Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Immunoglobulin – normal (human)

Proprietary Product Name: Intratect

Sponsor: Link Medical Products P/L

March 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	3 February 2011
Active ingredient(s):	Immunoglobulin – normal (human)
Product Name(s):	Intratect
Sponsor's Name and Address:	Link Medical Products Pty Ltd 18/6A Prosperity Parade, Warriewood NSW 2102
Dose form(s):	Solution
Strength(s):	1 g/20 mL, 2.5 g/50mL, 5 g/100 mL and 10 g/200 mL (50g/L)
Container(s):	vial
Pack size(s):	1 vial/ box
Approved Therapeutic use:	-Replacement therapy in primary immunodeficiency syndromes (congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiencies and Wiscott-Aldrich syndrome), myeloma or chronic lymphocytic leukemia with severe secondary hypogammaglobulinaemia and recurrent infections and for children with congenital AIDS[1] who have repeated bacterial infections. Immunomodulatory effect in idiopathic thrombocytopenic purpura, in adults or children with high risk of bleeding or prior surgery to correct platelet count, Guillain-Barré syndrome, Kawasaki disease or allogenic bone marrow transplant.
Route(s) of administration:	Intravenous (IV)
Dosage:	The dosage strength and intervals depend on the intended use (substitution or anaphylaxis) and patient's age and disease. Summary of the dosage recommendations for the different indications are listed in the Product Information (see Attachment 1).
ARTG Number (s)	164548, 164549, 164550 and 164551

Product Background

Intratect is a polyclonal human immunoglobulin preparation for IV use, using active material from two manufacturers. The product is virus-inactivated using tri-n-butyl phosphate (TNBP) and polysorbate 80, a two step viral inactivation procedure which is now considered standard (CPMP/BWP/269/95[2]). The proposed formulation, which contains glycine as a stabiliser, is similar to some other registered human normal immunoglobulin products.

[1] Aquired Immune Deficiency Syndrome

[2] http://www.tga.gov.au/docs/pdf/euguide/bwp/026995r3en.pdf. Note for guidance on plasma-derived medicinal

Regulatory Status

Intratect was first registered in Germany in 2004 and has been approved under mutual recognition procedures in other EU countries; Austria, Cyprus, Greece, Hungary, Ireland, Italy, Netherlands, Poland, UK. Outside EU it is registered in Columbia, India, Iran, Jordan, Russian Federation, Switzerland and Tunisia.

The product is under evaluation status in Belgium, Saudi Arabia and Thailand.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Introduction

Intratect is a clear to slightly opalescent and colourless to pale yellow solution. It contains 50g/L human plasma protein with ≥ 96% IgG (IgG1 57%, IgG2 37%, IgG 3%, IgG4 3%) and maximum of 2mg/mL of IgA from human blood/plasma donors. It also contains the excipients glycine, sodium hydroxide, hydrochloric acid and Water for Injection. Intratect is presented in 20mL, 50mL, 100mL and 200mL glass vials for intravenous (IV) administration. Intratect complies with the European Pharmacopeia (PhEur.) Monograph 0918 on *Human normal immunoglobulin for intravenous administration* and *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration* (CPMP/BPWG/388/95, rev.1)[3].

Drug Substance (active ingredient)

Structure

Intratect is composed of human immunoglobulin G (IgG) protein with a molecular weight of 150 000 Dalton. Amino acid sequences of the N-terminal part of the heavy and light chains (the Fab part of immunoglobulin G) are variable which provides the different specificities for different antigens. The Fc fragment is important for complement activation and Fc receptor interactions.

Manufacturing process

Intratect manufacturing process involves the use of cold ethanol for plasma fractionation to isolate the crude immunoglobulin containing fraction II which is subsequently virus inactivated and further purified to the drug substances.

Physical and Chemical Properties

Intratect contains a mixture of different immunoglobulin classes. It contains all four subclasses of human normal IgG in relative concentrations corresponding to their concentration in human normal plasma. Testing of the biological characteristics and activities of batches of Intratect drug product was performed in accordance with the *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration,* CPMP/BPWG/388/95, rev.1.

Impurities arising from the source material (human plasma) and routinely investigated at release of the drug substance are those which are required according to the PhEur. Monograph 0918 on *Human normal immunoglobulin for intravenous administration.*

products. Revision 3.

[3] www.tga.gov.au/docs/pdf/euguide/bwp/026995r3en.pdf

Impurities arising from the manufacturing process have been investigated and all except those that are found at limits below detection levels or at very low levels, are routinely tested.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use were included. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time conditions (2-8°C) to characterise the stability/degradation profile of the substance and to establish a shelf life of 2 years. The stability results demonstrated a decrease in antibodies to hepatitis B surface antigen (HBs) (19%) and streptolysin-O-antibody titre (17%) after 24 months storage. Most of the decline in both antibodies levels' occurred within the first 3-6 months storage; however, they remained within specifications during the remaining period of the study. All the other tested parameters were within specifications when stored at 2-8°C for 24 months. The provided real time data submitted supports the proposed shelf life of 24 months.

Drug Product

Formulation(s)

Intratect is provided as an electrolyte-poor and isotonic infusion solution containing human normal immunoglobulin for IV administration. The product contains the excipients glycine, sodium hydroxide, hydrochloric acid and Water for Injection.

Glycine is tested according to the PhEur and its properties are well defined and have been used in other pharmaceutical products. Water for Injection is also tested according to the PhEur and it is used as a vehicle for the preparation of medicines for parenteral administration.

Manufacture

The product is formulated by the addition of Water for Injections to the required protein specification and glycine is added to the required limit specified in the final product.

There are two different production procedures for the final product used depending of the size of the fill pool. Then the final product is filled into the final container through a filter, quality control tested, labelled and packaged with the approved package insert.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were included. The dossier indicates that Intratect specifications comply with the PhEur monograph 0918 *Human normal immunoglobulin for intravenous administration.* Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under accelerated and real time conditions to characterise the stability profile of the product. The proposed shelf life is 24 months when stored at 25±2°C (for details see above). Stability batches stored at 4ºC were also within the specified limits with a slight decrease in the Anti-HBs and Anti-stereptolysin-O-antibodies level.

Sterility

Following correspondence with the sponsor, all sterility issues were resolved.

Container safety

The primary container of the drug product is a 20, 50, 100 or 200mL Type II glass vial, enclosed with a bromobutyl rubber stopper and aluminium cap with a polypropylene flip-off canter portion. The provided information was sufficient to demonstrate material safety compliance for the final container.

Viral safety

All viral/prion safety issues have been addressed. None of the excipients used in the manufacturing process are of animal origin. In summary, the virus safety of Intratect was investigated by stepwise validation of selected steps of the manufacturing process.

Bioavailability

Biopharmaceutic data are not required for this product because the product is a liquid for intravenous injection.

Quality Summary and Conclusions

The quality data submitted in support of this application including the manufacturing, specifications, stability, container safety, sterility, endotoxin, viral safety and labels have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

Issues of concern

A number of deficiencies and issues requiring resolution before the product could be recommended for approval were identified during the quality evaluation and these were referred to the applicant for comment or resolution before registration.

III. Nonclinical Findings

Introduction

Immunoglobulins are normal constituents of the human body. Single dose toxicity testing in animals is of limited relevance since high doses result in overloading and repeat dose testing and embryo-fetal toxicity studies are impractical due to induction of antibodies in animals. Primary pharmacology was tested *in vitro* in terms of binding to bacteria, viruses, fungi and protozoa and IgG Fc part activity. The nonclinical safety testing was limited to a single combined safety pharmacology – acute toxicity study in beagle dogs. This Good Laboratory Practice (GLP) compliant study used a small but adequate number of animals and endpoints. Intraglobin CP, which is registered in Germany but not in Australia, was used as a comparator.

The limited number of studies with the complete Intratect product is acceptable as animal studies have practical limitations. The use of immunoglobulins also has a long clinical history and the proposed formulation is similar to other registered immunoglobulin products.

Some 46 published references were submitted with the current Australian submission. The majority of these references were not evaluated by the TGA as most were review articles, many were of clinical relevance and/or they were published 10 or more years ago. Papers considered to impact on the safety of the product, the toxicity of immunoglobulin, tri-n-butyl phosphate (TNBP) or polysorbate 80 are discussed in relevant sections of this evaluation.

Pharmacology

The general safety and efficacy of human immunoglobulins have been established by their history of clinical use. *In vitro* testing for binding to bacteria, viruses, fungi and protozoa as well as the IgG Fc activity (complement fixation, phagocytosis testing and opsonisation) in the sponsor's product demonstrated the functional integrity of the IgG.

Pharmacokinetics

No nonclinical pharmacokinetic studies have been conducted. The plasma half-life in animals is usually considerably shorter than that in humans (hours to days in animals compared to approximately 4 weeks in humans) and such studies are therefore of limited predictive value. The absorption, distribution, metabolism (protein degradation) and excretion pathways for immunoglobulins are also well described in humans. Therefore, the lack of animal pharmacokinetic studies is considered acceptable since clinical studies are more relevant for this type of product.

Toxicology

Acute toxicity

A combination safety pharmacology – acute toxicity study was conducted in un-anaesthetised dogs using a very similar formulation to that proposed for registration. The comparator is manufactured without the nanometre filtration step. This step was introduced late in the development as an additional virus removing step. The sponsor states that it has no other impact on product quality. This study is therefore considered acceptable as a test of the acute toxicity of Intratect.

The dose administered to dogs (4.8 mL/kg infused as 0.6 mL/kg/minute) was lower than that anticipated in patients. This constraint was dictated by the requirement to keep the infusion period brief in un-anesthetised animals and that large infusion volumes could increase the blood volume and thereby alter the circulatory and respiratory functions of the animals..

There were no signs of severe systemic intolerance (no changes in respiratory rate or body temperature were noted) in any of the treatment groups. Treatment did not affect the blood pressure in dogs. However, heart rate was markedly increased by 30-40% by Intratect and Intraglobin CP for a short period of about 10 minutes following the infusion. The reason for this increase only in IgG-treated dogs and not in dogs in the control group[4] is uncertain and is difficult to explain on physiological or pharmacological factors but may have been due to stress. An increase in heart rate has not been associated with Intratect administration in humans (according to the proposed Australian PI document).

The liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH)) of the dogs showed slight to moderate increases when compared to controls, however the group mean values were influenced by "outlier values" for two dogs and the increases were less marked when compared with pre-treatment values. No increases in liver enzyme measurements were detected in Intratect human clinical trials.

In dogs, the leukocyte and platelet counts were reversibly reduced and the ratio of lymphocytes to segmented neutrophil granulocytes was shifted (reversibly) towards lymphocytes in the first day after Intratect and Intraglobin CP treatment. No thrombo-embolic events as a possible cause of the increased leukocyte and platelet turnover were noted at post-mortem. Although very rare, thromboembolic reactions have occurred with treatment of humans and a cautionary statement has been included in the proposed Australian

[4] Dogs in the control group where infused with 0.9% saline at the same rate (0.6 mL/kg/minute) as Intratect was infused in the treated group dogs.

PI document (under *Precautions*). Reductions in total leukocyte counts were also reported in human clinical studies with Intratect. The effects in beagle dogs may also reflect the interaction of human (Gal) antibodies with antigenic structures present in dogs (Gal antigen) which may lead to complement activation and cell destruction. IgG-antibody-antigen complexes may also cause platelet activation via a receptor mediated action. The Fc[5] receptor is also present in monocytes, macrophages, lymphocytes as well as in neutrophilic and eosinophilic granulocytes. In the case of thrombocytes, this could lead to increased sequestration or destruction in the reticulo-endothelial system. The fall in leucocytes points to an increased utilisation of these cells. This is however unlikely to occur in humans who have no Gal antigen. Humans also lack the platelet C3b receptor but instead have a Fcγ R-II receptor which is missing from blood platelets in non-primates. The low human concern is further strengthened by the fact that a similar product had similar effects in this animal model.

Genotoxicity

There is no mutagenic potential indicated by immunoglobulin molecules in general. Genotoxicity have been linked to TNBP and polysorbate 80 but only at high concentrations. Concern for humans is low at the proposed concentrations of TNBP and polysorbate 80 in the proposed formulation.

Carcinogenicity

No studies have been conducted. This is considered acceptable in view of the type of product.

Both TNBP and polysorbate 80 at very high concentrations have been linked to neoplasm formations in rodents and polysorbate 80 has been shown to stimulate DNA synthesis which could enhance the activity of other chemical carcinogens[6]. Since the concentrations proposed for this product are much lower than those used in these animal studies, concern for humans is low.

Toxicity of TNBP and polysorbate 80

The toxicity of the solvent and the detergent, TNBP and polysorbate 80, used for the two-step viral inactivation procedure have been investigated in a series of studies[7], in a range of species[8] and have been assessed by the TGA previously.

The maximum doses of TNBP and polysorbate 80 that may be associated with IV administration of Intratect in the treatment of humans have been calculated below:

Maximum residual amount per mL product = 0.8 mg TNBP and 60 mg polysorbate 80.

Maximum administered amount (therapeutic administration to humans):

With single doses:

2 g of IV IgG/kg BW (Kawasaki syndrome) = 2.8 L of Intratect/70 kg patient (within 1 day) =32 mg TNBP and 2400 mg polysorbate 80/kg.

[5] Fc receptors are present on a variety of cells and bind the fc fragment of immunoglobulins.

[6] Final report on the safety assessment of Polysorbates 20, 21, 40, 60, 61, 65, 80, 81 and 85. *Journal of the American College of Toxicology* 1984, 3 (5):1-82.

[7] Including genotoxicity, carcinogenicity, reproductive toxicity and local tolerance studies.

[8] Registry of Toxic effects of chemical substances, National Institute for Occupational Safety and Health, Cincinnati, USA; Hazardous Substances data Bank, US National Library of Medicine, Bethesda, USA and Chemtox Online Resource Consultants Inc., Brentwood, USA

With multiple doses:

0.8 g IV IgG/kg/month (substitution therapy) = 1.2 L Intratect/administration to 70 kg person = 12.8 mg of TNBP and 960 mg polysorbate 80/kg.

Although the intended doses will vary with the indication and the patient response, maximum daily exposure to TNBP and/or polysorbate 80 is similar or slightly higher than other products registered in Australia. Experiments in rats subjected to IV administration of the product showed that the [9]LD_{lo} is equivalent to 100 mg of TNBP/kg and the 50% lethal dose (LD_{50}) is 1790 mg polysorbate 80/kg. The safety margins relative to the maximum clinical doses are equivalent to a factor of 500 for TNBP and a factor of 121 for polysorbate 80 (dose adjusted for body surface area, BSA). The LD_{lo} following IV administration in dogs (500 mg polysorbate/kg) is 112-fold higher than that expected in the clinic (based on dose adjusted for body surface area (BSA)).

These pharmacological and toxicological considerations based on animal experiments indicate that for a patient with a bodyweight of 70 kg, a single dose of 2.8 L Intratect (corresponding to 2 g IgG/kg) or multiple doses of 1.2 L/day for a few days or at intervals of 3-4 weeks life-long (corresponding to 0.8 g IgG/kg), should not present a toxicological concern.

Local tolerance

The safety pharmacology and acute toxicity study in dogs examined Intratect infusion sites histologically. The local tolerance noted in this study was considered to be within acceptable limits.

Studies with TNBP and polysorbate 80 have shown eye and/or skin irritation but only at concentrations much higher than those proposed for this product. These findings are therefore not of concern for human administration.

Nonclinical Summary and Conclusions

- One combined safety pharmacology/acute toxicity study conducted in unanaesthetised dogs and 46 published references were submitted in support of the current Australian application. The sponsor provided adequate justification for the limited nonclinical testing noting that animal studies using human immunoglobulins have practical limitations in terms of maximum feasible infusion volumes and immune responses to the heterologous IgG.
- Primary pharmacology studies *in vitro* showed normal IgG activity.
- The safety pharmacology/acute toxicity study in dogs showed transient and marked increases in heart rate. Blood pressure, respiration rate and body temperature were however unaffected. Blood leukocyte and platelet counts were reduced and liver enzymes showed slight to moderate increases but all had returned to normal 14 days post-infusion. These characteristic responses raise no safety concerns for humans. Infusion site histology in dogs showed acceptable local tolerance.
- Intratect is virus inactivated using TNBP and polysorbate 80 according to the procedures used for other registered products and recommended in CPMP/BWP/269/95. The potential for toxicity or local irritation due to these two compounds, at respective levels of less than 0.8 µg and 60 µg/mL contained in the final product, is minimal.

[9] LD_{lo}=lowest lethal dose (the lowest dose, other than LD_{50} of a substance introduced by any route, other than inhalation, over any given period of time in one or more divided portions and reported to have caused death in humans or animals).

- Published toxicity data indicated that the proposed limits for the residual virus inactivating agents TNBP and polysorbate 80 in the finished product are acceptable.
- The nonclinical data raise no objections to the registration of Intratect (human normal immunoglobulin) for the proposed indications, however in view of the practical limitations of nonclinical testing, demonstration of safety and efficacy will depend mainly on clinical data.

IV. Clinical Findings

Introduction

Clinical trials included two completed Phase III open label studies: Study 941 was performed on patients with primary immunodeficiency disease (PID) and Study 942 was performed on patients with immune idiopathic thrombocytopenic purpura (ITP). Information on safety and efficacy was available from both studies.

Clinical Studies

Study 941 was a multi-centre, open, prospective Phase III study investigating clinical efficacy, safety and pharmacokinetic properties of the human normal immunoglobulin for IV administration BT 681 (similar to the proposed product, Intratect) with intra-individual comparisons to previous standard treatment in patients with PID. The study was conducted in Germany between July 2000 and May 2001. Subjects were aged between 6 and 35 years (mean age was 19.2 years) with PID and established replacement therapy. Some 12 of 17 patients were male. A total of 17 patients were included in the ITT analysis and 16 patients in the analysis of pharmacokinetic properties. The average time from PID diagnosis was 7.2 years prior to the study. Brochiectasis was the most common concomitant disease and was present in 7/17 patients. Subjects received 5 g/100 ml of BT 681at a dose of 400 mg/kg body weight (bw) every 3 - 4 weeks as an IV infusion. [The established IVIg (Octagam) dosage and interval over the previous 6 months were maintained.] A total of 113 infusions of BT 681were administered; 16/17 patients received 7 or 8 infusions of BT681. The mean duration was 23.9 weeks from first BT 681 infusion to closing visit. The mean dose was between 455 mg /kg body weight (bw) and 530 mg/kg bw and similar to that reported for the 6 months prior to the study (469 +/- 148 mg/kg bw).

Efficacy criteria for evaluation included infection rate (new acute and relevant infections), use of antibiotics (number of occasions for treatment) and number of days with fever > 38 degrees C. Safety criteria for evaluation included number of adverse events (including laboratory parameters). Pharmacokinetic criteria included maximum plasma concentration (C_{max}), time of maximum plasma concentration (t_{max}), elimination half-life ($t_{1/2el}$) and area under the plasma concentration time curve (AUC) for serum concentration of IgG, number of trough levels below 6 g/l and serum concentration of the IgG subclasses. Statistical analysis was limited to descriptive statistical methods.

Study 942 was an open, prospective Phase III study investigating clinical efficacy and safety of BT 681 comparing historical data with reference IVIg in patients with ITP. This study was conducted in Yugoslavia between August 2000 and January 2001. Subjects were aged between 18 and 70 years with chronic ITP and a platelet count of about 20/nl. A total of 24 patients were included in the ITT analysis; 15 in the 2-day treatment group and 9 in the 5-day treatment group. Mean time since ITP diagnosis was 6.7 years. 54% of patients had previous ITP episodes documented. Patients received either 1 g/kg bw per day (in the 2-day group) or 0.4 g/kg per day (in the 5-day group), giving a total dose of 2 g/kg for the entire treatment course for all patients. A total of 75 infusions were administered and the mean duration of

study was 28.8 days. Efficacy criteria for evaluation included platelet response defined as platelet count >50/nl, regression of haemorrhages, duration of platelet response, time course of platelet count, time to platelet response and maximum/time to maximum platelet count. Safety criteria included number of adverse events and laboratory parameters and vital signs. Statistical analysis was limited to descriptive statistical methods.

Pharmacokinetics

Requirements for information on clinical pharmacology are discussed in the "Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)" (CPMP/BPWG/388/95, 2000). There is no requirement for comparative pharmacokinetics in healthy subjects for ethical reasons. The Note for Guidance requires that pharmacokinetic parameters should be studied in 15 patients with primary immunodeficiency syndromes and possibly in myeloma or chronic lymphocytic leukemia with severe secondary hypogammaglobulinaemia and recurrent infections. Patients may already be stabilised on treatment. Pharmacokinetics should be assessed over a period of 6 months and no cross-over study is necessary. Pharmacokinetics should include trough levels and treatment intervals, with values being comparable to those following treatment with the previous product.

Study 941 was conducted in accordance with the Note for Guidance mentioned above and provided the required pharmacokinetic data. This included C_{max}, t_{max}, elimination t ½, AUC for serum concentration of IgG, number of trough levels below 6 g/l and serum concentration of each of the four IgG subclasses. The pharmacokinetic evaluation revealed a mean elimination $t_{1/2}$ of 27 +/- 11 days (Table 1). This compares favourably with the mean elimination $t_{1/2}$ of approximately 4 weeks for natural IgG. The proportion of IgG subclasses remained almost unchanged after the first infusion (Figure 1). The mean dose of Intratect was approximately 450 mg/kg body weight. There was an increase in the mean serum concentration of IgG by approximately 900 mg/dl after each infusion. Only 17/112 (15.2%) trough levels were below 6 g/l during the study. This can be compared to 39/115 trough levels prior to the study (33.9% (Table 2). In comparison with pharmacokinetic information contained in the literature, Intratect was noted to be similar to other IVIg.

Table 1. Standard pharmacokinetic parameters.

		N	MEAN	SD	MIN	MEDIAN	MAX
max. concentration C max [mg/dl]	total, n=16	16	1643.1	320.04	1150.0	1620.0	2420.0
	centre 1, n=12	12	1571.7	261.74	1150.0	1575.0	1920.0
	centre 2, n=4	4	1857.5	423.35	1440.0	1785.0	2420.0
time of first max. conc. t max [days]	total, n=16	16	0.29	0.28	0.17	0.17	1.00
	centre 1, n=12	12	0.33	0.32	0.17	0.17	1.00
	centre 2, n=4	4	0.17	0.00	0.17	0.17	0.17
elimin. half life t 1/2 [days]	total, n=16	16	27.24	10.74	11.13	26.93	52.51
	centre 1, n=12	12	28.25	10.88	11.13	27.84	52.51
	centre 2, n=4	4	24.21	11.23	15.10	20.96	39.84
area under the curve AUC [days*mg/dl]	total, n=16	16	26943	9721.7	12707	25729	56789
	centre 1, n=12	12	25562	5714.3	12707	25729	34542
	centre 2, n=4	4	31086	17953	16958	25298	56789

Figure 1. Distribution of IgG subclasses before and after the first infusion of Intratect. (the number of patients was between 15 and 17).

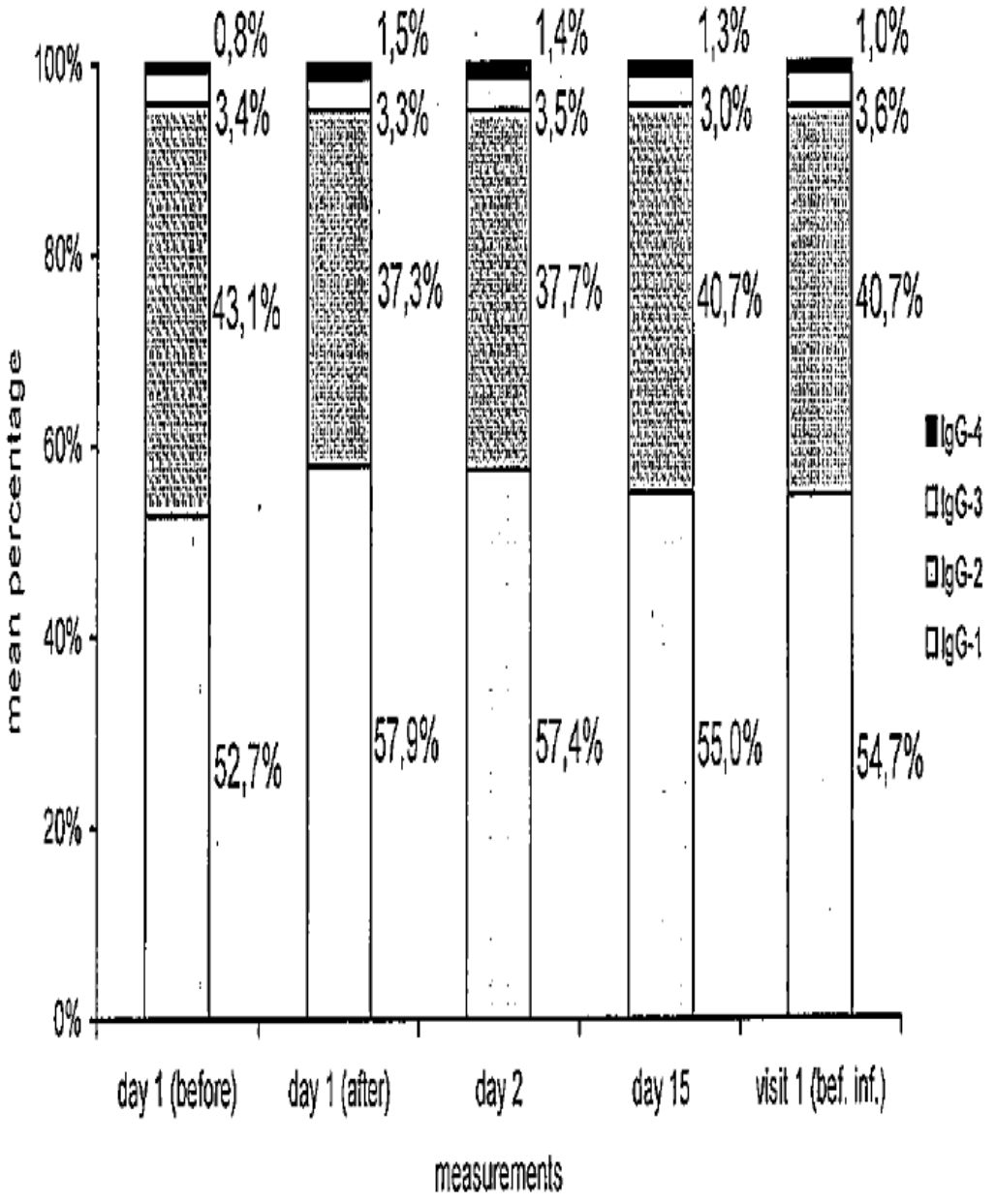


Table 2. Trough levels below 6 g/L.

Period of 6 months prior to the study		Patient no.	Period of BT681 treatment during the study	
No. of values measured	No. of values below 6 g/l (%)		No. of values below 6 g/l	No. of values measured
7	0 (0.0%)	1	0 (0.0%)	6
9	9 (100.0%)	2	8 (100.0%)	8
9	0 (0.0%)	3	0 (0.0%)	8
9	0 (0.0%)	4	0 (0.0%)	8
7	0 (0.0%)	5	0 (0.0%)	6
7	2 (28.6%)	6	0 (0.0%)	6
6	6 (100.0%)	7	2 (100.0%)	2
5	1 (20.0%)	8	1 (12.5%)	8
7	0 (0.0%)	9	0 (0.0%)	7
8	2 (25.0%)	10	2 (25.0%)	8
7	3 (42.9%)	11	0 (0.0%)	6
8	0 (0.0%)	12	0 (0.0%)	8
7	7 (100.0%)	13	1 (16.7%)	6
2	2 (100.0%)	14	1 (16.7%)	6
6	0 (0.0%)	15	0 (0.0%)	7
5	1 (20.0%)	16	0 (20.0%)	6
6	6 (100.0%)	17	2 (33.3%)	6
115	39 (33.9%)	Total	17 (15.2%)	112

Drug Interactions

No new data were submitted.

Pharmacodynamics

No new data were submitted.

Efficacy

Requirements for information on efficacy are discussed in the "Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration

(IVIg)" (CPMP/BPWG/388/95, 2000). For replacement therapy in primary immunodeficiency syndromes, the 15 patients included in the pharmacokinetic study should be followed for 6 months, including documentation of infection rate and use of antibiotics. On these results, additional indications including myeloma or chronic lymphocytic leukaemia and children with congenital acquired immune deficiency syndrome (AIDS) can be granted. A standard dose of 0.2 – 0.4 g/kg body weight every 3-4 weeks is defined for these indications.

A specific clinical study is required for treatment of ITP. There is no data to support equivalence of different IVIg preparations, in particular with respect to immunomodulatory activities. Clinical efficacy data should include an open study comparing literature data with reference IVIg, performed over a few days in acute phase on at least 15 adult chronic ITP patients with a platelet count of about 20/nl. Information required is platelet count >50/dl, duration of platelet response, time to reach platelet count >50/dl, maximum platelet level and regression of haemorrhages. Standard doses should be studied; 0.8 – 1 g/kg for 1 -2 days, or 0.4 g/kg/ day for 2-5 days.

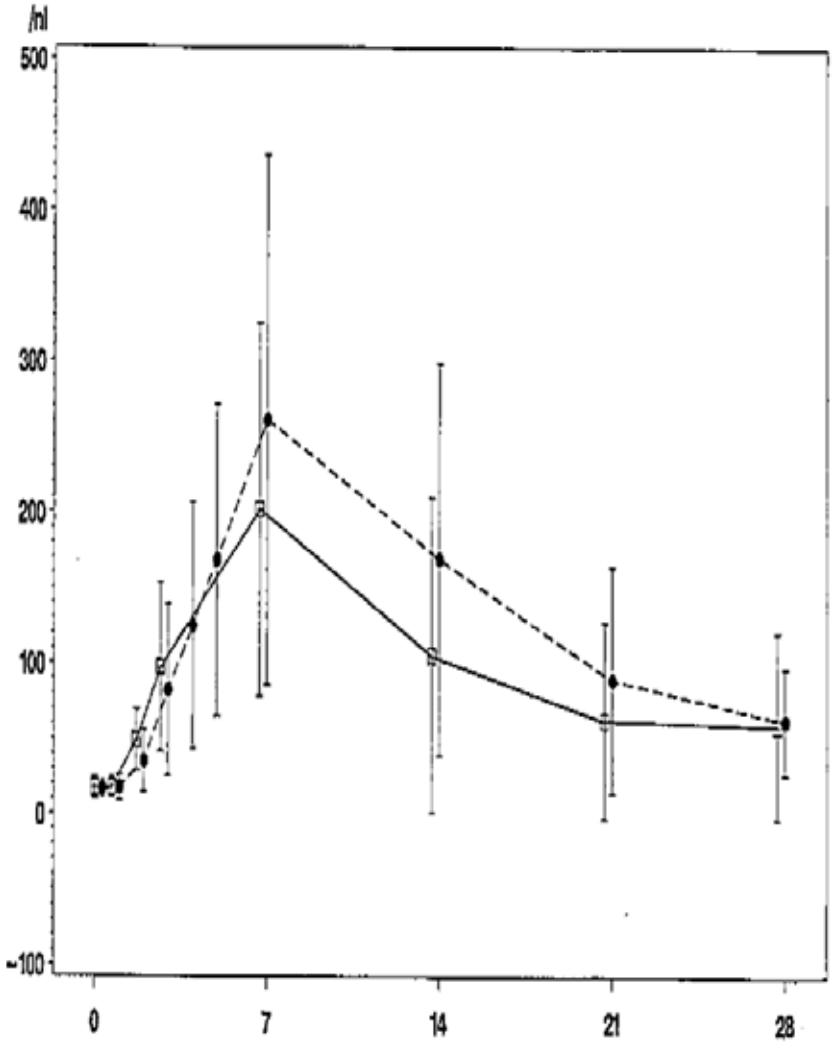
Study 941 was conducted in accordance with the Note for Guidance and provided the required efficacy data for replacement therapy. In terms of efficacy, rates of infection, antibiotics and fever were comparable between the 6 months prior to the study and the 6 months of the study. An annual infection rate of 4.0 +/- 3.6 infections per year under treatment with Intratect was noted which can be compared to 2.5 +/- 3.2 infections per year in the 6 months prior. The 95% confidence interval was noted to be -3.6 to 0.5 infections per year for the difference in annual rate. While all rates were higher during the study period, this was felt to be due to seasonal fluctuation (the Intratect treatment period fell over winter) and under reporting during the pre-study period. Review of the seasonal variation showed that the rate of infections was lower during the 6 months treated with Intratect than in the corresponding 6 months the year before. The most common infection was bronchitis, which was equally common before and during the study period. The mean annual rate of use of antibiotics was 3.4 +/- 2.6 under treatment with BT 681, compared with an annualised rate of 4 +/- 2.1 for the previous 6 month period. The mean annual days with fever was 3.5 +/- 5.1 per year during treatment with BT 681 compared to 2.5 +/- 4.7 for the previous treatment period.

Study 942 was conducted in accordance with the Note for Guidance and provided the required efficacy data for immunomodulatory effect therapy. In terms of efficacy, the platelet response (>50/nl) was the primary efficacy parameter. The overall response rate was 91.7 % (22/24), with a similar response rate in both groups (93.3% in the 2-day group versus 88.9% in the 5-day group). Total mean time to response was 3.9 +/- 2.4 days and mean duration of response 24.4 +/- 3.6 days (Table 3). The mean maximum platelet count was 245.3 +/- 136.9/nl and total mean time to maximum platelet count 8.8 +/- 5.2 days (Figure 2). At the end of the study period (28 days), platelet count was still above 50/nl in 11/22 patients. Regression of haemorrhages was noted in 88.9% of patients. All results compared favourably with historical data from 19 patients being treated with reference preparations at the same study centres.

Table 3. Time to and duration of response (ITT analysis).

		N	MEAN	SD	MIN	Q1	MEDIAN	Q3	MAX
time to response [days]	total, n=24	22	3.9	2.4	2.0	2.0	3.0	7.0	8.0
	1.0 g/kg BW (2d), n=15	14	4.4	2.8	2.0	2.0	2.5	7.0	8.0
	0.4 g/kg BW (5d), n= 9	8	2.9	0.6	2.0	2.5	3.0	3.0	4.0
duration of platelets ≥ 50/nl [days]	total, n=24	22	19.8	7.8	6.0	13.0	22.5	27.0	29.0
	1.0 g/kg BW (2d), n=15	14	17.6	8.0	6.0	13.0	18.0	25.0	27.0
	0.4 g/kg BW (5d), n= 9	8	23.6	6.3	11.0	21.0	25.5	28.0	29.0
duration of platelet response above baseline [days]	total, n=24	22	24.4	3.6	15.0	21.0	25.5	27.0	29.0
	1.0 g/kg BW (2d), n=15	14	23.0	3.7	15.0	21.0	22.5	26.0	27.0
	0.4 g/kg BW (5d), n= 9	8	26.8	1.7	25.0	25.0	27.0	28.0	29.0

Figure 2. Time course of platelet count (mean values ±Standard deviation (ITT analysis).



Square= 1g/kg (2 days) and circle=0.4 g/kg (5 days)

Safety

Requirements for information on safety are discussed in the "Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)" (CPMP/BPWG/388/95, 2000). All adverse events in clinical studies should be recorded in all patients treated, whatever the indication for treatment. Data from at least 30 patients or 180 infusions is required. Safety evaluation should include monitoring of blood pressure, heart rate, temperature and other adverse events at repeated intervals following infusion of the new product in patients in the pharmacokinetic studies. Renal function should be monitored, particularly in patients at risk and in those receiving high doses of IVIg.

Study 941 was conducted in accordance with the Note for Guidance and provided the required safety data for replacement therapy. With regard to adverse events, a total of 111 adverse events were observed in 16 /17 patients (94.1%). Infections were most common AEs (Table 4) with bronchitis (12 patients), sore throat (8 pts), rhinitis (8 pts) and sinusitis (5 pts). Headache was reported in 4 patients which was a symptom of sinusitis in one patient. Most adverse events were classed as mild or moderate and unrelated to study drug. Some 9 events in 6 patients were classed as possibly or probably related to study drug. These occurred on

day of infusion and were pyrexia (3 events in one patient), headache (3 patients), taste disturbance, gastrointestinal pain and shivering. Laboratory investigations did not reveal any significant safety issues. In One patient withdrew and had a serious adverse event after infusion 3 with neurological symptoms. This was a 15 year old female with common variable immunodeficiency diagnosed 5 years previously. A tentative diagnosis of multiple sclerosis or vasculitis was made 2 to 6 weeks after last infusion of BT 681. The patient died around 5 months after last infusion. After autopsy cause was of death described as progressive neurodegeneration and coded as multiple sclerosis.

Table 4. Adverse events by number of patients and frequency.

Adverse event (MedDRA 2.4)	N	%
Bronchitis NOS	12	70.6
Rhinitis NOS	8	47.1
Sore throat NOS	8	47.1
Sinusitis NOS	5	29.4
Headache NOS	4	23.5
Pyrexia	3	17.6
Cough	2	11.8
Accident NOS	2	11.8
Conjunctivitis NEC	2	11.8
Otitis media serous NOS	2	11.8
Gastritis NOS	1	5.9
Otitis media NOS	1	5.9
Enteritis	1	5.9
Gastroenteritis enteroviral	1	5.9
Iron deficiency anaemia	1	5.9
Pneumonia NOS	1	5.9
Wheezing	1	5.9
Infection NOS	1	5.9
Flatulence	1	5.9
Stomatitis	1	5.9
Taste disturbance	1	5.9
Anxiety NEC	1	5.9
Cerebral palsy	1	5.9
Difficulty in walking	1	5.9
Multiple sclerosis	1	5.9
Paraesthesia NEC	1	5.9
Sunburn	1	5.9
Writing impaired	1	5.9
Cystitis NOS	1	5.9
Urinary tract infection NOS	1	5.9
Acne NOS	1	5.9
Diarrhoea NOS	1	5.9
Gastrointestinal pain NOS	1	5.9
Musculoskeletal pain	1	5.9
Gastroenteritis NOS	1	5.9
Lymphadenopathy	1	5.9
Skin disorder NOS	1	5.9
Vomiting NOS	1	5.9
Epilepsy NOS	1	5.9
Tonsillar hypertrophy	1	5.9
Shivering	1	5.9

Study 942 was conducted in accordance with the Note for Guidance and provided the required safety data for immunomodulatory effect therapy. A total of 38 adverse events were recorded in 15/24 patients (62.5%) (Table 5). Some 27 AEs were recorded in 10/15 patients in the 2-day group and 11 AEs in 5/9 patients in the 5-day group. Headache (5 versus 4 patients), pyrexia (5 versus 1 patient), nausea (2 versus 1 patient), nausea (2 versus 1 patient) and haemolysis (3 versus 0 patients) were reported in more than one patient. Some 22 versus 10 AEs were classed as possible related to study drug. The majority were classed as mild with one classed as severe (hypertension). There were no serious AEs and no deaths. Haemolysis of mild severity possibly related to study drug was reported in 3 patients after assessment of laboratory investigations to study Day 7.

Table 5. Summary of adverse events classifications by episode (safety analysis).

System Organ Classes (SOC) and Preferred Terms (PT)		total, n=24	1.0 g/kg BW (2d), n=16	0.4 g/kg BW (5d), n= 9
		N	N	N
total		38	27	11
Blood and lymphatic system disorders	total, thereof	3	3	.
	Haemolysis NOS	3	3	.
Gastrointestinal disorders	total, thereof	6	4	2
	Gingival bleeding	1	1	.
	Nausea	3	2	1
	Vomiting NOS	2	1	1
General disorders and administration site conditions	total, thereof	7	5	2
	Pyrexia	6	5	1
	Haemorrhage NOS aggravated	1	.	1
Infections and infestations	total, thereof	1	1	.
	Urinary tract infection NOS	1	1	.
Investigations	total, thereof	2	2	.
	Body temperature increased	2	2	.
Nervous system disorders	total, thereof	13	6	7
	Headache NOS	13	6	7
Respiratory, thoracic and mediastinal disorders	total, thereof	1	1	.
	Epistaxis	1	1	.
Skin & subcutaneous tissue disorders	total, thereof	1	1	.
	Petechiae	1	1	.
Vascular disorders	total, thereof	4	4	.
	Haematoma NOS	1	1	.
	Hypertension NOS	1	1	.
Vascular disorders	Hypertensive crisis	1	1	.
	Thrombophlebitis superficial	1	1	.

POST MARKETING EXPERIENCE

Information on post marketing experience was extensive as Intratect has been marketed in Europe since 27 September 2004. Periodic safety update reports (PSURs) were provided to cover the period between 27 September 2004 and 31 March 2008. For the period covered by the PSURs, a total of 153 cases of suspected adverse reactions were received. Of these cases, 45 were regarded as serious and 108 as non-serious. A total of 13 allergic anaphylactic reactions were identified directly related to Intratect, which equates to a frequency of less than one allergic reaction for more than 50,000 applications. A total of 127 of the 153 reported adverse reactions were classified as unspecific hypersensitivity. These were largely mild in nature and often related to higher infusion rates than recommended.

No new safety issues were identified as a result of the post marketing surveillance.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a “list of questions” to the sponsor is generated.

No questions were generated for the sponsor regarding this product.

Clinical Summary and Conclusions

Polyvalent intravenous immunoglobulin preparations have been used for many years in the treatment of individuals with humoral immunodeficiency such as congenital agammaglobulinaemia, myeloma and children with congenital AIDS. These conditions are

well defined. However, IVIg has also been used for its immunomodulatory effect in a number of other conditions, particularly auto-immune related diseases where the indication is less clear cut. To assist in this process, formal guidelines exist for the development of human normal immunoglobulin, in the form of; "Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)" (CPMP/BPWG/388/95, 2000).

This application follows this guidance and seeks approval for Intratect in the replacement treatment of primary immunodeficiency disease, as well as the immunomodularity effect of other conditions such as ITP. Clinical information supporting this application consisted of two studies as well as post marketing surveillance.

The pharmacokinetic data from Study 941 indicated that Intratect performed in a similar way to other IVIg, particularly with regard to mean elimination half life and trough levels, particularly at the recommended standard dose. This was noted to be predictable over the 6 month study period, Efficacy data, in particular infection rate, was noted to be comparable (if slightly higher) than the pre-study rate, but was influenced by seasonal factors. Safety data indicated that most adverse events were unrelated to the study medication. One death was noted 5 months after the study, but was considered to be unrelated to treatment.

Efficacy data from Study 942 indicated a good response in terms of platelet response, with 91.7 % of patients responding effectively. This compared favourably to historical data. Safety data indicated that the most common adverse events were headache, pyrexia, nausea and haemolysis. These tended to be of mild severity only.

The application was also supported by extensive post marketing surveillance. This data indicated an excellent safety profile. Most adverse events were not related to the study medication, with an allergy/ anaphylaxis rate of less than 1 in 50,000.

As such, the application for registration of Intratect is supported for the proposed indications.

V. Pharmacovigilance Findings

Risk Management Plan

The risk management plan submitted by the sponsor is dated September 2008 and safety data is presented for the period from September 2004 to March 2008. Exposure to Intratect includes that from two clinical trials and from post marketing use. Many of the adverse reactions reported have occurred in association with rapid infusion rates. The use of polyvalent intravenous immunoglobulins (IVIg) in Australia has been well established with other bio-similar products. No new safety concerns have been identified for Intratect.

The proposed product information covers the important safety specifications however the addition of transfusion-related acute lung injury (TRALI) and further information on infection risk relating to transmissible spongiform encephalopathy is recommended. Other specific recommendations have been made to the sponsor in this RMP evaluation. In summary, the RMP has been evaluated as adequate with the addition of RMP amendments to:

- Important identified risks, potential risks and missing information sections of the RMP that require updating.
- Adverse drug reaction (ADR) data presentation and conclusions.
- Medication class effects.
- Potential for off-label use.
- Provision of a description of stated additional PhV measures.
- Information on the product insert.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Proposed specifications control the identity, potency, dose delivery and other physical, chemical and microbiological properties. The Intratect specifications comply with PhEur monograph 0918. PMF issues have been satisfactorily addressed. Only plasma collected from US collection centres which comply with TGO81 requirements[10] will be used for manufacture for the Australian market. All viral/prion safety issues have been addressed.

Nonclinical

The sponsor provided adequate justification for limited nonclinical testing. Animal studies of human immunoglobulins have practical limitations due to maximal feasible infusion volumes and immune responses to heterologous IgG. Primary pharmacology studies *in vitro* showed normal IgG activity. A safety pharmacology and acute toxicity study in dogs showed transient increases in heart rate, reduction in blood leucocyte and platelet counts and increase in liver enzymes. Infusion site histology showed acceptable local tolerance. The responses in the acute toxicity study raise no human safety concerns.

Clinical

Clinical evaluator's conclusion:

The clinical product development has followed the "Note for Guidance on clinical investigation of human normal immunoglobulin for intravenous administration (CPMP/BPWP/388/95, Rev 1). Two completed clinical studies supported expected pharmacokinetic parameters, efficacy in prevention of infection in patients with primary immunodeficiency diseases, strong support for efficacy in patients with idiopathic thrombocytopaenic purpura and acceptable safety profile in clinical studies. The minimum requirement for safety data in clinical studies involving at least 30 patients and 180 infusions has been met. Safety profile of Intratect also appears to be acceptable in post-marketing experience. The clinical evaluator supported registration for indications consistent with the CPMP/BPWP/388/95, Rev 1 guideline.

Risk Management Plan

The RMP has been evaluated and assessed as adequate with the addition of some RMP amendments. Routine pharmacovigilance is considered adequate to address safety concerns.

Risk-Benefit Analysis

Delegate Considerations

Minor quality aspects remain outstanding. There are no nonclinical objections to registration.

Clinical studies with immunoglobulin preparation BT681 were conducted in 2000-2001. In their Pre-Advisory Committee on Prescription Medicines (ACPM) response the sponsor was requested to identify any difference in specifications between BT681 and Intratect as proposed for registration and also to identify any major changes in manufacture process between preparation BT681 and Intratect proposed for registration.

[10]Therapeutic Goods Order No. 81. Standards for blood and blood components. http://www.tga.gov.au/legis/tgo/tgo81.htm

The Delegate concurred with the clinical evaluator that the minimal requirements of CPMP/BPWG/388/95 have been met by the submitted clinical studies which supported acceptable efficacy and safety. In the primary immunodeficiency study although the numbers of infections, use of antibiotics and days with fever were higher on Intratect treatment compared to the previous six months, there was support for lower rates of infection compared to corresponding months of the previous year.

The safety profile of Intratect in post-marketing experience to 2008 appeared to be acceptable. PSUR reports covering the period to 2010 are required in the sponsor's Pre-ACPM response.

Delegate's Proposed Action

The Delegate proposed to register Human Normal Immunoglobulin, Intratect 1 g/20 mL, 2.5 g/50 mL, 5 g/100 mL and 10 g/200 mL solution for infusion in vials for the indications

Replacement Therapy:

- Primary immunodeficiency syndromes
  - Congenital agammaglobulinaemia and hypogammaglobulinaemia
  - Common variable immunodeficiency
  - Severe combined immunodeficiencies
  - Wiscott Aldrich syndrome.
- Myeloma or chronic lymphocytic leukaemia with secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital Acquired Immune Deficiency Syndrome (AIDS) who have repeated bacterial infections.

Immunomodulatory effect:

- Idiopathic thrombocytopaenic purpure, in adults or children with a high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barre syndrome.
- Kawasaki disease.
- Allogenic bone marrow transplant.

The advice of ACPM was requested.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Link Medical Products Pty Ltd to register the new chemical entity, human normal immunoglobulin (Intratect) intravenous infusion, 50 mg/mL as 1 g/20 mL; 2.5 g/50 mL; 5 g/100 mL; and 10 g/200 mL for the indication:

Replacement therapy in

Primary immunodeficiency syndromes:

- Congenital agammaglobulinaemia and hypogammaglobulinaemia

- Common variable immunodeficiency

- Severe combined immunodeficiencies

- Wiskott Aldrich syndrome.

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections

Children with congenital Acquired Immune Deficiency Syndrome (AIDS) who have repeated bacterial infections

Immunomodulation

Idiopathic thrombocytopenic purpura, in adults or children with a high risk of bleeding or prior to surgery to correct the platelet count

Guillain-Barré syndrome

Kawasaki disease

Allogeneic bone marrow transplant

In making this recommendation, the ACPM advised that the risk/benefit profile was appropriate in this instance, however, expressed disappointment that the sponsor had not taken the opportunity to align the indication and usage of this product with recently approved equivalent products. The committee noted that the reported incidence of infusion-related adverse events was lower than would be expected and recommended revision of the Risk Management Plan.

ACPM noted that the sponsor had not provided any information in response to the Delegate's request for details of manufacturing changes or on the link between the formulation used in clinical studies and that proposed for marketing. .

The specific conditions of registration should include:

The inclusion in the Risk Management Plan (RMP) of routine monitoring of thrombo-embolic events in view of the emerging concerns with the similar but now-withdrawn products.

Provision to the TGA delegate of details of manufacturing changes and comment on the link between the formulation used in clinical studies and that is to be registered.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of *Intratect 2.5g in 50mL, 10g in 200 mL, 1g in 20 mL and 5g in 100mL human normal immunoglobulin solutions for intravenous infusion (vial)* indicated for:

Replacement therapy in.

- *Primary immunodeficiency syndromes:*
  - *congenital agammaglobulinaemia and hypogammaglobulinaemia;*
  - *common variable immunodeficiency.*
  - *severe combined immunodeficiency*
  - *Wiskott Aldrich syndrome.*
- *Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.*
- *Children with congenital Acquired Immune Deficiency Syndrome (AIDS) and recurrent infections.*

Immunomodulation

- *Idiopathic thrombocytopenic purpura, in adults or children at high risk of bleeding or prior to surgery to correct the platelet count.*
- *Guillain-Barré syndrome.*
- *Kawasaki disease*
- *Allogeneic bone marrow transplant.*

Special conditions of registration included:

The full implementation of the Risk Management Plan submitted with the current Australian application must be implemented taking into account comments from Advisory Committee on Prescription Medicines (ACPM) and the report from the Office of Product Review (OPR).

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

Intratect® 50 mg/mL Solution for infusion (20 mL, 50 mL, 100 mL, 200 mL)
(Human Normal Immunoglobulin for Intravenous Administration)

NAME OF MEDICINE

Intratect ® Human Normal Immunoglobulin for Intravenous Administration 50 mg/mL Solution for Infusion.

DESCRIPTION

The **Intratect®** solution is clear to slightly opalescent and colourless to pale yellow. The pH of the solution is approximately 5.2.

Human protein 50 mg/mL of which at least 96% is IgG, derived from human blood /plasma donors.

One vial of 20 mL contains: 1 g; one vial of 50 mL contains: 2.5 g; one vial of 100 mL contains: 5 g and one vial of 200 mL contains: 10 g of human protein.

Distribution of IgG subclasses:
IgG1 57%, IgG2 37%, IgG3 3%, IgG4 3%

IgA max 2 mg/mL.

Excipients: Glycine, Sodium Hydroxide, Hydrochloric Acid, Water for Injections.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06B A02

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments. IgG and IgG–complexes are broken down in cells of the reticulo-endothelial system.

The pharmacokinetics of Intratect® was studied in a multicentre, open, prospective study in patients with primary immunodeficiency disease. **Intratect®** was administered by intravenous infusion at about 400 mg/kg body weight (8 mL/kg) every 3-4 week intervals over a period of 6 months.

The pharmacokinetic evaluation revealed a mean elimination half life of 27 $\pm$ 11 days. This half-life may vary from patient to patient, in particular, in primary immunodeficiency.
The proportions of IgG subclasses 1-4 remained unchanged after the 1st infusion. The mean dose was approximately 450 mg/kg body weight. On average, mean serum concentrations of IgG increased by about 900 mg/dl after each infusion. Trough levels below 6 g/L were only observed in 17 of 112 measured trough levels during the study (15.2%), but in 39 of 115 trough levels reported in the 6 months prior to the study (33.9%).

The pharmacokinetics displayed, as well as the proportions of IgG subclasses 1-4, are similar to those of natural IgG.

CLINICAL TRIALS

Two open label studies have been conducted with **Intratect** ®. One study was a multicentre, open, prospective study in 17 patients with primary immunodeficiency disease. **Intratect®** was administered by intravenous infusion at about 400 mg/kg body weight (8mL/kg) every 3-4 week intervals over a period of 6 months. Criteria for evaluations included: efficacy: infection rate (number of new acute and relevant infections); use of antibiotics (number of occasions for treatment with antibiotics; prophylactic antibiotic treatment evaluated separately); number of days with fever > 38.0°C.

The number of patients with at least one event (i.e. an acute and relevant infection, use of antibiotics, or a day with fever > 38.0°C) and the number of events are displayed below for the relevant periods (17 evaluated patients in both periods):

	In the 6 months prior to the study		During the Study	
	No. of patients	No. of events	No. of patients	No. of events
Infections	9	21	13	32
Use of antibiotics	8	12	13	26
Days with fever	5	21	8	29

The resulting annual rates per patient (mean ± standard deviation) for the 3 main efficacy parameters were as follows:

	In the 6 months prior to the study	During the Study	Difference	95% confidence interval for difference
Infections	2.5 ± 3.2	4.0 ± 3.6	-1.5 ± 3.9	[-3.6; +0.5]
Use of antibiotics	1.4 ± 2.1	3.4 ± 2.6	-2.0 ± 2.3	[-3.2; -0.8]
Days with fever	2.5 ± 4.7	3.5 ± 5.1	-1.0 ± 5.9	[-4.1; +2.0]

The difference is regarded to be mainly related to seasonal influences and the underreporting of historical events/data.

By far the most common acute and relevant infection was bronchitis which was equally common (14x) before and during the study. Sinusitis was reported more frequently during the study (6x) than prior to the study (0x) as an acute and relevant infection. Acute and relevant infections corresponded well to the use of antibiotics.

The second trial was an open prospective study in 24 patients with idiopathic thrompocytopenic purpura. **Intratect®** was administered as 1g/kg body weight per day for 2 days or 0.4g/kg body weight per day for 5 consecutive days. A total dose of 2g/kg body weight per treatment course as intravenous administration.

Criteria for evaluation included: efficacy: platelet response (response rate) defined as platelet count ≥ 50/nl; regression of haemorrhages; duration of platelet response; time course of platelet count; time to platelet response; maximum/time to maximum platelet count.

The primary efficacy parameter was the platelet response. A patient was regarded as a responder if the platelet count increased to values ≥ 50/nl during the study. 22/24 patients responded to **Intratect®** treatment, i.e. the overall response rate was 91.7%; 14/15 (93.3%) in the 2 days group vs 8/9 (88.9%) patients in the 5 days group, thus showing a remarkable response on **Intratect®** with both dosage regimens. The evaluation of the 95% confidence intervals according to Pearson and Clopper for the response rates confirmed the above described findings with a confidence interval of [73.0%; 99.0%] for the entire study population: [68.1%; 99.8%] in the 2 days group vs [51.8%; 99.7%] in the 5 days group.
The total mean time to response was 3.9 ± 2.4 days (2d/4.4 ± 2.8 days vs 5d/2.9 ± 0.6 days), the duration of response was 24.4 ± 3.6 days (2d/23.0 ± 3.7 days vs 5d/26.8 ± 1.7 days).
The mean maximum platelet count in the responder population was 245.3 ± 136.9/nl; in 14 vs 8 responders 218.0 ± 120.1/nl (2d) vs 293.1 ± 159.1/nl (5d). The total mean time to maximum platelet count was 8.8 ± 5.2 days; in 14 vs 8 responders 9.7 ± 6.4 days (2d) vs 7.3 ± 1.0 days (5d).
In most of the patients the individual time course of platelet count during the 28 days study period showed an increase of platelet count until day 7 or day 14, respectively, and a decrease on day 21 and 28.
However, at the end of the study period platelet count was still above 50/nl in 11/22 responders.
Overall, the evaluation of platelet parameters shows a slight tendency in favour of the 5 days group.
Corresponding to the high response rates in both treatment groups, a high overall regression of haemorrhages (88.9%) was achieved in this study with slight advantages in favour of the 2

days group. Since only one patient was excluded due to a major protocol violation the baseline and efficacy data of the per-protocol analysis were rather similar to those of the intention-to-treat analysis.
In summary, the efficacy results indicate that treatment with **Intratect®** was effective with regard to platelet response rate, time and duration of response, maximum platelet counts and regression of haemorrhages. The comparison of findings in the study population to a historical data set of 19 patients with IVIg monotherapy in the same study centres revealed lower response rates for reference preparations.

INDICATIONS

Replacement therapy in

- Primary immunodeficiency syndromes:
  - Congenital agammaglobulinaemia and hypogammaglobulinaemia
  - Common variable immunodeficiency
  - Severe combined immunodeficiency
  - Wiskott Aldrich syndrome
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital Acquired Immune Deficiency Syndrome (AIDS) and recurrent infections

Immunomodulation

- Idiopathic thrombocytopenic purpura, in adults or children at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome
- Kawasaki disease

Allogeneic bone marrow transplant

CONTRAINDICATIONS

Hypersensitivity to any of the components.
Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

PRECAUTIONS

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "**DOSAGE AND ADMINISTRATION**" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently

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

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (0.024 mL/kg/min),
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

There is clinical evidence of an association between IVIg administration and thromboembolic events such a myocardial infarction, stroke, pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients and in patients with pre-existing risk factors for thrombotic events such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypovolemic patients, patients with diseases which increase blood viscosity.

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

In cases of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the

licensed IVIg products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg,
- monitoring of urine output,
- monitoring of serum creatinine levels,
- avoidance of concomitant use of loop diuretics.

In cases of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect.

In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The manufacturing process of Intratect ® was also investigated for its capacity to remove prions, the infectious agents of TSE, e.g CJD and its variant vCJD. Steps of the production process were investigated for removal of prions. TSE removal steps include cold ethanol fractionation ($\geq$3.3 $\log_{10}$) and 20 nm nano filtration ($\geq$4.1$\log_{10}$). These studies provide assurance on strong evidence that agents of vCJD/CJD, if present in the starting material, are removed effectively.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes and important contribution to the viral safety.

Intratect ® is made from human plasma. Based on careful donor selection and screening of donations and on effective product manufacturing processes, Intratect ® carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) or its variant vCJD is also considered to be extremely remote. No cases of transmission of viral diseases or CJD have been associated with the use of Intratect ®.

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS

within several days without sequelae. The syndrome usually begins within several hours to two days following IVIg treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu.mm. predominantly from the granulocytic series, and elevated protein levels up to several hundred g/L. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. It appears that patients with a history of migraine may be more susceptible.

IVIg products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration [see Adverse Effects]. IVIg recipients should be monitored for clinical signs and symptoms of hemolysis.

Transfusion-Related Acute Lung Injury (TRALI): Noncardiogenic pulmonary edema may occur in patients following IVIg treatment. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.
Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient's serum.
TRALI may be managed using oxygen therapy with adequate ventilatory support.

In patients with a normal acid base compensatory mechanism, the acid load delivered by the larget dose of preparation would be neutralised by the buffering capacity of whole blood alone, even if the dose were to be infused instantaneously. In patients with limited or compromised acid base compensatory mechanisms including neonates, consideration should be given to the effect of additional acid load that the preparation might present.
It is strongly recommended that every time that Intratect ® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Interactions with other medicines

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of the measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests including the antiglobulin test (Coomb's test).

Pregnancy (Category C)

No animal reproduction studies have been conducted with Intratect®. The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and it therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Lactation

The safety of this medicinal product for use in lactation has not been established in clinical trials and it should only be given with caution to breast-feeding mothers. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

Effects on fertility

No reproductive toxicity studies have been conducted with Intratect®.

ADVERSE EFFECTS

Less common
Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild back pain may occur occasionally.

Rare
Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulins.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely
Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

Details of further spontaneously reported adverse reactions:

Cardiac disorder: Angina pectoris (very rare)
General disorders and administrations site conditions: Rigors (very rare)
Immune system disorders: Anaphylactoid shock (very rare),
hypersensitivity (very rare)

Investigations: Blood pressure decreased (very rare)
Musculoskeletal and connective tissue disorders: Back pain (very rare)
Respiratory, thoracic and mediastinal disorders: Dyspnoe NOS (very rare)
Vascular disorders: Shock (very rare)

Adverse Events Reported During Clinical Trials:

Three clinical studies have been performed with Intratect®: Two in patients with primary immunodeficiencies (PID) and one in patients with immune thrombocytopenic purpura (ITP). In the two PID studies, overall, 68 patients were treated with Intratect® and evaluated for safety. Treatment period was 6 and 12 months respectively. The ITP study was performed in 24 patients.

These 92 patients received a total of 830 infusions of Intratect®, whereby a total of 51 suspected adverse drug reactions (ADRs) were recorded. The majority of these ADRs were mild to moderate and self-limiting. No serious ADRs were observed during the studies.
The ADRs reported in the three studies are summarised and categorised according to the MedDRA System organ class and frequency below. Frequencies are calculated on the basis of administered infusions (n=830) using the following criteria:

Very common (≥1/10); common (≥1/100 to ≤1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

Frequency of Adverse Drug Reactions (ADRs) in clinical studies with Intratect®

MedDRA Coded System Organ Class	**MeDRA preferred term**	**ADR frequency category**
Blood and lymphatic system disorders	Haemolysis (mild)	Uncommon
Gastrointestinal disorders	Nausea, vomiting, gastrointestinal pain	Uncommon
General disorders and administration site conditions	Pyrexia, chills, feeling hot	Uncommon
Investigations	Body temperature increased, Coombs test (indirect and direct) positive	Uncommon

Nervous system disorders	Headache	Common
	Dysgeusia	Uncommon
Skin and subcutaneous tissue disorder	Papular rash	Uncommon
Vascular disorders	Hypertension, thrombophlebitis superficial	Uncommon

For safety with respect to transmissible agents, see Precautions

DOSAGE AND ADMINISTRATION

Dosage

The dose and dosage regimen is dependent on the indication.

In replacement therapy the dosage may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. The following dosage regiments are given as a guideline:

Replacement therapy in primary immunodeficiencies

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of a least 4-6 g/L. three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 8-16 mL (0.4-0.8 g)/kg followed by at least 4 mL (0.2 g)/kg every three weeks.

The dose required to achieve a trough level of 6 g/L is of the order of 4-16 mL (0.2-0.8 g)/kg/month. The dosage interval when steady state has been reached varies from 2-4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammagloulinemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections
The recommended dose is 4-8 mL (0.2-0.4 g)/kg every three to four weeks.

Idiopathic thrombocytopenic purpura

For treatment of an acute episode, 16-20 mL (0.8-1 g)/kg on day one, which may be repeated once within 3 days, or 8 mL (0.4 g)/kg daily for two to five days. The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

8 mL (0.4 g)/kg/day for 3 to 7 days. Experience in children is limited.

Kawaski disease

32-40 mL (1.6-2 g)/kg should be administered in divided doses over two to five days or 40 mL (2 g)/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Allogeneic bone marrow transplantation

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.
For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 10 mL (0.5 g)/kg/week, starting seven days before transplantation and for up to 3 months after transplantation.
In case of persistent lack of antibody production, a dosage of 0.2 - 0.4 g/kg every three to four weeks is recommended. The trough levels should be maintained above 5 g/L.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of infusions
Replacement therapy in primary immunodeficiency	- starting dose: 0.4-0.8 g/kg - thereafter: 0.2-0.8 g/kg	every 2-4 weeks to obtain IgG trough level of at least 4-6 g/L
Replacement therapy in secondary immunodeficiency	0.2-0.4 g/kg	every 3-4 weeks to obtain IgG trough level of at least 4-6 g/L
Children with AIDS	0.2-0.4 g/kg	every 3-4 weeks
Immunomodulation:		
Idiopathic Thrombocytopenic Purpura	0.8-1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2-5 days
Guillain Barré syndrome	0.4 g/kg/d	for 3-7 days
Kawasaki disease	1.6-2 g/kg or 2 g/kg	in several doses for 2-5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid
Allogeneic bone marrow transplantation: - treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day -7 up to 3 months after transplantation
- persistent lack of antibody production	0.2 - 0.4 g/kg	every three to four weeks. The trough levels should be maintained above 5 g/L.

METHOD OF ADMINISTRATION

Intratect® should be infused intravenously at an initial rate of not more than 1.4 mL/kg/hr for 30 minutes.
If well tolerated, the rate of administration may gradually be increased to a maximum of 1.9 mL/kg/hr for the remainder of the infusion.

OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients and patients with renal impairment.

Contact the Poisons Information Centre on 13 11 26 for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

20 mL or 50 mL or 100 mL or 200 mL of solution in a vial (Type II glass) with a stoppers (bromobutyl) and a cap (aluminium) – pack size of one vial.

Intratect® 20 (AUST R 164550), Intratect® 50 (AUST R 164548), Intratect® 100 (AUST R 164551) and Intratect® 200 (AUST R 164549)

STORAGE

Store below 25ºC. Do not freeze. Keep the container in the outer carton.

SHELF LIFE

2 years.
After first opening, immediate use is recommended.

INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL

The product should be brought to room or body temperature before use.
The solution should be clear to slightly opalescent. Do not use solutions that are cloudy or have deposits.
Any unused product or waste material should be disposed of in accordance with local requirements.
Product is for single use in one patient only. Discard any residue.

NAME AND ADDRESS OF THE SPONSOR

Link Medical Products Pty Ltd
5 Apollo Street
Warriewood NSW 2102
Australia
Tel: (61) 2 9997 7176
Website: www.linkhealthcare.com.au

POISON SCHEDULE OF THE MEDICINE

PRESCRIPTION ONLY MEDICINE – S4

DATE OF APPROVAL

3 February 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au