–	0.01% Thiomersal
10% (w/v) Maltose*	–

\* Maltose is a disaccharide sugar consisting of two molecules of glucose.

**Figure 1: Plasma (kg) collected by States/ Territories (1990/91-1997/98)**



**Figure 2: Plasma collected per capita by States/Territories (1990/91-1997/98)**



Pooled plasma is initially fractionated by the Cohn-Oncley cold ethanol fractionation process<sup>3,4</sup> to yield three protein fractions:

- an immunoglobulin concentrate which consists mainly of IgG;
- an intermediate in the production of coagulation factors VIII and IX; and
- human serum albumin.

The current method used by CSL\* to manufacture IMIG and IVIG is outlined in Figure 4.

The IgG fraction is used to produce the two preparations of immunoglobulins. No further processing of the fraction is required for the intramuscular preparation. It is made up as a 16% solution in a sterile medium. Thiomersal (0.01% weight/volume) is added as an antimicrobial agent. Preservative will no longer be added, commencing in 1999. The preparation is currently available in 2-ml and 5-ml bottles. Additional viral inactivation steps are used in the production of IVIG (see section on Product Safety). The IgG protein is formulated as a 6% solution in a preservative-free sterile medium containing maltose (10% weight/volume) which acts to maintain isotonicity and stabilise the IgG. IVIG is currently available in 50-ml and 200-ml bottles.

Because both IMIG and IVIG are produced from a common starting material, IMIG is produced at the expense of IVIG. For many years the production ratio was 80:20. Since 1995 a number of States have increased the amount of plasma they collect as part of the Factor VIII enhancement scheme. The additional plasma has been used to source both extra Factor VIII and IVIG rather than IMIG. As a consequence the IVIG:IMIG ratio has changed from 80:20 to 90:10.

Figure 3 shows the amount of IVIG and IMIG produced during the years 1989/90 – 1997/98.

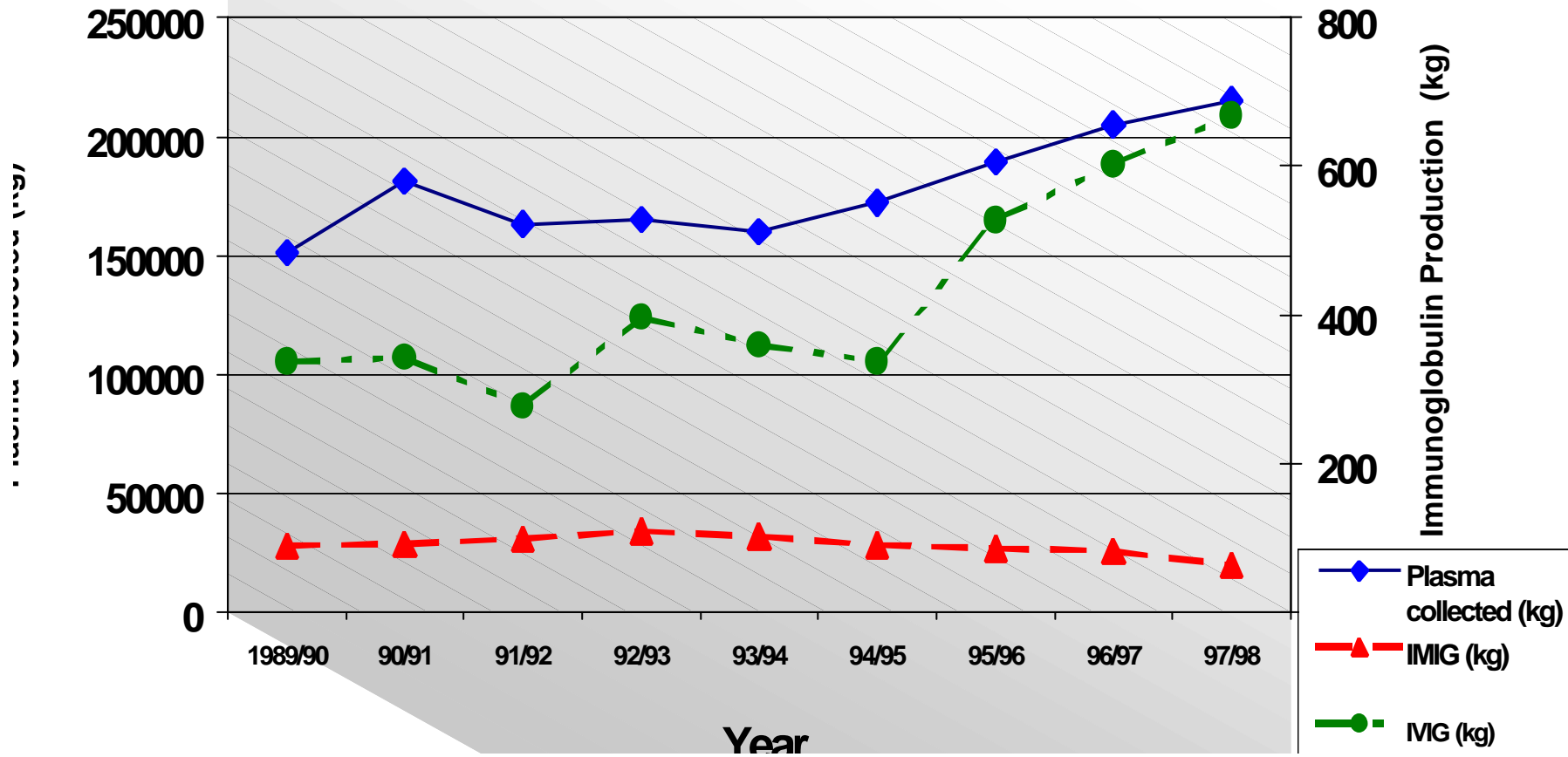
The amount of IVIG produced per annum depends on:

- the volume of plasma used
- the amount of IMIG produced, and
- the yield of the process;

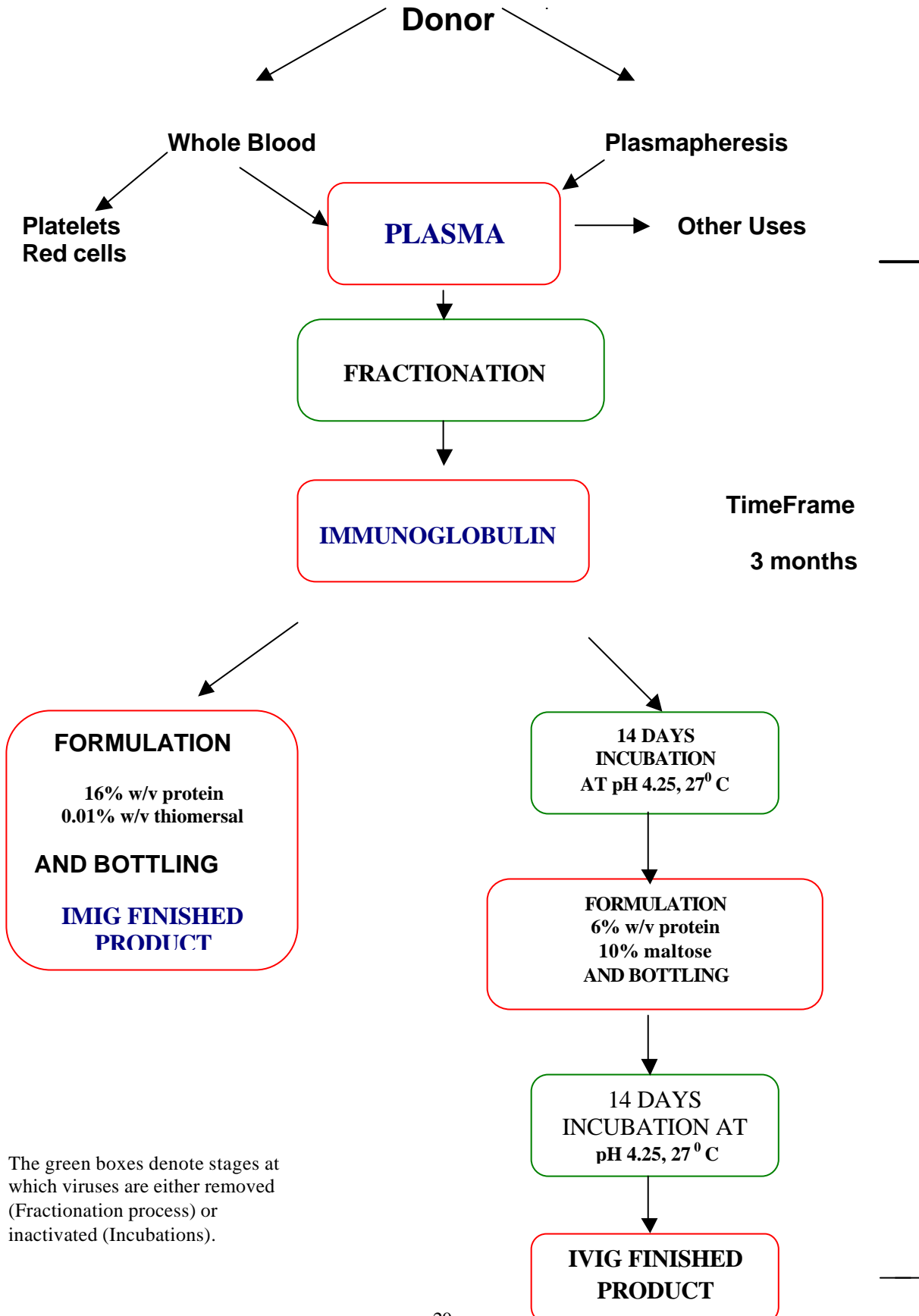
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\* At the time of writing CSL is in the process of changing from the Cohn-Oncley cold ethanol fractionation process to chromatographic purification. This method produces purer protein concentrates and offers the possibility of higher yields of IVIG. It is also more amenable to computerised process control. It is well validated for its ability to eliminate viruses but does not have the large body of safety data associated with the Cohn-Oncley fractionated products.

Figure 3: Plasma Collection vs Immunoglobulin Production



**Figure 4: Production of IMIG and IVIG**



In 1997/98 approximately 205,128 kg of plasma were used for the production of IVIG and IMIG and from this 670 kg of IVIG were produced. This figure does not reflect the maximum capacity of CSL's plasma processing plant at Broadmeadows, Melbourne since it has the ability to increase production by approximately 40%, and further plant capacity expansion is planned.

### **Product safety**

With the advent of HIV/AIDS, there has been increasing concern about the potential contamination of blood and plasma products with pathogenic viruses. Since 1985 all States/Territories have had legislation in place to ensure that donors from high-risk groups are excluded from donating plasma/blood. In addition, all donations are screened by the ARCBS for syphilis, hepatitis B surface antigen, hepatitis C antibody and HIV-1 and HIV-2 antibodies and only donations which are negative are sent to CSL. The ARCBS also screens for HTLV but donations do not have to be negative in order to be sent to CSL. Small samples of plasma from every donation are mixed or pooled and screened a second time by CSL and if these samples test negative, the donations are pooled and processed. The IVIG/IMIG manufacturing process used by CSL contains additional viral inactivation steps<sup>6,7</sup>. The cold ethanol fractionation process used for the production of IMIG and IVIG is extremely efficient at removing viruses from plasma. Additional viral inactivation steps are used in the production of IVIG. The method used by CSL since 1998 is a double 14-day incubation at pH 4.25 and 27° C. This process inactivates blood borne viruses such as HIV, HBV and HCV. After the first incubation step the IgG protein formulated, bottled and then incubated for a second time.

### **Cost of production of IVIG**

CSL's cost of manufacturing plasma products including IVIG and IMIG are borne entirely by the Commonwealth through its contract with CSL. The products are for use in Australia free of charge. For commercial reasons CSL elects not to disclose the figure for the cost of production of IVIG in Australia.

## **RECOMMENDATION**

**In relation to the collection of plasma and production of IVIG and IMIG the Working Party recommends that CSL and the ARCBS provide the AHMAC Blood and Blood Products Committee with annual reports which detail on both a national and State/Territory basis:**

- **The amount of plasma (kg) collected and sent to CSL each year;**
- **The amount of plasma pooled (kg) and used to make immunoglobulins;**

- **The quantities of IMIG and IVIG produced each year (kg);**
- **The IMIG:IVIG production ratio;**
- **The production yield; and**
- **Stock in hand held by the ARCBS and CSL on behalf of the ARCBS at the beginning and end of each year.**

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## SUPPLY OF IVIG

### Suppliers of IVIG in Australia

There are currently two suppliers of IVIG in Australia: the ARCBS and Novartis Pharmaceuticals Australia Pty Ltd. The ARCBS is the principal supplier and IVIG from this source is free of charge to the end-user.

Intravenous immunoglobulins supplied by the ARCBS are manufactured by CSL from plasma collected by the ARCBS. CSL subsequently returns the IVIG to the ARCBS for distribution around the nation.\*

Novartis is a Pharmaceutical Company created by the merger of Ciba-Geigy and Sandoz in December 1996. The product supplied by Novartis is sold under the trade name *Sandoglobulin*. It is manufactured by the Swiss Red Cross from plasma collected under a voluntary donor scheme. Small quantities of this product have been imported into Australia since 1985. *Sandoglobulin* is used by States to supplement Australian-produced IVIG in times of acute shortage. In 1998 a total of 6.6kg was purchased by different States. Funding for the purchase of *Sandoglobulin* comes from hospital budgets and, in some cases, individual patients.

Other IVIG products suitable for use in Australia are available on the world market but, unlike *Sandoglobulin*, they are not registered with the TGA.

### Current IVIG allocation policy and supply

At the time of writing, the allocation policy for Australian-produced IVIG is State/Territory based. The quantity of IVIG received by the ARCBS in a particular State/Territory is in approximate proportion to the amount of plasma collected by that State/Territory (see Table 3) and may, therefore, bear little relation to the State/Territory's clinical requirement for IVIG.

A State/Territory's annual allocation of IVIG is received from CSL in instalments, usually on a monthly basis. These monthly allocations are not quantitatively uniform and tend to be greater during the latter half of the year. This is partly due to the seasonal variation in plasma donations and partly due to CSL's production scheduling. The ARCBS and CSL meet on a regular basis to determine ways of evening out IVIG supply.

Interruptions to supply or production due to other external influences may also affect the supply of IVIG.

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\* The arrangement for plasma collection and IVIG distribution by the ARCBS and production of IVIG by CSL was secured by a contract between the ARCBS and CSL in 1994.

From time to time the impact of one or more of the factors influencing supply results in acute shortages of IVIG. When this occurs, the effect is felt most keenly by States holding low stock reserves since they have little buffering capacity.

Acute shortages of IVIG experienced by particular States/Territories may be met by one or more of the following methods: using stock in hand, supplementing the Australian product with imported IVIG and ad hoc 'loans' from other States/Territories, although sometimes this is not possible\*.

**Table 3 : Reported annual allocations of IVIG to the States/Territories**

States/Territories	Plasma collected and sent to CSL (kg)		IVIG received from CSL (kg) ( ) <sup>+</sup>	
	1996 – 97	1997 – 98	1996 – 97	1997 – 98
Victoria	53,089	55,691	126.9 (147.4)	165.7 (211.3)
Queensland	38,585	43,246	114.9 (111.0)	129.1 (131.1)
New South Wales	58,797	58,975	146.2 (151.9)	157.3 (160.9)
South Australia	18,480	21,291	53.7 (51.9)	61.5 (64.1)
Western Australia	23,726	23,421	64.6 (66.7)	76.2 (76.0)
Northern Territory	2,201	2,232	7.6 (7.4)	6.8 (7.9)
ACT	4,167	4,304	11.02 (12.9)	14.0 (14.0)
Tasmania	6,093	6,180	21.9 (23.4)	21.1 (21.9)
National <sup>†</sup>	205,138	215,340	602.2 (572.5)	667.8 (687.2)

Data for plasma collected obtained from CSL.

Data for IVIG issues obtained from the 1996-97 and 1997-98 Sales and Marketing Reports issued by CSL.

+ Figures in brackets ( ) obtained from Reports to the Australian Red Cross Blood Service, Product Receipts and Issues Reports July 1996 – June 1997 and July 1997 – June 1998. There are discrepancies between the two sets of figures.

† Data for allocations for the States/Territories obtained from the Sales and Marketing Reports do not summate to equate with the National Figures.

### Current ARCBS IVIG distribution policy

A State/Territory's allocated quantity of IVIG is distributed by that State/Territory's ARCBS. Requests for IVIG are made directly by clinicians to their State/Territory ARCBS. The ARCBS Medical Officers review the requests and in general distribute IVIG in accordance with the 1992 ASBT Consensus Guidelines.

\* Statement based on data taken from Reports to the Australian Red Cross Blood Service, Products Receipts and Issues Reports July 1996-June 1997 and July 1997 – June 1998 prepared by CSL..

Requests for IVIG for conditions which fall into Category C of the Guidelines are considered on a case by case basis; supply of IVIG in these cases is conditional on both availability of IVIG and the weight of accompanying documentary evidence of the efficacy of IVIG for that particular condition. In times of acute shortage, issue of IVIG is restricted to life threatening conditions only.

### **Impact of the current IVIG allocation policy on patients requiring IVIG**

The current allocation policy does not ensure for the equitable treatment of patients requiring IVIG in Australia. Availability is underpinned by economics, disease distribution and variations in clinical practice. Patients are better served in States and Territories that provide more funding for plasma collection and hence IVIG receipts. Similarly, access to imported IVIG in times of shortage is dependent on funding from individual hospital budgets and/or the patients themselves.

### **Future IVIG allocation policy and supply**

Following a recommendation in the 1995 McKay Wells Report "**Commonwealth Review of Australian Blood and Blood Product System**"\* the eight separate State and Territory Red Cross Blood Transfusion Services were consolidated to form the Australian Red Cross Blood Service (ARCBS). In March 1998 an AHMAC working group known as the CEO's Working Party was established to develop funding and management strategies that would optimise the national benefits that potentially arose from the formation of the ARCBS. The Working Party recommended the establishment of a National Managed Fund to provide financial indemnity for the provision of blood and blood products supplied by the ARCBS and it considered funding for the production of blood and blood products. The CEO Working Party recognised that the current funding arrangements reflect the State/Territory-based organizational structure of the blood service and they considered that this was inconsistent with the newly established, nationally focused blood service. Furthermore, they felt that the full potential of the ARCBS would be restricted unless the funding arrangement was changed.

Three funding options were considered by the CEO's working group:

1. Transfer of funding of the national blood service to either the Commonwealth or the States/Territories;
2. Funding of whole blood and plasma-based products by both levels of government;

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\* This report was undertaken on behalf of the Commonwealth Department of Health and Human Services.

3. States/Territories to fund fresh blood products and the Commonwealth to fund plasma for the production of blood products by CSL.

At its meeting on 22 April 1999, AHMAC endorsed Option 3 so that from the beginning of the financial year 2000/2001 the Commonwealth government will be responsible for funding plasma products and their substitutes, for use in Australia, irrespective of whether or not they are manufactured in Australia.

Now that AHMAC has endorsed the new method of funding blood and blood products, the ARCBS in conjunction with the Commonwealth government will determine the national plasma requirements for the production of IVIG. The current IVIG State/Territory-based allocation policy will be replaced with a national policy that ensures that persons in all parts of Australia are given equal access to IVIG. This will be achieved by allocating IVIG to the different States and Territories according to their clinical requirements rather than on the basis of how much plasma they provide. As now, the ARCBS will continue to distribute IVIG but in accordance with national guidelines, if endorsed, proposed by the current Working Party (see section on Demand).

## **RECOMMENDATION**

**In recognising the current problems associated with the production and supply of IVIG, the Working Party recommends that:**

- **The ARCBS and CSL continue to work together to ensure optimisation of production in relation to demand, monitoring of the production schedules and improved reliability of the data provided.**

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## CURRENT DEMAND FOR IMMUNOGLOBULINS IN AUSTRALIA

Although not covered by its Terms of Reference, the Working Party considered that it was legitimate to look at the current uses of normal IMIG because the amount produced impacts on the amount of IVIG that is produced.

### A. Intramuscular immunoglobulins

#### *Indications currently treated with IMIG*

Current approved uses of normal IMIG are replacement therapy for some patients who have abnormal antibody production and passive immunization as prophylactic protection for contact Hepatitis A and for travelers going to regions endemic for the Hepatitis A virus. In addition to these approved uses, there are anecdotal reports of it being used to treat patients with Chronic Fatigue Syndrome.

The Working Party established that the exact uses of IMIG in Australia were unknown and that the method of distribution of the product meant that the information was unavailable. The product is issued directly by CSL and the current practice in most States and Territories is for General Practitioners to order direct from CSL by telephone. No check is made of the intended use of the product. The system in New South Wales is different. Requests for unusually large volumes of the product or requests of a greater than normal frequency by any one General Practitioner are referred to the ARCBS-NSW to be vetted. Depending on the stated intended use, the request is either allowed or disallowed. In order to have a better idea of the current uses of IMIG an audit was carried out on behalf of the Working Party by the ARCBS-NSW. The review took the form of a retrospective telephone survey of the use of IMIG in NSW during the two-week period, 1-16 October 1998. All practitioners who had requested IMIG, however small a volume, during the allocated survey time were contacted and asked to give details of what it had been used for.

The audit showed that only a small percentage (11.11%) of the issued IMIG had been used for primary immunodeficiency disorders and contact Hepatitis A and that just over half the IMIG issued was for travel prophylaxis (see Table 4). The use of IMIG issued for stock is unknown.

**Table 4 : Uses of IMIG in NSW**

Indication	Quantity issued (g)	% Total IMIG issued
Travel prophylaxis	128.8	55.24
Hepatitis A contacts - prophylaxis	22.72	9.74
Hypogammaglobulinaemia	3.2	1.37
Stock	78.44	33.64
Total	233.16	100.0

The majority of IMIG currently produced is used for routine passive immunisation of travellers going to Hepatitis A high-risk countries. There are currently two specific Hepatitis A vaccines on the market. Both are very effective; they stimulate higher antibody levels and provide more sustained protection than can be achieved by passive immunisation with IMIG. Both vaccines require approximately two weeks before they become effective. The current cost of the Hepatitis A vaccination is \$80. The cost of production of IMIG is borne by the Commonwealth and, although free to the public, there is a “cost” associated with its use; diversion of IgG to form IMIG to be used to prevent infection or modify disease for a condition preventable by vaccination is an inefficient use of a scarce resource<sup>8</sup>. The use of IMIG for emergency Public Health reasons is, however, justified even during a time of chronic IVIG shortage. The Working Party questioned the appropriateness of using IMIG (a scarce resource) for routine elective travel when a safe and effective vaccine is available.

## RECOMMENDATION

**The Working Party recommends a national review of use and supply of normal IMIG:**

- to establish the national requirements for normal IMIG, particularly for emergency foreign travel and Public Health indications; and
- to develop Guidelines for the usage of normal IMIG.

## B. Intravenous immunoglobulins

### *Indications currently treated with IVIG*

At the commencement of the review, the Working Party determined that:

- the indications currently treated with IVIG were those determined by the ASBT 1992 Guidelines;
- there were no national data available to show which indications were currently being treated with IVIG;
- there were no national data available to show the proportion of IVIG used to treat these indications;
- there were no available comparative data for the different States and Territories; and
- there were no available outcome data on which to base cost-effectiveness studies.

Over a four-month period audits were carried out by the ARCBS to determine indications treated with IVIG in New South Wales, Queensland and in Australia as a whole. In addition, the Working Party was supplied with data for indications treated in 1997 and the first half of 1998 in Western Australia.

The indications currently being treated with IVIG throughout Australia and on the limited State basis are shown in Table 5. Analysis of the audits revealed the following facts:

- The total number of patients receiving IVIG in Australia is small compared with the total population. It is estimated that approximately 0.005% (1104 of approximately 18 million) of the population are currently being treated with IVIG. Of these patients, some have indications that require a single course of treatment with IVIG; others with immunodeficiencies, require recurrent treatment.
- The major indications for IVIG in Australia (28%) are documented primary immunodeficiencies. Variations exist between the States. In Queensland 19.3% of the total IVIG issued during the audit period was used to treat primary immunodeficiencies. This figure was higher in New South Wales (36.6%) and Western Australia (40.7%).
- The range of indications treated with IVIG in Western Australia is smaller than in the other States.

Table 5: Comparison of the indications treated in Australia with IVIG during the four-month audit period in 1998 - based on the 1992 ASBT Consensus Guidelines.

	Australia	Queensland	New South Wales	Western Australia
Category	% Total IVIG issued	% Total IVIG issued	% Total IVIG issued	% Total IVIG issued
<b>A</b>				
Primary immunodeficiency	28.13	19.3	36.64	40.7
Idiopathic thrombocytopenic purpura in children	0.75	1.7	0.29	13.1 <sup>1</sup>
Idiopathic thrombocytopenic purpura in adults	15.74	28.1	12.61	9.9 <sup>2</sup> (B) <sup>3</sup>
Post-transfusion purpura	-	-	-	
Bone marrow transplantation	6.69	9.1	4.69	0.21
Bacterial infection with HIV	0.17	-	-	
Chronic lymphocytic leukaemia with hypogammaglobulinaemia	6.8	4.7	7.68	1.64
Kawasaki's disease	1.26	0.2	1.12	
Chronic inflammatory demyelinating polyneuropathy in children	0.15	-	-	17.8 <sup>1</sup>
<b>Sub-total</b>	<b>59.68</b>	<b>62.9</b>	<b>63.03</b>	<b>83.35</b>
<b>B</b>				
Other lymphoid malignancy with hypogammaglobulinaemia	2.99		3.65	
Myeloma		2.8		
Non Hodgkin's lymphoma		1.9		
Waldenstrom's macroglobulinaemia		0.2		
Factor VIII antibodies	-	-	0.19	
IgG subclass deficiency	7.36	4.7	4.78	
Chronic inflammatory demyelinating polyneuropathy	9.58	6.4	4.99	
Guillain-Barre syndrome	4.85	9.4	6.77	8.6 2 (A)
Myasthenia gravis	0.53	-	1.42	6.5
Autoimmune neutropenia	0.80	0.4	-	
Autoimmune haemolytic anaemia	0.28	1.8	1.04	
Pregnancy complicated by neonatal allo-immune thrombocytopenia	1.82	4.2	0.66	
Autoimmune thrombocytopenia in pregnancy	0.43	0.3	1.07	
<b>Sub-total</b>	<b>28.67</b>	<b>32.1</b>	<b>24.57</b>	<b>16.4</b>
<b>C</b>				
Multi-focal peripheral neuropathy		2.3	1.53	1.2 (A)
Sensory peripheral neuropathy		0.2	-	-
Neuropathy associated with IgG paraproteinaemia		0.2	-	
Autoimmune neuropathy		-	1.77	
Dermatomyositis/ Polymyositis		0.7	4.46	
Inclusion body myositis		0.4	-	
Severe streptococcal sepsis		0.1	-	
Steroid resistant asthma		0.1	0.09	
Hyper IgE syndrome		0.4	-	
Miscellaneous		0.6	4.55	0.3 <sup>4</sup>
No diagnosis recorded				
<b>Sub-total</b>	<b>11.65</b>	<b>5.0</b>	<b>12.4</b>	<b>0.3</b>
<b>Total</b>	<b>100.0</b>	<b>100.0</b>	<b>100.0</b>	<b>100.0</b>

<sup>1</sup> No distinction has been made between adults and children.

<sup>2</sup> Used to treat chronic thrombocytopenia.

<sup>3</sup> Modification of 1992 Guidelines by Western Australia; letters in brackets show the classification used in Western Australia.

<sup>4</sup> Indication treated was necrotising fasciitis – where there was uncontrollable bleeding despite the use of blood products.

- A varying number of the 1992 Category C indications are treated in Queensland and New South Wales with virtually none in Western Australia.
- In Eastern Australia IVIG is routinely used for a limited period to treat recipients of allogeneic bone marrow or peripheral blood stem cell transplantations. Virtually none is used in Western Australia and it is never used for this purpose at the Royal Perth Hospital. This difference results from the fact that many of the specialists in Western Australia do not support the use of IVIG in this situation.
- The percentage of IVIG used to treat conditions in Categories A, B and C in Queensland and New South Wales and at the national level is similar, although the amount of IVIG allocated to Category C conditions was lower in Queensland (5%) than in New South Wales (12.4%) or on the national basis (11.65%). Nevertheless, as a general approximation, **60%** of IVIG issued is used to treat **Category A** conditions, **30%** to treat conditions in **Category B** and **10%** is used to treat conditions in **Category C**. In **Western Australia** this pattern does not hold; the approximate ratio is **83:16:1**. The reason for this is that certain indications that are classified as Category B indications by the 1992 Consensus Guidelines are treated as Category A indications in Western Australia (see Table 5).

### ***Current usage of IVIG***

During 1997/98 607.8 kg of IVIG produced by CSL was used to treat indications in Australia. This was supplemented by an additional 6.6 kg of IVIG purchased from Novartis. National IVIG usage (excluding *Sandoglobulin*) per 100,000 population was 3.39 kg.

Figure 5 shows the national monthly issues of IVIG for the years 1996/97 and 1997/98. From this it is apparent that availability is a major factor in determining IVIG usage. The annual national usage figure for 1997/8, therefore, does not reflect the nation's true requirement for IVIG for treating indications currently covered by the 1992 Guidelines. Instead, it represents usage during periods when IVIG is both freely available and when all legitimate requests are met and usage during acute shortages when IVIG issues are restricted to life threatening conditions only.

At the State/Territory level, figures for the per capita use of IVIG reveal that while the usage in most States/Territories is similar, usage in New South Wales and the Northern Territory is low (see Table 6). The reason for the low usage in the Northern Territory is unknown; it would appear not to be related to lack of supplies since in the past two years both the Northern Territory and Tasmania have acted as the main sources for inter-State IVIG loans. The low

usage in New South Wales is clearly inextricably linked to the current IVIG allocation policy. Of all the States and Territories, New South Wales collects the most plasma, yet, on a per capita basis, it collects the least. Therefore, on a per capita basis, it receives the least amount of IVIG and its usage is, of necessity, correspondingly lower compared with most other States/Territories.

**Table 6: Per capita usage of IVIG in the different States and Territories** \*

States/Territories	IVIG usage (kg) / 100,000 population
Victoria	3.96
New South Wales	2.45
Queensland	3.63
South Australia	4.12
Northern Territory	2.51
Western Australia	4.22
Tasmania	3.10
ACT	4.40

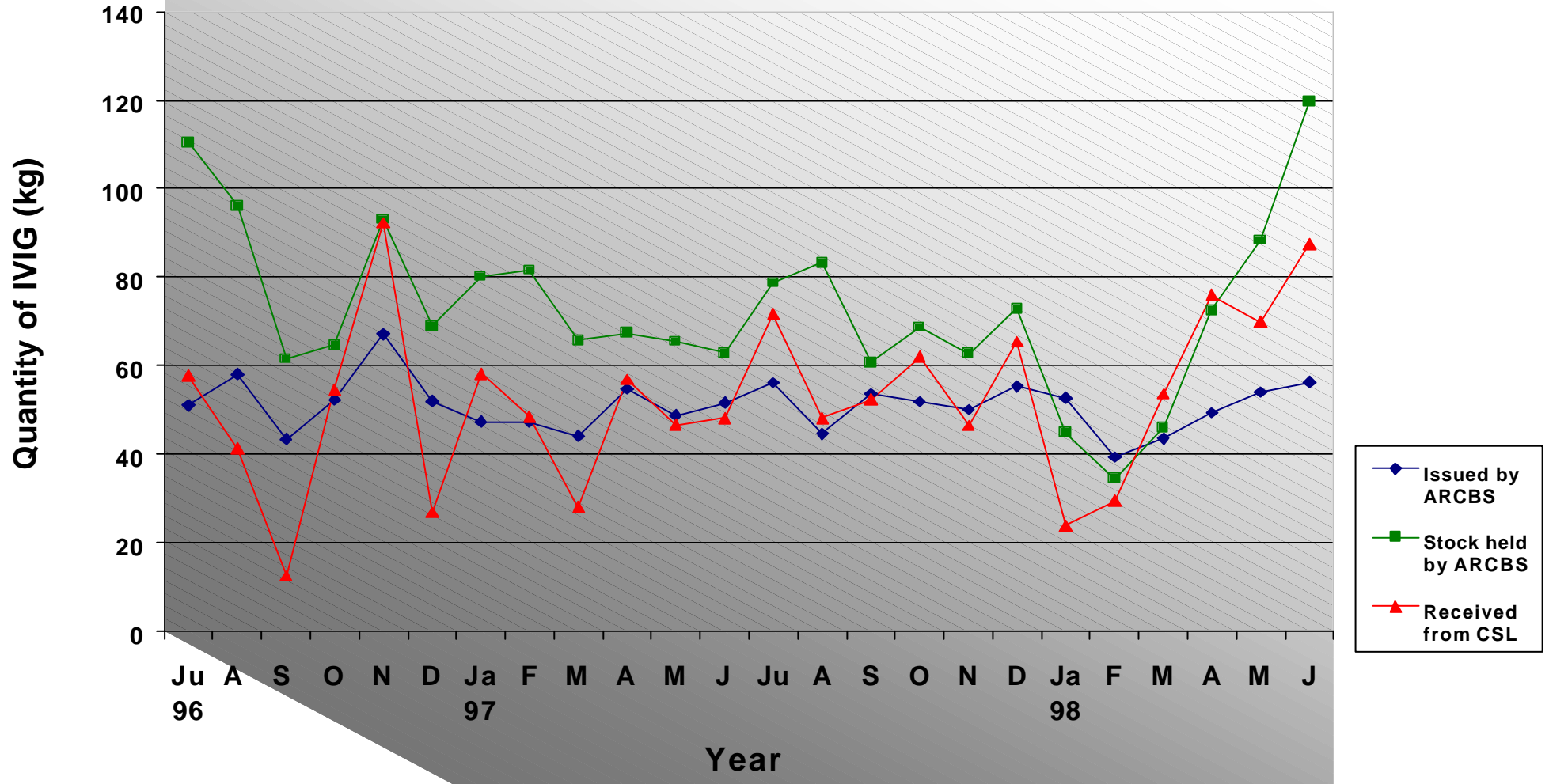
\* Data relating to quantities of IVIG obtained from Report to the Australian Red Cross Blood Service, Product receipts and Issues Report July 1997 – June 1998 prepared by CSL. Population figures obtained from the Australian Bureau of Statistics for the 1996 population census.

### **Current annual national requirement for IVIG**

The Working Party was unable to accurately determine the true current annual national IVIG requirement since there are no data relating to unmet requests for IVIG during times of IVIG shortage. Furthermore, the Clinical Reference Group advised the Working Party that following a period of acute IVIG shortage, requests for IVIG will be artificially low because clinicians become so accustomed to having their requests denied that they stop making requests and only resume when word 'filters' through that stocks of IVIG are again available. This information was endorsed by the Working Party member representing the ARCBS.

The extent of the shortfall can not be ascertained from the amount of *Sandoglobulin* purchased since this reflects only what hospital budgets and, in some cases, individual patients could afford to purchase. At best, a rough guesstimate of the figure can be obtained from the national monthly issues by the ARCBS shown in Figure 5. This figure varies between 40 kg and 60 kg per month depending on availability of supply and stock in hand. Since the figure of 60 kg relates to issues when there is a more plentiful supply of IVIG, this figure has been used. Based on this figure, the national IVIG requirement is 720 kg so that there is currently a national annual IVIG shortfall of

**Figure 5: IVIG Receipts from CSL and IVIG Issues by ARCBS (1996/97-1997/98)**



approximately 50 kg. The figure of 720 kg does not include supplies of IVIG required for stock in hand.

## **FUTURE DEMAND FOR INTRAVENOUS IMMUNOGLOBULINS**

### **Recommended indications to be treated with IVIG in the future**

The Working Party recognized that the clinical use of IVIG is based on evidence for its efficacy and that although the uses of IVIG had been reviewed in 1996, no recommendations had been implemented so that the indications currently treated are largely those determined by evidence available in 1992.

Since 1992, many more clinical studies have been reported in the scientific literature; these provide evidence for the use of IVIG for both new conditions and previously reported conditions for which there had been insufficient evidence

In view of the outdated nature of the 1992 Guidelines the Clinical Reference Group reviewed the use of IVIG as determined by current available scientific evidence for its efficacy. On-line searches using the databases MEDLINE and EMBASE were carried out for the years 1989-1998. A combined search using mesh headings IMMUNOGLOBULINS and CLINICAL TRIALS limited to human and English was initially conducted. A second combined search against IMMUNOGLOBULINS, THERAPEUTIC USE and disease name was then made. The reference sections of key papers obtained from the searches were subsequently examined to identify citations that had been missed in the search.

Because of the short time frame of the AHMAC review, a systematic review was not carried out. Instead, the Clinical Reference Group selected from the available references those it considered to be the best working papers for each of the indications; these were the papers that were reviewed. Evidence was graded in accordance with the NHMRC guidelines.

The Clinical Reference Group acknowledged that the review was biased in favour of reported studies and that the extent of the bias could not be ascertained.

As in the past, conditions were categorised. However, a new model for categorising the indications/conditions was adopted. It has the advantages of being simple, unambiguous and flexible. The model has three categories:

- **Category 1: Indications for which there is now convincing evidence of benefit.** Indications in this category include those that

were in the old Category A and the old category B where the available evidence now justifies their inclusion.

- **Category 2: Indications for which currently there is inconclusive evidence of benefit** because of :
  - Conflicting evidence
  - Low level evidence
  - Little research, possibly because the condition is rare

This Category also allows for special case considerations.

- **Category 3: Conditions for which there is convincing evidence that IVIG is ineffective.**

The Clinical Reference Group's findings are summarised in Appendix 1.

More than 77 indications were identified by the literature search. The Clinical Reference Group determined that the published evidence justified the use of IVIG for a small number of these indications, and that for some of the indications, the use of IVIG was only justified under specified conditions. Evidence for the use of IVIG for some of the neuropathies and myopathies was found to be good and IVIG use is now recommended for these conditions. In the 1992 Guidelines these indications were classified as Category B and C indications.

No consensus was reached for the use of IVIG for recipients of allogeneic transplants. Nevertheless, the Australian and New Zealand Bone Marrow Transplant Co-operative Group has endorsed its use for this indication for a limited, specified period post - transplantation.

There are no placebo-controlled clinical trials to support the use of IVIG for most primary immunodeficiency diseases because the British Medical Research Council considered such trials would be unethical in these situations. Nevertheless, clinical observations are sufficient to support the use of IVIG for these indications.

Evidence for many of the indications was low grade and took the form of open label studies, case series and case reports. The Clinical Reference Group recognized that it was unlikely that randomised, double blind, placebo-controlled trials could or would ever be conducted for some of the conditions because of their rarity. Many of the Category 2 conditions come in this latter category. Since a number of these conditions are rare and serious diseases, the Clinical Reference Group considered that they needed to be addressed on a case by case basis with respect to the provision of IVIG.

Evidence for some indications for example, prevention of recurrent spontaneous abortions, was graded highly i.e. graded 1 or 2 because of its scientific rigour. Nevertheless, it was not good enough to support the use of IVIG because it was either inconclusive or conflicting.

The Clinical Reference Group identified two potential new indications - recurrent spontaneous abortions<sup>9-18</sup> and relapsing - remitting multiple sclerosis<sup>19-23</sup>. The evidence supporting the use of IVIG in these conditions is considered currently not strong enough; however, additional studies in these areas might provide the necessary evidence. It is recommended that cost-benefit studies should be carried out for these conditions.

With respect to chronic fatigue syndrome, the evidence<sup>24 -27</sup> for the efficacy of IVIG was conflicting and the Clinical Reference Group was unanimous in not supporting its use for this condition.

## **Prioritisation**

The Working Party recognized that additional supplies of IVIG would be required in order to treat the revised indications. Equally, they recognized that even with an increase in IVIG, situations could arise that would result in a transient shortage of IVIG. To cover this contingency, a prioritisation list was drawn up for use by the Medical Officer at the ARCBS during a period of IVIG shortage.

The Clinical Reference Group considered that prioritisation within a category should not be based simply on the indication since this would not necessarily result in an equitable outcome. It considered that prioritisation should be based on clinical need using the following consensus criteria:

- clinical significance using the level of therapeutic effect of IVIG as judged by improvement of quality of life and/or survival;
- availability of other forms of treatment including a consideration of cost-effectiveness; and
- risks involved with IVIG treatment.

## **RECOMMENDATIONS**

**The Working Party recommends:**

- **The adoption of a national policy for the clinical use of IVIG based on a new categorisation of clinical indications i.e.**
  - **Category 1: Indications for which there is now convincing evidence of benefit.**

- 
- **Category 2: Indications for which currently there is inconclusive evidence of benefit.**
  - **Category 3: Conditions for which there is convincing evidence that IVIG has no benefit.**
  - **That the indications in these categories undergo regular review (on an annual basis) by a Clinical Reference Group to ensure that the therapeutic use of IVIG is kept current.**
  - **That during times of acute shortage, prioritisation of the use of IVIG should be based on clinical need as determined by the following consensus criteria:**
    - **clinical significance using the level of therapeutic effect of IVIG as judged by improvement of quality of life and/or survival;**
    - **availability of other forms of treatment including a consideration of cost-effectiveness; and**
    - **risks involved with IVIG treatment.**
  - **That in order to monitor the impact of the new categorisation and to provide data on indications treated, all requests for IVIG, including requests approved, be recorded by the ARCBS and that the records include:**
    - **Date**
    - **The requesting Medical Officer's name**
    - **The requesting institution**
    - **Clinical indication**
    - **Patient's age/sex**
    - **Amount of IVIG requested**
    - **The amount of IVIG issued (in grams, number of bottles and bottle volume)**
    - **Response to alternative treatments where appropriate**
  - **That further research needs to be undertaken in order to determine cost-effectiveness issues and evaluations of the efficacy of IVIG. The Working Party acknowledged that funding would be required to support the necessary staff (secretarial support and a co-ordinating Research Officer) to carry out this research which could be part of a broader Blood and Blood Products Committee program for plasma.**

## Recommended new IVIG requirements

The Working Party considered that the current quantity of IVIG available for use in Australia should be increased to:

- cover demand generated by the revised clinical indications;
- provide for a contingency stock to off-set the uneven supply caused by both seasonal factors and factors that impact on the production of IVIG; and
- enable clinical trials to be carried out.

The Working Party noted that the Commonwealth government has been involved in discussions relating to the establishment of a National IVIG Reserve to cover national disasters, major accidents or contamination which would materially reduce the supply of the product. This is a separate issue and does not come under the Working Party's Terms of Reference. The National Reserve will be separately funded and have its own criteria for when IVIG from this source can be accessed. It is totally distinct from the contingency stock considered by the Working Party.

An estimation of the annual national quantity of IVIG required to treat the revised indications was made. The Clinical Reference Group provided estimates of the amounts of IVIG required to treat indications in Category 1 (see Table 7). The estimates are based on published Australian data, usual doses and published prevalence and incidence figures and information from the ARCBS. The precise derivations are given in the Appendix 2.

**Table 7: Estimates of the quantities of IVIG required on an annual and national basis for the treatment of Category 1 indications.**

Indication	IVIG (kg)
Primary immunodeficiency syndromes	182
Idiopathic thrombocytopenic purpura	60
Post transfusion purpura	1
Allogeneic bone marrow transplantation	97
Chronic lymphocytic leukaemia	40
Myeloma	67
Kawasaki's disease	4
Chronic inflammatory demyelinating polyneuropathy	133
Guillain-Barre syndrome	56
Multifocal motor neuropathy	51
Other inflammatory myopathies	89
Antibodies to coagulation Factor VIII	20
Miscellaneous haematology disorders	10
<b>TOTAL</b>	<b>810</b>

From Table 7 it can be seen that 810 kg IVIG are required annually to treat the Category 1 indications.

The Working Party considered that the IVIG usage pattern under the new system of categorisation most closely resembles that of Western Australia. Based on this usage pattern, the quantity of IVIG required to treat indications in the new Category 1 represents approximately 90% of the new annual national IVIG requirement. An additional 10% (90 kg) is therefore required to treat Category 2 indications. The figure of 900 kg does not include IVIG to be used for research purposes. Neither does it take into account the amount by which IVIG should be increased each year in order to keep pace with demand; based on data from the USA, this figure stands at 10%.

It should be noted that the Working Party has identified a national requirement of 900 kg IVIG for indications where IVIG is of proven benefit. However, the currently registered CSL product is only registered, on the basis of Product Information approved by the TGA, for primary immunodeficiency syndromes. The proposed new IVIG product from CSL has been clinically trialled in patients with primary immunodeficiency and will be recommended for registration for that indication. Clinical trials for immune thrombocytopenic purpura are still underway and the product's initial registration will not cover this indication.

All the other indications identified as clearly benefiting from the drug are not covered by suitable clinical trials and will not be included in the product's registration. This includes 70% of all the projected use, or 61% of projected use if the immune thrombocytopenic purpura indication achieves registration. This will result in the continuation of the current practice of 'off-label' use, which, although not illegal, is considered by the TGA to be unsatisfactory. The Working Party was advised by the TGA that a possible solution to this problem would be for sponsors (including CSL) to apply for registration of the product under the TGA's Orphan Drug Program with the application being supported by bibliographic submissions where data from full-scale clinical trials are not available. This is a matter to be taken up by the TGA and the Sponsors and falls outside the scope of the Working Party's Terms of Reference.

### **Ensuring the continuity of supply of IVIG**

The Working Party noted that issues of IVIG are restricted by the ARCBS when acute shortages of IVIG occur and that, if very severe, issues are restricted to life-threatening conditions only. As previously noted, acute shortages of IVIG result from a number of factors including those that impact on the production of IVIG.

A number of submissions received by the Working Party commented on the impact the acute shortages had on patients' lives (see extracts in the Appendix 3). It was stated that not only did the shortages affect the treatment received by patients but that the fear of such shortages meant that patients relying on IVIG lived in a state of constant uncertainty.

The Working Party considered that the continuity of supply of IVIG would be achieved by having a contingency stock of IVIG to even out the current uneven supply. by ensuring that there was a sufficient contingency stock of IVIG for use when any adverse factors impacted on the production of IVIG; in this way any unevenness in supply could be evened out. It was considered that a 'one-off' stock equating to three months' supply of IVIG would be sufficient. The rationale for selecting this quantity is that it takes three months to produce a batch of IVIG. The contingency stock would therefore be sufficient for the nation's needs in the event of an IVIG batch-failure. The quantity of IVIG (225 kg) recommended by the Working Party for the contingency stock equates to three months' supply of the projected IVIG requirement of 900 kg.

## **RECOMMENDATIONS**

**The Working Party recommends:**

- **That the amount of IVIG be increased to 900kg (ie. 5.03 kg/100,000 population) in the first year and that this figure be reviewed annually.**
- **That AHMAC endorse that 900 kg (5.03 kg IVIG/100,000 population) is a national target figure.**
- **That there is a contingency stock of IVIG of 225 kg to maintain the consistency of supply of IVIG. This quantity is to be reviewed at the end of the first year.**
- **That the usage of IVIG be reviewed annually to assess the adequacy of the figures.**
- **That estimates of the amounts of IVIG required for research purposes (clinical trials for new indications where there is currently insufficient evidence of efficacy of IVIG) be considered in one year's time. By that time there should be sufficient data available to indicate what the usage requirement is and whether or not it is feasible to factor in an additional amount of IVIG for research purposes.**

## STRATEGIES FOR IMPROVING THE SUPPLY OF IVIG IN AUSTRALIA

The Working Party found that the supply of IVIG in Australia does not meet its current demands and that additional supplies of IVIG of adequate quality, safety and efficacy are required to cover the projected increased demand, a contingency reserve and clinical research. The Working Party conceded that in the first instance, IVIG for research purposes was not a priority.

An increase in IVIG could be achieved by adopting one or more of the following options:

- Option 1:** Increasing the Australian plasma supply by increasing funding required for plasma collection;
- Option 2:** Importing additional IVIG from commercial sources into Australia;
- Option 3:** Importing plasma for local manufacture in Australia;
- Option 4:** Altering the current IVIG : IMIG ratio so as to increase the amount of IVIG produced.

### **Option 1: Increasing Australian plasma for the production of IVIG**

From a national perspective, Option 1 is clearly desirable in order to achieve self-sufficiency in relation to blood products.

The ARCBS has indicated its ability to significantly expand its plasma collection through apheresis if funding is made available. In addition, CSL has indicated that its plasma fractionation plant at Broadmeadows is currently not working at its maximum capacity; it has the capacity to increase output by a further 40%. Lack of manufacturing capacity should not prove an impediment to this option.

Two benefits attach to this option. First, the plasma antibody make-up would reflect local pathogens. Second, procurement of plasma by plasmapheresis would permit restriction of the donor base to a smaller pool of dedicated and well characterised donors that would enhance product safety. However, in

view of the costs associated with plasmapheresis, it is imperative that accurate estimates of current and projected needs are obtained to ensure that resources are allocated appropriately.

The difficulty with this option is that, even if immediate action is taken to implement it and funding is made available, there will be an estimated delay of approximately two years before it is fully operational because of the inherent delays in obtaining additional donors and “gearing up” production. On this basis, Option 1 alone will not address the immediate shortage of IVIG.

## **OPTION 2: IMPORTING ADDITIONAL IVIG FROM COMMERCIAL SOURCES INTO AUSTRALIA**

This option is contrary to Australia’s policy of achieving self-sufficiency in the production of blood products. Nevertheless, it avoids reliance on a single product should problems arise.

There are a number of established products with good safety records on the international market that would be suitable for use in Australia. However, current legislative requirements act as an impediment to them being imported into the country. Appendix 19 of the Australian Guidelines for the Registration of Drugs\* [AGRD] requires that imported products derived from human blood or plasma are registered in the Australian Register of Therapeutic Goods. Such products will only be registered if they “have a demonstrably significant clinical advantage over the local product”. In addition, foreign-sourced blood products must have an Australian sponsor.

At present there is only one registered overseas source of IVIG - *Sandoglobulin*. This product was registered in May 1987. It achieved registration on the basis of its quality (at that time it was considered the ‘gold standard’ for intravenous immunoglobulins) and its efficacy relative to the IVIG manufactured in Australia at that time. Nevertheless, strong clinical representation was required before the Australian Drug Evaluation Committee could be persuaded to register the product.

In recent years the Commonwealth government has acknowledged that from time to time locally produced blood products are subject to “short-term supply

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\* Appendix 19 of the Australian Guidelines for the Registration of Drugs STATES:

Intending sponsors of products derived from human blood or plasma should note that Australia favours national self-sufficiency in products derived from human blood or plasma, believing that a policy of not being reliant on donors in other countries is not only in the national interest but an international responsibility.

Blood products sourced from foreign countries will be registered only if the foreign product has a demonstrably significant clinical advantage over the local product. Intending sponsors of foreign-sourced blood products should discuss their prospects of satisfying this criterion before lodging an application for registration.

and /or quality problems” and that this creates problems for Australia. As a consequence, Appendix 19 of the AGRD was amended to include a new clause (cl 19a) which is intended to cover such eventualities:

From time to time, locally produced blood products are subject to short-term supply and/or quality problems. To cover such contingencies, the Commonwealth wishes to establish a short list of suitable foreign-sourced products that could be imported when the need arises. Sponsors are invited to express interest in having appropriate foreign blood-derived products entered on this 'Blood Product Replacement List'. In case of shortage of registered blood products of adequate quality, the blood product replacement list would assist Australian governments in choosing between available alternatives which could be supplied under special regulatory arrangements (eg s 19a of the Therapeutic Goods Act).

The new clause has the effect of circumventing the need to show that an imported blood product is superior to the equivalent Australian product. Sponsors have been invited to enter the names of foreign blood-derived products on a list – The Blood Product Replacement List. In times of need the list can be used to assist Australian governments in choosing available alternative products, which could be supplied under special regulatory arrangements.

In practice the TGA has experienced great difficulties in inducing companies to participate in the list. There are two main reasons for this. First, for legal and insurance reasons companies are reluctant to submit their products for anything other than full registration. And second, companies are either reluctant or unable to enter into arrangements to provide products on an *ad hoc* emergency basis, without some indication of a commitment by the Australian authorities. The Working Party was advised by the TGA that, in view of the low prevalence of the indications for which registration of IVIG might be sought, the Australian Orphan Drug Program might provide the way for sponsors of overseas products to achieve registration. Prospective sponsors should contact the TGA for further information.

An alternative to increasing the number of overseas sources of IVIG would be to increase the amount of IVIG purchased from Novartis since this is already registered with the TGA. However because of the present bw demand for *Sandoglobulin*, Novartis, quite justifiably, does not maintain a large stock supply in Australia so there would be a time delay associated with obtaining extra product for use in Australia.

If Option 2 were pursued it would be necessary to consider government funding. Funding for *Sandoglobulin* currently comes out of hospital budgets or from individual patients and not the Commonwealth. The current cost of *Sandoglobulin* supplied by Novartis is A\$598.36 for 6 grams. The commercial cost includes the purchase/cost of collection of plasma, production costs, importation costs, contribution to litigation funds and a profit component. It is envisaged that one of the benefits of contracting with Novartis for large quantities of *Sandoglobulin* would be the negotiation of a lower price.

### Option 3: Importing plasma for local manufacture in Australia

This option is also subject to Appendix 19 of the AGRD. If this hurdle were overcome, the time frame involved to increase the supply of IVIG in Australia using this option would be the time required to obtain the necessary funding, find an approved plasma source, purchase sufficient plasma and manufacture product batches (3 months). When the UK authorities elected to suspend the manufacture of plasma derivatives from UK plasma as a result of the CJD problem, the English manufacturer BPL was able to rapidly access plasma from the US commercial apheresis sector and maintain its manufacturing capacity. The cost associated with purchasing and importing plasma remains to be determined and is outside the scope of the current review.

The most important consideration associated with Option 3 is that of safety. Unlike Australia, which has a voluntary blood donation program, the USA and some European countries have paid blood donation programs. In the McKay/Wells Report (1995) [**Commonwealth Review of Australian Blood and Blood Product System**] it was stated that:

Whereas voluntary blood donors tend to come from the more socially responsible and safer living groups in society, paid donors often sell their blood simply because they need the money, and frequently this impoverishment is associated with relatively unsafe lifestyles, including poor nutrition, intravenous drug usage and other potentially increased risks of exposure to infectious diseases. With paid donors there are increased risks that relevant information will be concealed in the donor selection procedures. There is also a much increased chance that blood from a commercial donor in the "window period" for HIV and other infections will pass laboratory screening tests compared with blood from a voluntary unpaid donor.

If this third option is pursued, consideration needs to be given to the plasma Source and to CSL's introduction of improved fractionation technology (chromatography). While there is evidence that markers of bloodborne viruses are more prevalent among paid donors, this difference can be minimised by using only plasma from accredited donors, and donations could be subjected to nucleic acid amplification testing for viruses of particular concern (HCV, HBV). Furthermore, potential risks from window period donors apply to recipients of whole blood and cellular products, not to plasma products which undergo viral inactivation steps.

CSL intends to modify the traditional Cohn fractionation technology for the production of IVIG by adding two chromatography steps late in the process, and has data that this both improves yield of product and increases potential viral clearance. The latter was demonstrated by spiking fractions with virus and measuring their removal. Clinical trials with the new product have demonstrated safety and efficacy in patients with primary immune deficiencies.

Unlike locally sourced plasma, imported plasma will not necessarily contain high titres of antibodies directed at pathogens occurring in Australia.

#### **Option 4: Changing the production ratio of IVIG:IMIG without increasing plasma collection**

This option provides for increased availability of IVIG without having to increase the current quantities of plasma collected in Australia.

For many years the IVIG:IMIG production ratio was 80:20. However, since 1995 a number of States have increased the amount of plasma they collect as part of the Factor VIII enhancement scheme. The additional plasma has been used to source both extra Factor VIII and IVIG rather than IMIG. As a consequence the IVIG:IMIG ratio has changed from 80:20 to 90:10. Therefore, the additional yield of IVIG obtained by altering the IVIG: IMIG production ratio from 90:10 to 95:5 would be small and on its own this option would not ameliorate the supply situation.

Implementation of this strategy will impact on the amount of IMIG available for use in Australia and it is important that its availability for treating Hypogammaglobulinemia and as prophylaxis for acute post Hepatitis A exposure is not compromised. The Working Party therefore considered that it could not recommend this option until Australia's IMIG requirements have been ascertained.

#### **The Working Party's consideration of the various options**

The Working Party concluded that in the long term the best option for increasing supplies of IVIG in Australia would be to at least increase the collection of Australian plasma for the production of IVIG. However, the ARCBS and CSL advised that adoption of this option would not provide for an immediate increase in IVIG. For even if funding were made available, it would take at least two years from that point before the target figure of 900 kg could be attained providing that the ARCBS is able to find suitable donors, the yield of IVIG remains at 3.5 kg / kg plasma and no fractionation problems are experienced. The Working Party considered that until the target figure is achieved, the difference in the target IVIG figure and the amount of IVIG produced in Australia should be made up with IVIG obtained from overseas sources and that sponsors wishing to market imported IVIG in Australia should apply to the TGA to have their products registered under the Orphan Drug Program. The Working Party also recognized that the national requirement for IVIG needs to be reviewed on an annual basis to determine whether the projected requirements are sufficient to meet Australia's demand for IVIG.

#### **Cost of Options 1 and 2**

Under the recent AHMAC-endorsed funding arrangement for whole blood and plasma-based products, the Commonwealth government will assume sole responsibility for funding plasma products and their substitutes, for use in Australia, (irrespective of whether or not they are manufactured in Australia) from the beginning of the financial year 2000/2001.

The Working Party's requirement of 900 kg IVIG equates to a national per capita production figure of 5.03 kg per 100,000 population. In 1998/99 661 kg of IVIG were produced by CSL. In order to meet the projected demand for 900 kg IVIG, an extra 239 kg of IVIG is required. The cost for collecting the requisite quantity of plasma (68,286kg) to produce 239 kg of IVIG is \$13,657,200. This figure is based on the current IVIG yield of 3.5g/kg plasma and a collection cost of \$200 per kilogram of plasma; production costs are not included. Until 2000/01, the cost for collecting the additional plasma will be borne by the Commonwealth and States/Territories under the existing funding arrangements. The cost of an equivalent quantity of imported IVIG is \$23,900,000. This figure is based on the current quoted cost of \$100 per gram for *Sandoglobulin*.

If imported IVIG is used to fill the shortfall between the quantity of IVIG produced by CSL and the new national IVIG target, the cost based on CSL's production figures of 661 kg for 1998/1999 will be \$23,900,000 pa; this will fall over time as the ARCBS provides additional plasma.

The cost of collecting the requisite quantity of plasma (64,286 kg) to produce 225 kg IVIG for a contingency stock is \$12,857,200. This is a 'one -off' cost and is based on an IVIG yield of 3.5g/kg plasma and a plasma collection cost of \$200 per kilogram of plasma. Funding for the collection of additional plasma is to be borne by the States/Territories and Commonwealth on a 50:50 cost-share basis. The equivalent quantity of imported IVIG (*Sandoglobulin*) costs \$22,500,000.

**It should be noted that any agreement to purchase overseas IVIG during the financial year 1999/2000 will be borne jointly by the Commonwealth and the States on a 50:50 cost-share basis. From the beginning of the financial year 2000/2001, the Commonwealth government will be responsible for the full cost.**

## RECOMMENDATIONS

The Working Party recommends that:

- The supply of IVIG be increased through a combination of :
  - Option 1: Increasing the amount of plasma collected within Australia; and
  - Option 2: Increasing the amount of IVIG obtained from overseas sources.

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- In relation to Option 1, a proposal be developed by ARCBS, CSL Limited and the Commonwealth government to implement the production of the additional IVIG.
  - In relation to Option 1, the extra plasma collected should be used for IVIG production. In this way the IVIG: IMIG ratio can be increased without impacting on the current supply of IMIG.
  - In relation to Option 2, suppliers of IVIG on the Australian market are required to submit clinical data or bibliographic submissions in support of their application to register the product for as wide a range of Category 1 indications as possible. This should include, as a minimum, the following indications:
    - Primary Immunodeficiencies
    - Immune thrombocytopenic purpura
    - Chronic inflammatory demyelinating polyneuropathy
    - Guillain-Barre syndrome
    - Inflammatory myopathies

Suppliers should note that the Working Party's strategy for achieving the levels of IVIG described in this report requires that Category 1 indications be supported by the appropriate registration procedure. Suppliers should contact the Therapeutic Goods Administration for information about the Orphan Drug Program and relevant submissions.

- Even if the ultimate aim is to increase the amount of IVIG by increasing the amount of plasma collected in Australia, the difference between the projected IVIG target figure and the quantity of IVIG produced in Australia should, in the short term, be made up with IVIG obtained from overseas sources.
- The cost of any imported IVIG during the financial year 1999/2000 be borne by the Commonwealth and State/Territory governments on a 50:50 cost-share basis. From the beginning of 2000/2001 the cost is to be borne solely by the Commonwealth government.

## **ON GOING MANAGEMENT OF ISSUES RELATING TO THE USE AND SUPPLY OF IVIG**

The Working Party considered that the Commonwealth government should be responsible for the continuing management of the use and supply of IVIG in Australia since, under the new funding arrangements, the Commonwealth will be solely responsible for funding plasma-based products from 2000/2001. In addition, the Working Party considered that the AHMAC Blood and Blood Products Committee should continue to monitor the supply of IVIG on an ongoing basis. This Committee will be responsible for monitoring data collected by the ARCBS relating to plasma collection, IVIG production, indications treated with IVIG and outcome data. It will also be responsible for any relevant policy decisions.

### **RECOMMENDATIONS**

**The Working Party recommends that:**

- **The AHMAC Blood and Blood Products Committee be advised and assisted by a Clinical Reference Group.**
- **The Clinical Reference Group be supported by a secretariat with expertise in research and analysis.**

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## APPENDICES

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## Primary Immunodeficiencies

CONDITION	CATEGORY	EVIDENCE GRADE	STUDY TYPE	PREREQUISITE	REVIEW AND OUTCOME MEASURES
<b>X-linked hypogammaglobulinaemia</b>	1	IV	K Refs:28 - 30; see also 36	Diagnosis	Six-monthly trough IgG levels. Lifelong treatment.
<b>Common variable immunodeficiency</b>	1	IV	K See Ref: 36	Persistent reduction in total IgG	Six-monthly trough IgG levels. Lifelong treatment.
<b>IgG subclass deficiencies</b>	1	IV	J (1); G (3); Refs:31- 33; see also 36	Persistent reduction in IgG subclass levels. Two or more proven bacterial infections pr annum. Failure of antibody response to vaccine antigens. Failure to respond to other therapy.	Six-monthly therapy and review effect on frequency of infections. If good response, prolonged therapy.
<b>Wiskott-Aldrich syndrome</b>	1	IV	K Refs: 34 - 36	Reduction in immunoglobulins or impaired antibody response to vaccine antigens.	IVIg until bone marrow transplantation.

### Appendix 1

### Primary Immunodeficiencies - Appendix 1

\*Not currently treated



## Other Immunological Disorders

CONDITION	CATEGORY	EVIDENCE GRADE	STUDY TYPE	PREREQUISITE	REVIEW AND OUTCOME
<b>Transplantations</b>					
Allogeneic stem cell or bone marrow transplantations	1	II	D (4); B (1) Refs: 37 - 41		
<i>Solid organ transplantations</i>					
Kidney	2	II	D (3); M (1) Refs: 42 - 44, 47		
Liver	2	II	D (1); M (2) Refs: 45 - 47		
Heart/Lung/Pancreas	2	II	M (2) Refs: 48, 49		
Autologous bone marrow transplantations	3	III 2	G (1) Ref: 50		
<b>HIV / AIDS</b>					
Paediatric*	1	III 2 / II	Early: G (1); C(1); C (1) Refs: 51 -53	Late: Recurrent bacterial infections. Hypogammaglobulinaemia. Impaired antibody response.	Six-monthly review.
Adult	2	II	D (2); M (1) Refs: 54 - 56	Thrombocytopenia. Failed corticosteroids / Danazol. Alternative treatment - splenectomy.	Review in six months.



## Other Immunological Disorders

<b>Kawasaki's disease</b>	1	II	L (2); M (1); B (1) Refs: 57 -61	At diagnosis	One dose 2 g/kg. May repeat dose in 24 hours.
<b>Systemic necrotizing vasculitis</b>					
ANCA-positive vasculitis (including Wegener's like disease)	2	IV / III 2	J (1); G (3) Refs: 62 -65	Failed corticosteroids and immunosuppression (including alkylating agents) Major life-threatening disease. Contra-indication to standard therapy (eg. Pregnancy).	Six-month trial. Clinical improvement.
Henoch-Schonlein pupura	2	IV	J (1); G (1) Refs: 66, 67	Failed corticosteroids and immunosuppression (including alkylating agents) Major life-threatening disease. Contra-indication to standard therapy (eg. Pregnancy).	Six-month trial. Clinical improvement.
Churg -Strauss vasculitis	2	IV	J (1) Ref: 68	Failed corticosteroids and immunosuppression (including alkylating agents) Major life-threatening disease. Contra-indication to standard therapy (eg. Pregnancy).	Six-month trial. Clinical improvement.
Systemic lupus erythematosus (SLE)	Motor neuron disease	Motor neuron disease	J (5); G (1) Refs: 69 - 74	Failed corticosteroids and immunosuppression (including alkylating agents) Major life-threatening disease. Contra-indication to standard therapy (eg. Pregnancy).	Six-month trial. Clinical improvement.



## Other Immunological Disorders

<b>Still's disease - Adults</b>	2	IV	J (1); H (1) Refs: 75, 76	Failed corticosteroids and immunosuppression. Major life-threatening disease. Contra-indication to standard therapy.	Six-month trial
<b>Rheumatoid arthritis</b>					
Juvenile	2	III 2 / II	G (5); D(1) Refs: 77 - 82	Failed corticosteroids and immunosuppression. Failed other pharmacological therapy	Review every 6 months
Adult	2	III 2 / II	G (4); pilot D (1) Refs: 83 - 87	Failed corticosteroids and immunosuppression. Major life-threatening disease. Contra-indication to standard therapy.	Six-month trial
<b>Idiopathic inflammatory bowel disease</b>	2	IV/ III 2	H (1); G (3) Refs: 88 - 91	Failed corticosteroids and immunosuppression. Alternative treatment - surgery.	Six month review
Crohn's disease Ulcerative colitis					
<b>Bullous pemphigoid / pemphigus</b>	2	IV	H (2) Ref: 92, 93	Failed corticosteroids; immunosuppression; plasmapheresis	Six month trial



## Neurological Disorders

CONDITION	CATEGORY	EVIDENCE GRADE	STUDY TYPE	PREREQUISITE	REVIEW AND OUTCOME MEASURE
<b>Guillain Barre syndrome</b>	1	II	D (2); C (2) Refs: 94 - 97	IVIG treatment of choice. Plasma exchange an alternative.	One course only. A further course justified only if relapse occurs after initial improvement.
<b>Chronic inflammatory demyelinating polyneuropathy</b>	1	III 2 / II	G (5); E (3); D (2) Refs: 98 - 107	IVIG treatment of choice. Plasma exchange with/without immunosuppression an alternative.	Five day's therapy followed by one day every three weeks. Review at two and three months. Continued IVIG contingent upon objective improvement (MRC Function Scale) at three months. The maintenance dose varies. A single dose (0.4 g/kg) every two to three weeks is usually needed.
<b>Multifocal motor neuropathy with persistent conduction block</b>	1	III2 / II	G (3); D (1) Refs: 108 - 112	IVIG treatment of choice. Cyclophosphamide an alternative treatment.	Five day's therapy followed by one day every three weeks. Review at two and three months. Continued IVIG contingent upon objective improvement (MRC Function Scale) at three months. The maintenance dose varies. A single dose (0.4 g/kg) every two to three weeks is usually needed.
<b>Polymyositis</b>	1	III 2 / II	G (4) Refs: 113 - 115, 119	Failed corticosteroids with/without immunosuppression	Review at two and three months. Continued IVIG contingent upon objective improvement in strength (MRC Function Scale) at three months.



## Neurological Disorders

<b>Dermatomyositis</b>	1	III 2 / II	G (4); D (1) Refs: 113, 115 - 117, 119	Failed corticosteroids with/without immunosuppression	Review at two and three months. Continued IVIG contingent upon objective improvement in strength (MRC Function Scale) at three months.
<b>Polymyositis and systemic connective tissue disease (overlap syndrome)</b>	1	III 2	G ( 2) Refs: 118, 119	Failed corticosteroids with/without immunosuppression	Review at two and three months. Continued IVIG contingent upon objective improvement in strength (MRC Function Scale) at three months.
<b>Myasthenia Gravis</b>	1	III 2	G (3) Refs: 120 - 123	*Failed corticosteroids with immunosuppression and anticholinesterases or *as an alternative to plasma exchange in myasthenic crisis.	*Review at two months. Continued IVIG contingent upon objective improvement in strength. *For patients in crisis one five-day course only indicated.
<b>Lambert-Eaton myasthenic syndrome</b>	1	III 2 / II	G(1); D (1) Ref: 124, 125	Failed treatment for underlying tumour and failed plasma exchange.	Review at three months. Objective evidence of improvement essential for continued supply.
<b>IgM paraproteinaemic neuropathy</b>	1	II	E (1) Ref: 126	* Failed plasma exchange combined with immunosuppression. *Progression to severe disability	Review at three months. Further supply dependent on evidence of clinical improvement..
<b>Childhood epilepsy -Resistant: Rasmussen syndrome; Lennox-Gastaut syndrome; mixed seizures of early onset associated with IgG subclass deficiency</b>	2	IV / III 2	J (1) ; G (1) : D Refs : 127, 128, 128A	Resistant to routine anticonvulsant therapy	Review at three months. Further supply dependent on evidence of improved seizure control.
<b>Opsoclonus myoclonus</b>	2	IV	J (3) Refs: 129 - 131	Failed plasmapheresis and other treatments	Review at one month. Further supply dependant on evidence of clinical improvement.



## Neurological Disorders

<b>Paraneoplastic cerebellar degeneration with Yo antibodies</b>	2	IV/III2	J (1) ; G (1) Refs: 132, 133
<b>Encephalomyelitis and sensory neuropathy with anti HU antibodies</b>	2	III2	G (1) Ref: 133
<b>Myelopathy due to HLTV -1</b>	2	IV	J (1) Ref: 134
<b>Acute idiopathic dysautonomia</b>	2	IV	J (1) Ref: 135
<b>Amyotrophic lateral sclerosis</b>	2	IV / II	H (1); D (1) Refs: 136, 137
<b>Adrenoleukodystrophy</b>	2	IV	J (2) Refs: 138, 139
<b>Autoimmune diabetic neuropathy</b>	2	IV	J (1) Ref: 140
<b>Stiff-man syndrome</b>	2	IV	H (1) Ref: 141
<b>Polyneuropathy of critical illness</b>	3	IV	H (1) Ref: 142
<b>Vogt-Koyanagi-Harada syndrome</b>	3	IV	H (1) Ref: 143
<b>Motor neuron disease</b>	3	IV	K
<b>Multiple sclerosis</b> Chronic progressive	3	III2	G (2) Refs:144, 145
Relapsing-remitting			See page 35



## Haematological Disorders

CONDITION	CATEGORY	EVIDENCE GRADE	STUDY TYPE	PREREQUISITE	REVIEW AND OUTCOME MEASURES
<b>Immune thrombocytopenia</b>					
Idiopathic thrombocytopenic purpura	1	II	Prior to 1998 D; Post 1998 L (1) Ref: 146	Persistent or potentially life-threatening haemorrhage. Unresponsive to corticosteroid treatment or steroids contraindicated.	
Idiopathic thrombocytopenic purpura - antenatal	2	IV	H (1) Ref: 147	Previous history of ITP +/- or affected child. Maternal platelet count of $75 \times 10^9/l$ . Following maternal splenectomy treatment may be necessary at a higher platelet count.	Ongoing throughout pregnancy
Post-transfusion purpura	1	IV	H (2) Refs: 148, 149	Steroids an alternative	
Alloimmune thrombocytopenia antenatal	1	IV/II	H (7); D(1) Refs: 150 -156	To be used in conjunction with corticosteroids	
<b>HIV-associated thrombocytopenia</b>	1	II	D(1); L(1) Refs: 157, 158	Use of corticosteroids is controversial.	
		II			

**Septic thrombocytopenia\***

2

D (1)

Ref: 159

# Haematological Disorders

<b>Chronic lymphocytic leukaemia with hypogammaglobulinaemia and documented recurrent infections</b>	1	II	D (2); E (2); L (1) Refs: 160 - 164	IgG < 6 g/l; Recurrent bacterial infections-significant or life-threatening - more than two in the last 12 months. A single life-threatening relevant infection is also sufficient indication. Consideration should also be given to amelioration of other risk factors for bacterial infection eg. neutropenia.	Review every 6 months.
<b>Acute leukemia in childhood*</b>	1	II	D (1) Ref: 165		
<b>Multiple myeloma</b>	1	II	D (1); E (1) Refs: 166, 167. See also 168	IgG <6g/l (not with IgG myeloma, however); Recurrent bacterial infections - significant or life-threatening- more than two in the previous 6 -12 months. A single life-threatening relevant infection would also be sufficient indication. Consideration should also be given to amelioration of other risk factors for bacterial infection eg. neutropenia.	Review every 6 months
<b>Rhesus D haemolytic disease</b>					
antenatal	2	IV/III2	H (3); G (1) Refs: 169 - 172		Review after course of treatment
<b>Virus associated haemophagic syndrome</b>	2	IV	H (1) Ref: 173		Review after course of treatment

## Haematological Disorders

Autoimmune neutropenia

2

IV

H (2)

Refs:174, 175

Neutrophil count  $<0.8 \times 10^9/l$ .  
Documented evidence of recurrent  
bacterial infections and failure of  
prophylactic antibiotics.

Review after course of treatment



## Haematological Disorders

<b>Allo-immune neutropenia in infancy*</b>	2	IV	H (1) Ref: 175		
<b>Autoantibodies to Factor VIII or Acquired Von Willebrand disease</b>	2	IV	H (5) Refs: 176 - 180	Life threatening haemorrhage. May be used in conjunction with other therapeutic modalities.	Review after course of treatment
<b>Aplastic anaemia / pancytopenia</b>	2	IV	J (2) Refs: 181, 182		Review after course of treatment
<b>Autoimmune haemolytic anaemia (Evans syndrome)</b>	2	IV	J (1); H (1) Refs: 183, 184		Review after course of treatment
<b>Red cell aplasia</b>	2	IV	H (2) Refs:185, 186	Failed corticosteroid therapy. If caused by chronic Parvovirus B 19 infection and accompanied by systemic pathology eg necrotising vasculitis, severe red cell aplasia. Dose 1 g/kg/day for 2 days each month	Review after course of treatment
<b>Haemolytic uraemic syndrome</b>	2	IV	J (1) Ref: 187		
<b>Pure white cell aplasia*</b>	2	IV	J (1) Ref: 188		
<b>Sickle cell anaemia*</b>	2	IV	J (1) Ref: 189		
<b>Neonatal ABO isoimmunisation*</b>	2	IV	J (1) Ref: 190		
<b>Haemolytic transfusion reaction*</b>	2	IV	J (1) Ref: 191		

**Diamond-Blackfan syndrome**

3

IV

J (1); H (1)  
Refs: 192, 193

# Haematological Disorders

CONDITION	CATEGORY	EVIDENCE GRADE	STUDY TYPE	PREREQUISITE	REVIEW AND OUTCOME MEASURE
<b>Asthma</b>	2	IV/III2/II	J (1); G (2); C (2) Refs: 194-198	Failed corticosteroid and immunosuppression	Improvement in lung function tests
<b>Autism - young adults</b>	2	IV	H (1)	Ref: 199	
<b>Grave's ophthalmopathy</b>	2	IV/II	H (1); D (1) Refs: 200, 201	Failed corticosteroid and immunosuppression	
<b>Trauma</b> Burns	3	II	D (1)	Ref: 202	
Paediatric head injury	3	II	D(1)	Ref: 203	



## KEY TO STUDY TYPE:

- A** Systematic review;
- B** Meta-analysis;
- C** Multicentre randomized controlled trial;
- D** Randomized controlled trial;
- E** Randomized controlled cross-over trial;
- F** Non-randomized controlled trial;
- G** Open label study;
- H** Case series;
- J** Case report;
- K** Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees;
- L** Dose comparing study;
- M** Randomized controlled combined treatment trial.





## Appendix 2 : Derivation of the annual quantities of IVIG required to treat Category 1 indications.

Indication	IVIG required (kg)	Source of Data	Reference
Primary immunodeficiency syndromes	182	Published data	K W Baumgart, WJ Britton, A Kemp et al (1997) The Spectrum of Primary Immunodeficiency Disorders in Australia. J Allergy Clin Immunol 100: 415-423.
Idiopathic thrombocytopenic purpura	60	Calculation based on the usual dosage of 400mg/kg/day for 5 days; with repeated dose as necessary and figures obtained from the NSW Branch of the ARCBS. In a four-month period, 88 adults received a total of 6.545 kg and two children received 153g. The data for NSW with a population of 6m was extrapolated to the current national population of 18m.	
Post transfusion purpura	1	Estimate based on previous usage figures obtained from the ARCBS.	
Allogeneic bone marrow transplantation	97	Calculation based on data supplied by the Australian Bone Marrow Transplant Recipient Registry (286 recipients in 1997 and 288 in 1996) and a dose of 400mg/kg/week for 12 weeks as reported in the literature.	
Chronic lymphocytic leukaemia	40	Data provided by NSW Cancer Council. Incidence rate of 3 per 100,000 population. Of these approximately 25% require IVIG. Dosage: 400 mg/kg every 4-6 weeks ( a mean of 5 weeks and a mean body weight of 70 kg used in the calculation).	
Kawasaki's disease	4	Published Data	JA Royle, K Williams, E Elliott, et al (1998) Kawasaki disease in Australia, 1993-95. Arch Dis Child 78: 33-39.
Chronic inflammatory demyelinating polyneuropathy	133	Calculations were based on reported prevalence figures of 400 cases per year. Approximately 70% of these patients will respond and need continuing treatment. Two courses will be required in order to ascertain the third who are non-responders. Patients who respond require continuing maintenance therapy of 0.4g/kg every 3 weeks i.e. 476g every 3 weeks. In addition to the quantity of IVIG required for maintenance treatment an additional amount of IVIG is required for newly presenting patients of which there are approximately 40 per year (0.2 per 100,000) This amounts to 40 x 140 IVIG i.e. 5.6 kg	Relevant reference: Inflammatory Neuropathies. Bailliere's Clinical Neurology. JG McLeod Ed. Bailliere Tindall.

Indication	IVIG required (kg)	Source of Data	Reference
Guillain-Barre syndrome	56	Calculation based on published incidence rate of between 1.5 - 2.0 per 100,000 worldwide and in Australia i.e. 400 cases per year and the usual dosage of 0.4g/kg/day for 5 days. For all but exceptional cases of GBS no repeat course is given.	Relevant reference: Peripheral Neuropathy, Vol 1. 3 <sup>rd</sup> Edition. Dyck, Thomas, Griffin, Low, Poduslo, Eds. WB Saunders, London.
Multifocal motor neuropathy	51	Estimate. This is a rare disease and there are no published prevalence or incidence figures. However, a world authority on inflammatory myopathies, Professor Frank Mastaglia, estimated that there are approximately 70 cases in Australia. The estimated annual quantity of IVIG required to treat this condition was based on this figure and the usual dose of 0.4g/kg every 2 weeks. The calculation was made using a mean body weight of 70 kg.	
Other inflammatory myopathies	89	Estimate. There are no reliable prevalence figures. However, Professor Mastaglia estimates that the prevalence rate is 3-4 per 100,000 so that there are approximately 600 patients in Australia. Most patients are treated with corticosteroids but about 20% require IVIG. These patients are given an initial dose of 2g/kg (mean body weight 70 kg) and then between 84 and 140g per month for 6 months. The calculated figure is a maximum figure since many patients would have recovered after 3-4 months.	
Antibodies to coagulation Factor VIII	20	Estimate based on previous usage figures. Dosage 400 mg/kg/day for 5 days and repeated on a regular basis as required.	
Miscellaneous haematological conditions	10	Estimate based on previous usage figures. Dosage: 400 mg /kg/day for 5 days and repeated on a regular basis as required.	

## SUBMISSIONS

The Working party received Submissions from the following groups/ organisations:

- The Council of GBS/CIDP Support Groups of Australia.
- The Guillain - Barré Syndrome Association of NSW Inc.
- The Guillain - Barré Syndrome Support Group of Tasmania.
- The IN Group (The Inflammatory Neuropathy Support Group of Victoria Inc).
- KIDS Foundation of Australia.
- Novartis Pharmaceuticals Australia Pty Ltd
- gbs.org.inc. (an Internet support group for people around the world who suffer from GBS and other related ailments such as CIDP).

## **QUOTES TAKEN FROM SUBMISSIONS RECEIVED BY THE WORKING PARTY:**

...We have members of our Organisation who rely heavily on this treatment for their day to day wellbeing; their ability to function, their ability to even walk. Please take account how insecure these people feel, not knowing whether their next treatment is going to be available, or, if so, how much will be administered. How they suffer from the loss of muscle strength and/or loss of feeling, which once lost can take months to regain. This would have an effect on not only their ability to remain in paid employment or the possibility of returning into the workforce but also being able to care for their families. It is very frightening for them to be faced with the prospect of losing these attributes and to have to face months of recovery to regain them, just because IVIG is not available to them. This creates a very scary and insecure life for these people.

***Per: Jan Ayres, Secretary of the Guillain-Barré Syndrome Association of NSW Inc.***

...I received Intragam 3-weekly then 2-weekly until approximately September 1997. From that time on, my treatments were extended to 3 weeks, 4 weeks, 5 weeks, until 2<sup>nd</sup> February 1998. Due to the shortage of the product at this time and the fact CIPD patients were in Category B, I received no more Intragam until the end of July 1998. During this time my condition worsened...

***Per: Jan Ayres, Secretary of the Guillain-Barré Syndrome Association of NSW Inc.***

...I cannot emphasise enough how important it has become for my body to receive IVIG, and for me to receive 18 grams (instead of 12 grams) per fortnight, the difference means having a more normal, pain free and mobile life...

***Per: Rosemary McQualter – submission received from the Council of GBS & CIPD Support Groups of Australia***

...As I write this, there are patients here in Victoria who have been refused their IVIG in the last few months, and/or have had their dose of IVIG reduced. This has led to them suffering even more than usual with poor health ...

***Per: Ruth Taylor, President, KID'S Foundation of Australia***

...people like me, who have CIPD, are tired of hearing about shortages and rationing. We need this stuff to have any chance at a somewhat normal life. I am able to work full time (after being an invalid for the last four months of 1997) and support my family thanks to the IVIG treatments I've been getting approximately monthly for the past year and a half. The inevitable relapse that would occur if not for these treatments would most likely land me back in the hospitals, for who knows how long, and my prognosis would be for a recovery to a lesser state of functionality than I now enjoy due to the well-known progressive axonal damage that occurs with repeated episodes of demyelination & remyelination...

***Per: John Lorentz, gbs.org.inc***

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## GLOSSARY

### **Antibodies:**

Proteins produced by B lymphocytes (a type of white blood cell) and plasma cells in response to a foreign molecule or invading organism (an antigen). Antibodies defend the body against infection by inactivating viruses and bacterial toxins and by recruiting the complement system and various other types of white blood cells to kill extracellular microorganisms and larger parasites. An antibody molecule is composed of two identical light chains (each containing about 220 amino acids) and two identical heavy chains (each containing about 440 amino acids). The heavy chains of antibodies differ and, based on the difference in the heavy chains, antibodies have been classified into five classes: IgA, IgD, IgE, IgG and IgM.

### **Antiglobulin test** (also known as Coombs' test):

A test for the presence of antibodies that coat and damage red blood cells. The test can be used to diagnose and screen for autoimmune haemolytic anaemias as well as determine the compatibility of blood types.

### **Apheresis:**

A procedure in which blood is temporarily withdrawn, one or more components are selectively removed, and the remainder of the blood is reinfused back into the donor.

### **Autoimmune:**

Pertaining to the development of an auto-immune response to one's own tissues – departure from usual recognition of self and non-self by the immune system contributing to a variety of diseases.

### **Aseptic meningitis syndrome:**

An inflammation of the meninges (three membranes that surround the brain and spinal cord) that is caused by one of a number of viruses eg. Coxsackievirus, non-paralytic poliovirus, echo virus and mumps.

### **Cardiovascular:**

Pertaining to heart and blood vessels.

### **Dermatomyositis:**

Disease of the connective tissues, characterised by pruritic or eczematous inflammation of the skin and tenderness and weakness of the muscle. Muscle tissue is damaged, and loss may be so severe that a person may become unable to walk or perform simple tasks.

### **Efficacy:**

The maximum ability of a drug/treatment to produce a result, regardless of dosage.

### **Fractionation:**

The separation of a substance into its basic constituents.

### **Guillain-Barré syndrome:**

An idiopathic, peripheral polyneuritis occurring between one and three weeks after a mild

episode of fever associated with a viral infection or with immunisation. Symmetric pain and weakness affect the extremities and paralysis may develop. The neuritis may spread, ascending to the trunk and involving the face, arms and thoracic muscles. The course of the disease is variable but is usually associated with recovery.

**Haemolysis** (of red blood cells):

The early breakdown of red blood cells and the release of haemoglobin that normally occurs at the end of the life span of a red blood cell. Haemolysis may occur in antigen/antibody reactions.

**Hypogammaglobulinaemia:**

A condition of immunologic deficiency marked by abnormally low levels, or the virtual absence, of immunoglobulins in the blood causing increased susceptibility to infectious diseases, especially bacterial.

**Idiopathic thrombocytopenic purpura:**

A deficiency in platelets that results in bleeding into the skin and other organs.

**IgG aggregates:**

The joining together (polymerisation) of individual IgG molecules (monomers) into polymers or aggregates.

**IgG class of antibodies:**

The major class of antibodies having a  $\gamma$  heavy chain.

**Immunodeficiency:**

Any deficiency in the capacity to respond immunologically, generally characterised by susceptibility to infectious diseases.

**Immunoglobulins** (abbreviated as Ig):

Antibodies are collectively called immunoglobulins.

**Intramuscular** (administration):

Pertaining to the interior of the muscle tissue. Intramuscular injection – the introduction of a hypodermic needle into muscle to administer medication.

**Isotonic solution** (isotonicity):

A solution which has the same concentration of solute particles as another solution, and hence exerts the same amount of osmotic pressure. For example, isotonic saline is a salt solution that contains an amount of salt equal to that found in the body fluids. Isotonicity is dependent on the nature of the salt solution; it depends only on the concentration of the dissolved particles.

**Kawasaki - Mucocutaneous lymph node syndrome:**

An acute febrile illness, primarily of young children, characterised by inflammation of mucous membranes of the mouth, 'strawberry tongue', cervical lymphadenopathy, polymorphous rash on the trunks and trunk and oedema, erythema and desquamation of the skin on the extremities. Often associated with cardiac involvement.

**Monomeric suspensions** (of IgG):

Monomers are molecules that are capable of joining together to produce a repeating chain (a polymer). A monomeric suspension of IgG is one in which the individual antibodies, which have the potential to polymerise or aggregate, remain in suspension as individual molecules.

**Multiple myeloma:**

A malignant neoplasm of the bone marrow. The tumour, which is composed of plasma cells, destroys osseous tissue especially in the vertebrae, pelvis, long bones and skull, causing pain, fractures, hypercalcaemia and skeletal deformities.

**Muscle proteases:**

Enzymes present in the muscle that catalyse the breakdown of proteins into amino acids by cleaving the peptide bonds.

**Myalgia:**

Diffuse muscle pain.

**Neutropenia:**

An abnormal decrease in the number of neutrophils in the blood. The decrease, which may be relative or absolute, is associated with a variety of diseases including acute leukaemia, infection, vitamin B12 deficiency or certain chemotherapeutic drugs.

**Pathogen** (adjective – pathogenic):

An organism or other agent that causes diseases.

**Pharmacokinetics:**

The study of the action of drugs within the body, including the routes and mechanisms of absorption, distribution, excretion and metabolism.

**Plasmapheresis:**

Removal of plasma from withdrawn blood by centrifugation, the reconstitution of the cellular elements in an isotonic solution, and the reinfusion of this solution back into the donor.

**Polymyositis:**

Inflammation of many muscles, usually associated with muscle pain, tenderness and weakness.

**Subcutaneous** (administration):

Pertaining to beneath the skin. Subcutaneous injection – introduction of a needle into subcutaneous tissue beneath the skin in order to administer a medication.

**Systemic necrotising vasculitis:**

Inflammatory condition of the blood vessels, characterised by necrosis, fibrosis and proliferation of the layers of the vascular wall, in some cases resulting in occlusion and infarction. Usually treated with corticosteroids and immunosuppression.

**Tachycardia:**

A condition in which the heart (myocardium) contracts at a rate greater than 100 beats per minute. Pathologic tachycardia accompanies low oxygen levels associated with anaemia, congestive heart failure, haemorrhage or shock.

**Thrombocytopenia:**

Reduction in the number of platelets, which may be due to a decrease in production of platelets, decreased survival of platelets or increased consumption of platelets. Thrombocytopenia is one of the most common causes of bleeding disorders.

**Thrombophlebitis:**

Inflammation of a vein associated with thrombosis (a clot or coagulation within a blood vessel).

**Vasomotor:**

Pertaining to the nerves and muscles that control the diameter of the lumen of blood vessels. The muscle fibres of arteries can contract, causing vasoconstriction, or relax, causing vasodilatation.

**Viral inactivation:**

Inactivation of a virus to render it non-infectious.

**Virus:**

Particle consisting of nucleic acid (RNA or DNA) enclosed in a protein coat and capable of replicating within a host cell and spreading from cell to cell. Often the cause of disease.

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