Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Normal Immunoglobulin (human)

Proprietary Product Name: Intragam 10 NF

Sponsor: CSL Bioplasma Ltd

October 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	Extension of indications and New Dosage
Decision:	Approved
Date of Decision:	3 March 2011
Active ingredient(s):	Normal Immunoglobulin (human)
Product Name(s):	Intragam 10 NF
Sponsor's Name and Address:	CSL Limited 189-209 Camp Road, Broadmeadows, Victoria 3047 Australia
Dose form(s):	Solution for injection
Strength(s):	2.5g/25 mL, 5 g/50 mL, 10 g/100 mL and 20 g/200 mL
Container(s):	Glass vial
Approved Therapeutic use:	*Replacement IgG therapy in;* · *primary immunodeficiency disease (PID)* · *myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections* · *congenital or acquired immune deficiency syndrome with recurrent infections.* *Intragam 10 NF is indicated for immunomodulatory therapy in:* · *immune thrombocytopenic purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count* · *allogeneic bone marrow transplantation* · *Kawasaki disease* · *Guillain-Barre syndrome (GBS)* · *chronic inflammatory demyelinating polyneuropathy (CIDP)* · *multifocal motor neuropathy (MMN)* · *myasthenia gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects* · *short-term therapy for severely affected nonparaneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients* · *treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.*
Route(s) of administration:	Intravenous (IV)
Dosage:	The optimal dose and frequency of administration of Intragam 10 NF must be determined for each patient. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state and the pre-infusion IgG level.

Product Background

The current Australian application proposes a variation to the product Intragam P (AUST R 68632-68635), with amendment of trade name to Intragam 10 NF, increase in strength from 6% weight/volume (w/v) to 10% w/v protein; replacement of the excipient maltose with glycine, addition of an additional viral filtration step in manufacture and addition of 5 additional indications (to provide closer alignment of product information with guidelines for clinical use of IV immunoglobulins). The additional indications are for immunomodulatory therapy in chronic inflammatory demyelinating polyneuropathy (CIDP); multifocal motor neuropathy (MMN); myasthenia gravis (MG); Lambert-Eaton myasthenic syndrome (LEMS) patients; and stiff person syndrome (SPS). Glycine is used as an excipient (stabiliser) in some other IV IgG products, such as Gamunex and Gammagard/Kiovig (Baxter), and an IM IgG product, Normal Immunoglobulin-VF.
The development of the Intragam 10 NF formulation was based on CSL's decision to produce an IVIg product with improvements over the parent product, Intragam P. The proposed, more concentrated, product is consistent with a recent global trend towards the use of 10% w/v formulations of IVIg preparations, allowing shorter infusion times (dependent on patient tolerability), resulting in a reduction in patient time in the clinic and smaller infusion volumes. The currently approved product Intragam P (6% Ig) is expected to be replaced in Australia by Intragam 10 NF over a period of time.

Regulatory Status

An application for registration of Intragam 10 NF has been lodged in New Zealand (31 July 2009) and the outcome is currently pending.

Product Information

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

II. Quality Findings

Drug product

Presentation and composition

Intragam 10 NF is a sterile, preservative-free solution containing 10 % w/v human protein (at least 98 % Immunoglobulin G (IgG)), 2.25 % glycine and water for injections. The solution has a pH of 4.25, with isotonicity achieved by the addition of glycine. It is manufactured from large pools of human plasma (Australian donors) by chromatographic fractionation, and distributed by the Australian Red Cross Blood Service (ARCBS). The company state that it complies with the British Pharmacopeia (BP) and European Pharmacopeia (Ph Eur) monograph for 'Normal Immunoglobulin (Human) for Intravenous Use'.

All of the validation studies provided with the dossier were performed on the two clinical batches of product that were used for the clinical trials.

Manufacture

An overview of the manufacturing process of the drug substance and drug product for Intragam 10 NF was evaluated.

The proposed in-process control specifications control the potency of the immunoglobulin and excipient ingredients. Appropriate validation data have been submitted in support of the test procedures.

The proposed release specifications for Intragam 10 NF were submitted. The analytical procedures for determining identity, potency, purity, dose delivery and other chemical and microbiological properties relevant to clinical use of the product are generally in accordance with the Ph. Eur/BP/US Pharmacopeia. Appropriate validation data have been submitted in support of the analytical procedures. All steps relating to the manufacture of the Intragam 10 NF drug substance have been previously approved by the TGA for Intragam P. The main change to the manufacturing process for Intragam 10 NF is the addition of a virus filtration which was fully validated.

Sterility safety

Sterility aspects of the product have been reviewed, with all issues resolved.

Pharmaceutical SubCommittee (PSC) supported the Evaluator's recommendation that the sponsor should lower the pre-sterilisation bioburden limit to a more acceptable level. CSL subsequently provided more information to the TGA and proposed to lower the bioburden. This has been evaluated by the Microbiology Section as suitable and consistent with other similar products on the market.

Container safety

The finished product is supplied in clear neutral Type I glass vials of capacity 50, 100 & 250 ml. This packaging format and the components are identical to those used with Intragam P, except with different fill volumes. There are no outstanding issues with regards to container safety.

Endotoxin/pyrogen safety

Endotoxin safety aspects of the product have been reviewed, with all issues now resolved.

Viral/prion safety

The Pathogen Safety Aspects have been reviewed, with all issues resolved. The manufacturing process for Intragam NF contains an additional virus removal step to the former Intragam P process. Therefore, all of the logarithmic reduction factors (LRFs) are comparable to or higher than those for the currently approved Intragam P process.

Bioavailability

Bioavailability data are not required for this product because the route of administration of Intragam NF is IV.

Stability

The proposed shelf-life is 24 months at 2 - 8°C and then 3 months at 26 - 28°C.
Stability data was generated under stressed and real time conditions to characterise the stability profile of the product. There was some question over whether stability data provided on the different presentations are sufficient to justify approval of all presentations. The PSC endorsed the recommendation of the evaluator to approve the shelf-life for all presentations, citing that the sponsor has given an undertaking to provide appropriate data to establish the stability of these products.

Quality Summary and Conclusions

All deficiencies and other issues identified during the evaluation of the manufacture and quality aspects have now been satisfactorily resolved and were endorsed by PSC.

III. Nonclinical Findings

Introduction

The main focus of the nonclinical assessment is the potential toxicity of the excipient glycine. Although glycine is used as an excipient in several of CSL's marketed IM IgG products[1] at similar specifications and concentrations, the effects of long-term, high dose administration, in particular during pregnancy and neonatal development, requires assessment.

Human IgG is a naturally occurring plasma protein with known pharmacological properties, and IgG products have been available for human use for more than 15 years in Australia. The information to be gained from animal toxicity studies is limited, as repeated dosing in animals can result in immune responses to human IgG, making interpretation of the results difficult. The nonclinical testing was therefore limited to one acute tolerance study evaluated by TGA in June 2006. Nonclinical repeat-dose toxicity, reproductive toxicity, mutagenic and carcinogenicity studies are generally not warranted for IgG products.

Several studies were conducted to support the substitution of maltose with glycine in the new formulation. These studies focused on the repeat-dose and developmental toxicity of glycine. L-proline was used as a comparator in these studies. The length of the pivotal repeat-dose study, 4 weeks, was considered appropriate considering the half-life of glycine (see *Pharmacokinetics* below) and the dosing regimens proposed for Intragam 10 NF. The rat was a suitable test species as it has a similar glycine kinetic profile to humans. The 7 hour (h) infusion/day regimen was chosen since intermittent daily administration is common in clinical practice. The highest dose (HD) of glycine of 945 mg/kg/day was the highest applicable dose, restricted by osmolarity of the solution and the dose volume. Animal numbers and endpoints were generally adequate across all studies.

Thirteen published references were submitted but only one was evaluated as the others were considered to be background references or were small reports highlighting technical inadequacies during human blood collection (including non-aseptic methods, incorrect labelling of vials and patient history notes) noted by the FDA. The published paper that was evaluated examined the effects of a high-dose, long-term glycine diet on rat brain cell morphology.

Pharmacology

No new data were submitted.

Pharmacokinetics

No nonclinical pharmacokinetic studies have been conducted with the new strength formulation. The absorption, distribution, metabolism (protein degradation) and excretion pathways for immunoglobulins are well-described in the literature and no further studies are considered necessary. The plasma half-life in animals is usually considerably shorter than in humans (hours-days compared to ~ 4 weeks), and such studies are therefore of limited value.

[1] Hepatitis B Immunoglobulin-VF (AUST R 612 13, 612 14), Normal Immunoglobulin-VF (AUST R 61225, 612 16), Rh(D) Immunoglobulin-VF (AUST R 61217, 76643), Tetanus Immunoglobulin (for IM use)-VF (AUST R 612 18) and Zoster Immunoglobulin-VF (AUST R 612 19).

In adult rats, glycine infusions ≤ 945 mg/kg/day (12.6 mmol/kg/day) daily for 5 or 28 days led to transient peak serum concentrations of up to 7 times baseline values. No significant accumulation of glycine was noted. Urinary excretion of glycine was increased by up to 2-5 fold the control level following 4 weeks of glycine infusions. A similar kinetic profile was revealed in pregnant animals except that glycine levels were somewhat lower in all groups (including controls) on gestation day (GD) 17 compared to GD 6. The reason for this is unclear.

Studies of glycine in healthy volunteers indicate that it is mainly distributed within the plasma and extracellular fluid compartments (apparent volume of distribution (V_d) was ca 0.1 L/kg). Glycine is subjected to the endogenous biotransformation routes of amino acids, with an estimated elimination rate constant (k_{le}) in healthy volunteers of 5.2/day.

Relative systemic exposures

Exposures to glycine were relatively low in the rat toxicity studies, particularly when compared on the basis of body surface area (see Table 1). Maximum doses in rats were limited by dose volumes and osmolarity.

Table 1. Animal/human glycine exposure ratios in nonclinical IV studies

Study type (no.)	Treatment	Glycine exposure multiple	
		mg/kg	mg/m²
Rat safety pharmacology[1]	Glycine 378, 945 mg/kg/day (7 h/day)	0.8, 2.1	0.2, 0.4
Rat acute toxicity	IgG 4 g/kg, glycine 750 mg/kg (2 h)	1.7	0.3
Rat repeat-dose toxicity	Glycine 378, 945 mg/kg/day (7 h/day) for (i) 5 days (ii) 28 days	0.8, 2.1	0.2, 0.4
Rat embryofetal development	Glycine 945 mg/kg/day (7 h/day) on GD 6-17	2.1	0.4
Human maximum proposed dose	IgG 2 g/kg, glycine 450 mg/kg	---	---

[1]Irwin test + body temperature

Toxicokinetic data were provided upon a TGA request by the sponsor for the subcutaneous (SC) route in young rats. These data showed that glycine was rapidly absorbed and cleared. No data were available on glycine bioavailability by the SC route.

Toxicology

Acute toxicity of Intragam 10NF

One acute IV toxicity study with a similar formulation (CSL0455) to Intragam 10 NF was evaluated by the TGA in 2006.

The single 2 h IV infusion of IgG 4 g/kg CSL0455 to Sprague-Dawley rats was associated with generalised oedema and red staining in the animal cage. The latter may be a reflection of haematuria or haemoglobinuria. Such findings are consistent with previous studies with human IgG in rats (for example, Intragam P). Infusion of glycine 750 mg/kg alone had no effect.

Glycine toxicity

The concentration of glycine excipient in Intragam 10 NF is similar to CSL's 16% Ig solutions, which are administered by deep intramuscular (IM) injection (Normal Immunoglobulin-VF), and slightly higher than in Gamunex. Glycine is an inhibitory neurotransmitter in the central nervous system (CNS), and most nonclinical studies for Intragam 10 NF focussed on its potential toxicity.

Safety pharmacology

The effects of glycine or L-proline infusion on behaviour (Irwin test) and body temperature were assessed in rats. Glycine (but not L-proline) triggered behavioural changes in adult rats at doses of 378 and 945 mg/kg/day IV for 5 days, with statistically significant effects on spontaneous activity, CNS excitability and autonomic measures. There were no effects on neuromuscular or sensorimotor function. A no observable effect level (NOEL) could not be set as only two dose levels of glycine were administered. Since glycine is one of the major inhibitory neurotransmitters of the CNS, behavioural changes were not unexpected. Glycine (and L-proline) also induced significant increases in rat body temperatures (0.2-0.4°C more than the control group) following 5 days of treatment. However, this effect was slightly greater, and more clearly dose-dependent, in response to L-proline.

Acute toxicity

An acute toxicity study showed no adverse effects in rats infused IV with 750 mg/kg glycine alone.

A publication reported that IV infusion (45 min) of glycine 100 or 200 mg/kg in humans dose-dependently increased serum and cerebrospinal fluid (CSF) glycine levels but had no significant effects on behaviour, cognition or acoustic startle responses, nor toxic effects (D'Souza *et al*., 2000[2]). Peak plasma glycine levels were 1352 ± 165 µmol/L and 5093 ± 823 µmol/L at 45 min, and 537 ± 224 µmol/L and 775 ± 304 µmol/L at 135 min (normal range 120-553 µmol/L).

Repeat-dose toxicity

Two repeat-dose studies of glycine (5 days and 4 weeks) were submitted. In both studies, doses of 378 and 945 mg/kg glycine were administered IV for 7 h/day. The HD of 945 mg/kg/day was the highest practical dose, restricted by osmolarity of the solution and the dose volume. There was no significant toxicity in the 5-day study. In the 4 week study, bodyweight gain was slightly reduced, and minimal to slight perivascular lymphoid cuffing, minimal to moderate alveolar histiocytosis and/or haemorrhage, and minimal to marked focal/multifocal granuloma were noted in the lungs, with similar severity in control and treated groups. Such findings can be common in IV infused rats as a result of the infusion procedure. Thromboembolic events have also been described as *very rare* in humans (in the proposed Australian PI document).

A published reference showed that high-dose, long-term glycine exposure (1 or 5 g/kg/day for 1-5 months) can induce morphological changes in the adult rat brain, including decreases in N-type Ca^{2+} channel density and a transient hypertrophy of

[2]D'Souza D.C. *et al.,* 2000. IV glycine and oral D-cycloserine effects on plasma and CSF amino acids in healthy humans. *Biological Psychiatry* 47(5): 450-462.

astrocytes. This occurred in the absence of overt signs of neurotoxicity (Shoham *et al*., 2001[3]).

Carcinogenicity and Genotoxicity

No genotoxicity or carcinogenicity studies have been conducted. This is acceptable for an IgG product formulated with glycine based on the known properties of these constituents.

Reproductive toxicity

The Note for Guidance on Core Summary of Product Characteristics (SPC) for human Normal Immunoglobulin (IVIg) (CPMP/BPWG/859/95 rev.2) states that "*Clinical experience with immunoglobulins suggest that no harmful effects on the course of the pregnancy, or on the foetus and the neonate are to be expected*". It is therefore acceptable that no reproductive or developmental toxicity studies have been undertaken with Intragam 10 NF.

The sponsor conducted an embryofetal development study in rats, and a developmental toxicity study (2 phases) in young rats with glycine (and L-proline) alone.

In the rat embryofetal development study, preimplantation loss was greater in females treated with glycine 945 mg/kg/day compared to controls, largely due to 2 females that each had a significant loss (>70%). In addition, enlarged ventricular chambers were noted at a slightly higher incidence in fetuses from glycine (at 945 mg/kg/day and 1447 mg/kg/day L-proline) treated groups. The incidence of this vascular change was greater than both the concurrent control and the historical control range from the sponsor's laboratory, but the distribution of the finding did not indicate a relation to treatment.

In young rats treated over postnatal days (PND) 9-23, 5 days of daily treatment with glycine 1000 mg/kg twice a day (*bid*) SC did not cause clinical signs of neurotoxicity. There was also no affect on the acquisition of reference memory or working memory as assessed in the Morris water maze task, one month post-treatment, on PND 54-57. Bodyweight gain and the general health of the treated animals appeared to be normal.

Local tolerance

No specific local tolerance studies have been conducted with the new strength formulation. Except for a slight increase in mural thrombus formation (in females) at the infusion site, no overt local toxicity was associated with glycine infusion in the 5 and 28 day toxicity studies in rats.

Nonclinical Summary and Conclusions

The sponsor provided adequate justification for the limited range of nonclinical studies using the proposed formulation.

Recommendations

The sponsor provided adequate justification for the lack of nonclinical studies with the proposed IgG formulation. Animal studies are limited by immune reactions against the human IgG, and dose volume constraints. The nonclinical data consisted of an acute toxicity study with a similar IgG formulation, and IV safety (neurotoxicity), repeat-dose and developmental toxicity studies with the glycine excipient.

The nonclinical data raise no objections to the registration of Intragam 10 NF solution (human normal immunoglobulin) for the proposed indications, however in view of the

[3] Shoham S *et al* (2001). Chronic high-dose glycine nutrition: effects on rat brain cell morphology. *Biological Psychiatry* 49(10): 876-885.

practical limitations of nonclinical testing, demonstration of safety and efficacy will depend mainly on clinical data.

IV. Clinical Findings

Introduction

The clinical trial program was designed in accordance with the European Union (EU) "Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg)"[4]. As Intragam 10 NF met the guideline criteria for a 'modified product', CSL proposed to adopt the same posology in all listed therapeutic indications (replacement IgG therapy and immunomodulatory therapy) as the currently registered parent IVIg product Intragam P. Support for the additional indications, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and stiff person syndrome was obtained from (submitted) published literature. Clinical data supported the changes to the product formulation and strength. Published references cited in this evaluation are listed at the end of this AusPAR document.

IVIg is used for two major therapeutic purposes in human disease: antibody replacement and immunomodulation. IVIg use as replacement therapy is the standard of care for patients with primary immunodeficiency disease (PID) characterised by absent or deficient antibody production and recurrent or unusually severe infections. IVIg replacement may also be required in antibody deficiency secondary to other diseases, such as lymphoproliferative diseases (non-Hodgkin's lymphoma and chronic lymphocytic leukaemia) and multiple myeloma. IVIg use as immunomodulatory therapy may have a beneficial effect in a range of auto-immune disorders such as idiopathic thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), and Kawasaki disease.

Clinical Trials Performed

To meet the requirements of the relevant guideline criteria (referred to above) as a modified product, Intragam 10 NF was required to show no change in the biological, pharmacokinetic (PK) or safety data from the parent product. Two clinical trials in patients with PID and ITP were conducted with Intragam 10 NF, the first clinical trials conducted with this product. The first study examined the PK profile in comparison with Intragam P in patients with PID currently receiving Intragam P (PID study), and assessed for the safety and tolerability. The second study, in patients with ITP, examined the safety and efficacy of Intragam 10 NF in this population.

New Indications. Literature Based Submission

The application states that the current use of IVIg in Australia follows international clinical guidelines and a recent document, "Criteria for the clinical use of IV immunoglobulin in Australia (2007)[5]", which reflects best clinical practice based on the best evidence of efficacy in the literature as well as expert opinion.

This section of the application was to extend the indication of IVIg, consistent with these criteria, and in particular, the neurological indications identified in Chapter 5 of these criteria, "Established Use".

[4] EU Note For Guidance on the Clinical Investigation of Human Normal Immunoglobulin For Intravenous Administration (IVIg) (CPMP/BPWG/388/95, rev. 1, 29 June 2000).

[5] http://www.nba.gov.au/ivig/pdf/criteria.pdf

As no clinical trials have been conducted with Intragam P or Intragam 10 NF in neurological indications, CSL submitted a Literature-Based Submission (LBS) based on a systematic review of the published literature to support the proposed extension of clinical indications. The TGA Guidelines for Literature-Based Submissions refer to the requirement that the product must have been on the market in Australia for 10 years or more. This is true for CSL's Intragam P formulation which has been marketed since 1999 (previously marketed as Intragam from 1989) and the submission for Intragam 10 NF was designed to show equivalence of the 10% formulation with the current registered formulation. The TGA accepted a literature based submission, based on the published literature for a range of IVIg formulations in the proposed neurological indications. The TGA reviewed the literature search, and revisions suggested by the TGA were incorporated into the final search strategies for each proposed indication.

Safety of the new formulation was based on the safety profile for Intragam P, updated with the safety findings for Intragam 10 NF and the specific PID and ITP clinical studies conducted with this new product.

Good Clinical Practice (GCP) and Ethical aspects

The studies were conducted under the Clinical Trial Exemption Scheme of the TGA, and were conducted in accordance with the following: Committee for Proprietary Medicinal Products, International Conference on Harmonisation. *Note for Guidance on Good Clinical Practice*. CPMP/ICH/135/95; annotated with TGA comments, Drug Safety and Evaluation Branch; July 2000; Committee for Proprietary Medicinal Products, Blood Product Working Group. *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg).* CPMP/BPWG/388/95 rev.1; June 2000 (adopted by the TGA for the registration of IV immunoglobulin (IVIg) medicinal products in Australia); the Declaration of Helsinki (June 1964/October 1996).

Informed consent was obtained in writing from each patient prior to entry into the study. The protocol, patient information and consent form and investigator Brochure were considered and approved by an Independent Ethics Committee (IEC) for each of the five Australian study centres of which four enrolled patients. Quarterly reports were provided to the IECs for review.

Safety Review Committee

An interim analysis was conducted to review the safety data available in the study database as of 14 March 2008, in particular the two reported cases of aseptic meningitis syndrome. A Safety Review Committee (SRC) comprising three independent members met with CSL representatives in March 2008. Minutes of the Meeting and the committee's recommendations were provided in an appendix to the study report.

Pharmacokinetics

The pharmacokinetic (PK) properties of Intragam 10 NF were investigated in patients with PID in the Phase III study CSLCT-PID-05-22, a multi centre, open-label, cross-over study to compare the pharmacokinetics, safety and tolerability of Intragam 10 NF with Intragam P in patients with PID. All patients had been receiving Intragam P for at least 6 months prior to study commencement. Patients were assigned to either a 3 or 4 weekly dosing schedule, consistent with their previous dosing schedule with Intragam P prior to entering the study.

The primary objective of the study was to compare steady state serum IgG trough levels (C_{min}) of Intragam 10 NF with those of Intragam P in patients with PID. The secondary objectives were to compare the PK profile of Intragam 10 NF to that of Intragam P in

patients with PID, and to assess the safety and tolerability of Intragam 10 NF in patients with PID.

Evaluator's comment: The stated objectives are acceptable to show the biosimilarity of Intragam 10NF and Intragam P, as recommended in the relevant guidelines for evaluating human immunoglobulins. As biosimilarity was to be shown, efficacy data were not required, and none are included. Safety data, as required, were included and combined with those from the second clinical study. They will be evaluated in the Safety section. Because the study did not include efficacy data, the following format of this evaluation combines the formats for Pharmacokinetics and Efficacy.

Methods

Criteria for Selecting Patients

All the inclusion and exclusion criteria have not been presented here, as many were standard for a study of this type and require no special comment. Inclusion Criterion 3 does need special mention because 10 of the 19 enrolled patients were in violation of the criterion. Inclusion Criterion 3 required patients to have received a consistent dose of Intragam P at 3 or 4 weekly intervals, within the range of 0.2-0.8 g/kg body weight for at least 6 months prior to screening. Also, inclusion Criterion 4 required patients to have maintained IgG trough serum concentrations of ≥ 5 g/L during the 6 months prior to screening, with at least two trough concentrations documented during this period. The possible effect of this violation will be discussed below.

The following exclusion criteria were special and are provided for information:

- patients with known selective IgA deficiency or antibodies to IgA;
- patients receiving immunosuppressive treatment other than topical and/or inhaled steroids and/or low dose oral steroids;
- patients with protein-losing enteropathies or kidney diseases with substantial proteinuria;
- patients with a history of malignancies of lymphoid cells such as chronic lymphocytic leukaemia, non-Hodgkin's lymphoma and immunodeficiency with thymoma were excluded.

Prior and Concomitant Therapy

Topical and/or inhaled and/or low dose oral steroids (that is, 5-10 mg) were permitted for the duration of the study provided that there was no change in treatment within the 15 days prior to screening. Pre-medication for infusion-related adverse events (AEs) prior to IVIg infusion was permitted at the discretion of the investigator or based on normal hospital procedures for the administration of IVIg. Patients were not permitted concomitant treatment for PID and this included any of the following medications or therapeutic class medications:

- other immunoglobulins, including anti-D preparations;
- IV steroids;
- immunosuppressant medications;
- blood products (for example, platelets or erythrocyte infusions) that may contain immunoglobulin.

If, in the opinion of the investigators, the prohibition of the above medication was not in the best interest of the patient, the patient was to be withdrawn from the study and the Final Visit conducted at least 30 days after Day 1 of the patient's last cycle.

Measurement of IVIg

Blood samples for measurement of serum IgG trough concentrations were collected from all patients prior to each infusion of either IVIg product and serum IgG trough concentrations analysed by the local laboratory at each site.

Evaluator's comment: The measurements were done at each of four different sites "to ensure no inter-laboratory variation". Of the four sites, three used the same system, presumably based on immunochemistry, while the fourth used an immunoturbidimetric assay. The sponsor should provide a comparison on these two systems of measurements. No Limits of Quantification (LOQ) were given[6]. On the other hand, serum samples for measurement of IgG and IgG subclass for the PK analysis were analysed at the same laboratory. The LOQ was not given for IgG_1 and IgG_2 but for IgG_3 and IgG_4 the values were < 0.05 g/L and < 0.07 g/L, respectively.

Sampling times for PK analysis

Blood samples were to be collected during two PK assessment periods (Cycle 0 and Cycle 4) to compare the PK parameters after administration of Intragam P and Intragam 10NF. IgG subclass analysis was only performed at Cycle 4 (Intragam 10NF). Sampling times and allowed windows were as follows during the two cycles: pre-infusion (Day 1), at the end of infusion and at 3 and 24 hours after the start of infusion, and on Days 4, 8, 15, 22 and 29 after the start of infusion (in patients on 4 week schedule only).

Evaluator's comments: The two treatments were administered successively to the each patient. The time between treatments at the start of each cycle was 22 days for those patients (about 16%) receiving 3 weekly infusions, and 29 days for those on 4 weekly infusions. The mean half-life of IgG is approximately 35 days. It thus follows that at the start of the new treatment with Intragam 10NF on Day 1 of Cycle 1, less than one half-life of the serum concentration of IgG had elapsed, meaning that about 50% of Intragam P would be present at the start of the infusion. However the PK parameters of Intragam 10NF were not evaluated until Day 1 of Cycle 4 of treatment, that is, 12 to 16 weeks (2.4 to 3.2 half-lives) from Day 1 of Cycle 0. This time was long enough to exclude significant carry-over effects from the first treatment with Intragam P. In addition, the duration of PK sampling was 22 or 29 days, which is less than one half-life and therefore were not long enough to determine the terminal half-life of Intragam 10NF with confidence.

Statistical Analysis

Summary statistics for continuous data included sample size (N), mean, standard deviation (SD), median, minimum and maximum values. For categorical variables, summary statistics included the frequency and percentage. In addition, the mean and 95% confidence intervals (CI) for serum IgG trough concentrations (Cmin) were calculated for each treatment and schedule (21 days for the 3 weekly dosage regimen and 28 days for the 4 weekly dosage regimen). The geometric mean and 95% CIs for the PK variables were calculated for each product at Cycle 0 (Intragam P) and Cycle 4 (Intragam 10NF).

[6] Sponsor comment:

The different methods of analysis are a reflection of the variation which exists in testing at different clinics across Australia and therefore is a reflection of the 'real life' scenario for clinicians measuring the trough IgG concentrations of their patients to assess the appropriate dose, outside of the clinical study setting and to also address the different requirements of a complete PK assessment.

The four populations analysed were:

1. Safety Population. Defined as all patients who had received at least one dose (partial or complete) of Intragam 10NF.

2. Intent-to-Treat (ITT) Population. Defined as all patients who received at least one dose (partial or complete) of Intragam 10NF and who had sufficient valid samples to evaluate the trough concentration for at least one cycle of each treatment.

Evaluator's comment: The original use of an ITT population (one that included all patients entered in the study) was to avoid the bias of selecting some patients and not others for analysis and also to better resemble the population to be treated outside the study. The question here is whether bias could be introduced by including only patients with adequate samples for analysis. However, if patients with samples that were not analysable were included, their results would be recorded as zero which would distort the results in a study of this type. For this reason, the stated definition of the ITT population can be accepted. In the present study, both populations were analysed and the results were comparable.

3. Per Protocol (PP) Population. Defined as all patients who completed the study without any major protocol violations or deviations and who had attended all study visits**.**

4. Pharmacokinetic (PK) Population. Defined as all patients who received a dose of Intragam P at Cycle 0 and at least three doses of Intragam 10NF (including the dose at Cycle 4) and who had sufficient valid samples to evaluate the PK profiles for both treatments.

The PP and ITT Populations were used to analyse the trough concentrations of IgG and presented separately from the PK analysis.

Analysis of IgG trough concentration

Patients received one cycle of Intragam P followed by up to seven cycles of Intragam 10 NF. Trough concentrations were assessed prior to dosing so that two trough levels were available for Intragam P (pre-dose at Cycles 0 and 1) and six trough levels for Intragam 10 NF (pre-dose at Cycles 2 to 7). The IgG trough concentrations were analysed for the ITT and PP Populations to determine the mean difference in trough concentrations between treatments as well as average trough concentrations across both treatments along with 95% CIs. The comparability of the two treatments was then be assessed by examining the CI for the within-patient difference in trough concentrations. No equivalence margins were specified in advance.

Pharmacokinetic Analysis

The secondary objective of the analysis was to compare the PK profile following the two treatments, Intragam 10 NF (during Cycle 4) and Intragam P (during Cycle 0). The IgG concentrations over time were presented by patient and cycle and summarized over time for the cycles, as well as the IgG subclasses (IgG1, IgG2, IgG3 and IgG4). The LOQ for IgG3 and IgG4 are given above.

Results

Disposition of patients

A total of 19 patients were enrolled in the study and received at least one dose of Intragam 10 NF. All patients completed the study.

Protocol Deviations

Ten (52.6%) patients entered the study but did not fulfill inclusion or exclusion criteria and were therefore considered as having major protocol deviations (failing to meet inclusion Criterion 3 (see above) and were given permission to enter the study by the CSL Medical Monitor. Eight of these 10 patients had not followed a strict schedule during the 6 months prior to screening; one patient had a dose increase during the 6 months prior to screening and another patient had an interval variation and a dose decrease during the 6 months prior to screening.

The above 10 patients were excluded from the per-protocol analysis according to the definitions detailed in the Statistical Analysis Plan. The results in the ITT, PK and Safety Populations are presented in the report with the IgG trough results reported for both the ITT and PP Populations.

There were a number of minor protocol deviations noted during the study. These included visits occurring outside protocol-specified time windows, blood samples for PK or specific laboratory parameters collected outside the protocol-specified windows or not being collected at all or study procedures not occurring as required by the protocol. These minor deviations were considered to have no impact on the interpretation of the results of the study.

Evaluator's Comments:

1. Did the major protocol violation of Inclusion Criterion 3 affect the study analysis and conclusions?

The intention of inclusion Criterion 3 was to have all enrolled patients on a consistent dose of IV IgG when they entered the study, presumably to avoid any effects of a dose change when the study began. Such a change could affect subsequent PK measurements. A consistent dose of IgG also would imply that a patient was at a steady state with respect to the serum concentration of IgG.

2. Pre-study conditions.

It is hard to see how a true steady state could be obtained pre-study if steady state conditions were defined conventionally as the state existing when the amount of drug administered equals the amount cleared from the body. In the pre-study period, all that was required clinically was that the dose of IgG be such as to maintain the serum concentration of IgG at 5g/L or more for therapeutic effectiveness. The trough concentrations of the patients in the pre-study period met this condition in almost all cases (and were usually much higher than 5g/L) so these conditions were not strictly steady state.

Although doses were changed in some patients pre-study, the data shows that patients had been treated for about 10 years. Over the 6 months preceding the study, the mean dose of IgG was 0.427g/kg with a small SD of 0.09, and a mean total dose per patient of 29.5g, with a SD of 5.9g. The small value of the SD indicates reasonable consistency of treatment under non-study conditions, and can be accepted as having no major effect on the study. It would not have been possible to obtain strict steady state conditions before study.

3. Were the trough concentrations of IgG during the study at approximate steady state compared to pre-study values?

FDA's guidance for industry entitled "Bioequivalence Guidance",[7] gives a formal method to determine steady state: "…to determine a steady state concentration, the C_{min} values should be regressed over time and the resultant slope should be tested for its difference from zero." This analysis was not a requirement, and more usually assessment is done by inspection.

For all but one patient the IgG trough concentrations are similar throughout the study. For one patient, the last two values are lower than expected[8]. Those with low values before the trial also tend to have lower values throughout. No range has been defined for steady state of the C_{min}, but the above variations are small and can be accepted as approximating steady state. This in turn means that the values of trough concentrations and those of the PK parameters would not be affected by the protocol violation above.

During the study, a change in dosage for a particular patient was allowed in the protocol within a stated dosing range. Such a change could also affect the steady state of that patient. This is considered below under treatment administered.

Demographics and patient characteristics

Eight (42%) patients were male and 11 (58%) were female with a mean age of 43.9 (median 44.2, range: 18.7 to 69.1) years. Some 90% had common variable immunodeficiency disease (CID). Some 94.7% were White. Disease (PID) characteristics are summarised in the table below (Table 2).

[7] http://www.fda.gov/dayownloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052363.pdf

[8] The sponsor added the comment that the evaluator references an FDA guideline not yet accepted in Australia and that their study followed the guidelines currently accepted in Australia which require trough levels to be documented for the two previous infusions prior to the introduction of the new IVIg preparation in order to demonstrate steady state. Furthermore, for the patient mentioned, the last two values are not lower than expected as they are within the range of values measured for this patient over the previous 12 months.

Table 2. Baseline characteristics of PID. All enrolled patients.

	Total Patients N=19
Type of PID	
n	19
XLA	2 (10.5%)
CVID	17 (89.5%)
Time since PID diagnosis (years)	
n	19
Mean (SD)	10.7 (8.7)
Median	10.0
Min, Max	1, 30
Intragam® P dosage (g/kg)	
n	19
Mean (SD)	0.427 (0.09)
Median	0.440
Min, Max	0.22, 0.64
Intragam® P total dose (g)	
n	19
Mean (SD)	29.5 (5.9)
Median	30.0
Min, Max	21, 42
Treatment schedule	
n	19
Three-week	3 (15.8%)
Four-week	16 (84.2%)

Abbreviations: CVID = common variable immunodeficiency; PID = Primary Immune Deficiency; XLA = X-linked agammaglobulinaemia.
Note: Percentages are based on the total number of patients.

Evaluator's comment: Of note is that the mean and median times since diagnosis were long, about 10 years, and the mean and median pre-trial doses of IVIg were within the range of doses (0.2-0.8g/kg) to be used in the study.

Concomitant Medications

No patients were taking concomitant medications that were prohibited in the protocol.

Treatment administered and possible effect on the steady state, trough values, and PK analysis

Two patients had a dose change during Cycles 1 to 7.In both patients, the increases occurred at the investigators' discretion as permitted in the protocol. These increases were appropriate and justifiable on clinical grounds as the patients' serum IgG trough levels and were also within the recommended dosage range of the protocol (0.2-0.8 g/kg). The laboratory analysis showed that there was no difference observed in the steady state serum IgG trough levels between the two treatments for both of these patients.

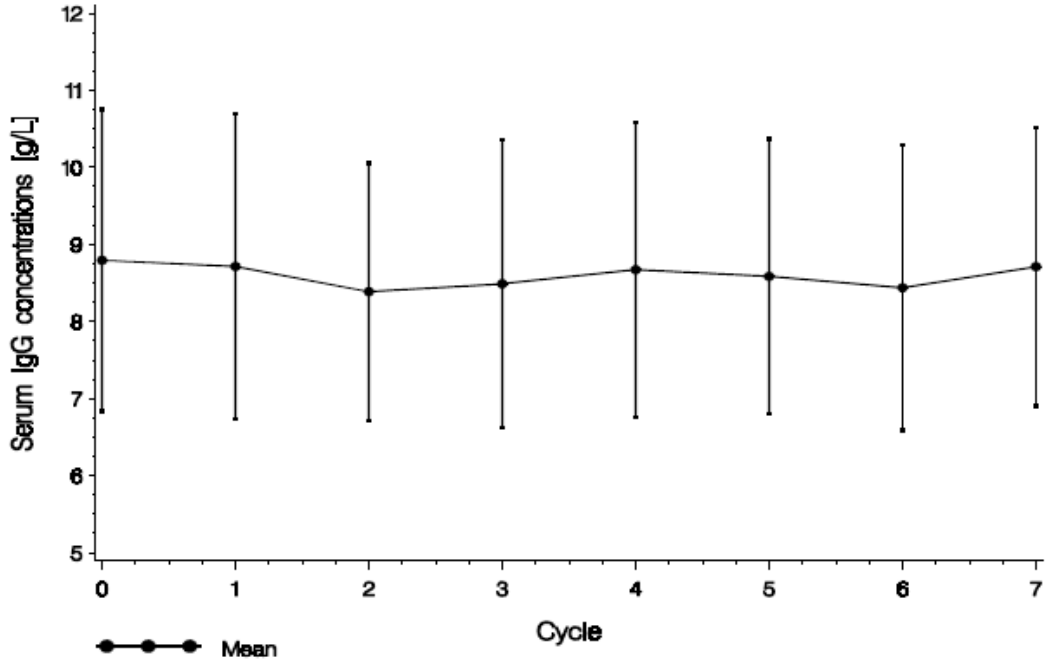
Analysis of Trough IgG Concentrations

The serum IgG trough concentrations achieved with Intragam P were assessed twice. For the ITT Population, the mean steady state IgG concentrations were 8.80 and 8.72 g/L (Cycles 0 and 1, respectively) and individual concentrations ranged from 5.0 to 12.8 g/L.

The mean serum IgG trough concentrations achieved with Intragam 10 NF were assessed for Cycle 2 through to Cycle 7 and ranged between 8.39 and 8.72 g/L (ITT Population). Individual trough serum IgG concentrations ranged between 5.2 and 12.9 g/L.

The eight assessment time points (two time points for Intragam P and six time points for Intragam 10 NF) are presented on a linear scale in Figure 1 (below), demonstrating a stable IgG concentration profile.

Figure 1. Mean trough serum IgG concentration by Cycle, ITT population (error bars show SDs).



Statistical Analysis

The results of the statistical analysis of serum trough IgG concentrations showed that the geometric mean trough concentrations for the two treatments (Intragam P [Cycle 0] and Intragam 10 NF [Cycle 4]) were similar, with a comparison ratio of 1.034 (95% CI 0.996 to 1.073).

Pharmacokinetic Parameters

Parameters for serum IgG and for its subclasses were determined.

Serum IgG Concentrations: Geometric mean serum IgG concentrations versus time profiles (Figure 2 below) showed that the IgG concentrations over time were similar for the two treatments (Intragam P [Cycle 0] and Intragam 10 NF [Cycle 4]).

Figure 2. Geometric mean serum IgG concentrations for Cycles 0 and 4. PK population (error bars show SDs).

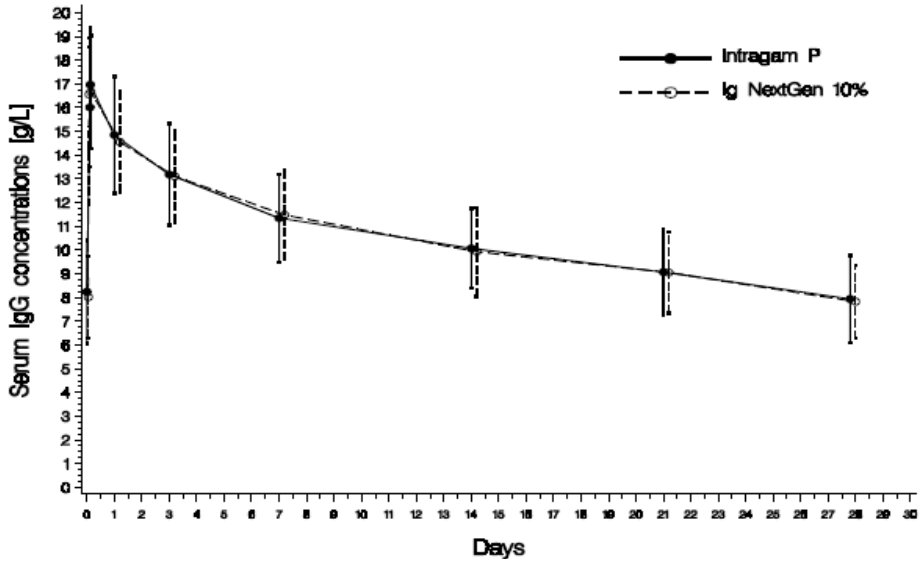


Table 3 shows the PK parameters for serum IgG.

Table 3. Serum IgG pharmacokinetic variables per treatment. PK population.

Variable	Statistic	Intragam® P (Cycle 0)	Ig NextGen 10% (Cycle 4)
C_{max} (g/L)	N	19	19
	Min ; Max	11.3 ; 20.9	11.9 ; 21.4
	Geometric mean	16.08	16.58
	95% CI[a]	14.79 ; 17.47	15.38 ; 17.88
t_{max} (day)	N	19	19
	Mean	0.21	0.09
	Median	0.12	0.08
	Min ; Max	0.09 ; 1.05	0.06 ; 0.13
	95% CI[a]	0.11 ; 0.20	0.08 ; 0.10
C_{min} (g/L)	N	19	19
	Min ; Max	4.7 ; 11.5	4.9 ; 11.3
	Geometric mean	7.65	7.65
	95% CI[a]	6.86 ; 8.52	6.89 ; 8.50
$AUC_{(0-t)}$ (day*g/L)	N	19	19
	Min ; Max	199.9 ; 407.8	188.2 ; 383.9
	Geometric mean	272.88	275.89
	95% CI[a]	247.79 ; 300.50	251.10 ; 303.12
CL (L/day)	N	19	19
	Min ; Max	0.06 ; 0.21	0.06 ; 0.22
	Geometric mean	0.11	0.11
	95% CI[a]	0.09 ; 0.12	0.09 ; 0.12
$t_{1/2}$ (days)	N	19	19
	Min ; Max	23.9 ; 52.3	25.0 ; 50.6
	Geometric mean	35.73	34.62
	95% CI[a]	31.64 ; 40.36	31.48 ; 38.07

[a] 95% CI = 95% confidence interval for the geometric mean.
Note: The CI for t_{max} was not conducted on the mean but on the geometric mean.

The statistical analysis of the above data gave ratios of the above parameters (with the 95% CI) as shown in Table 4.

Table 4. Serum IgG pharmacokinetic variables comparison. PK population.

Variable	Statistic	Comparison Ratio (Intragam® P vs Ig NextGen 10%)
C_{max} (g/L)	Point estimate[a]	0.97
	95% CI[b]	0.93 ; 1.01
t_{max} (day)	Point estimate[a]	1.71
	95% CI[b]	1.16 ; 2.52
C_{min} (g/L)	Point estimate[a]	1.00
	95% CI[b]	0.97 ; 1.03
$AUC_{(0-t)}$ (day*g/L)	Point estimate[a]	0.99
	95% CI[b]	0.95 ; 1.03
CL (L/day)	Point estimate[a]	1.00
	95% CI[b]	0.96 ; 1.05
$t_{1/2}$ (days)	Point estimate[a]	1.03
	95% CI[b]	0.96 ; 1.11

[a] Point estimate: 'Intragam® P/Ig NextGen 10%' mean ratio (antilog of the least square mean estimate of 'Intragam® P – Ig NextGen 10%' mean difference on the logarithmic scale) from the analysis of variance.

[b] 95% confidence interval: conventional confidence interval of the 'Intragam® P/Ig NextGen 10%' mean ratio (point estimate) from the analysis of variance after logarithmic transformation of the data.

Note: If the confidence interval contains 1 then treatments are considered similar.

The results of the statistical analysis confirm that the two treatments were similar regarding all PK variables (the 95% CI contains 1), with the exception of t_{max}, which occurred earlier with Intragam 10 NF (0.09 days) than with Intragam P (0.21 days). This may be due to the shorter infusion times of Intragam 10 NF (the Intragam 10 NF mean infusion time was 45 minutes shorter than the Intragam P infusion time), and the effect of the two outliers (with t_{max} values of 0.97 and 1.05) in the Intragam P data.

Evaluator's Conclusions about Clinical Pharmacology

A major problem with the study was whether the changes in dosing pre-study and during the study affected analyses of the serum trough concentration during the study or the PK parameters measured. Although steady state may not have been strictly present, the analyses would not have been affected. A minor problem was that the sampling time to determine the terminal half-life of IgG was short, equal to one half-life from other studies which may have made the determined values unreliable. Also a significant difference was found in the t_{max} values for the two formulations (see discussions above).

Serum Trough levels of the two formulations

The first analysis of differences in patient serum trough levels between treatments across all Cycles using repeated measures analysis found that the 95% CI for the within-patient difference was 0.996 to 1.073; (*p-value* of 0.079). The least square mean ratio for Intragam P/Intragam 10 NF (within-patient difference) was 1.034.

The second analysis, comparing difference in patient serum trough levels between Cycle 0 (Intragam P) and Cycle 4 (Intragam 10 NF) using an analysis of variance (ANOVA), found that for the comparison of C_{min} at Cycle 0 and Cycle 4, the 95% CI for the within-patient difference was 0.97 to 1.03 and the least square mean ratio for Intragam P/Intragam 10 NF (within-patient difference) was 1.00. Since the 95% CI encompassed 1.00 for both analyses, it was concluded that no significant difference was shown between the two treatments, and that the two formulations can be considered biosimilar in maintaining trough concentrations at therapeutic levels.

PK parameters of IgG administered in the two formulations

Except for a difference in t_{max} values, no significant differences were found in the PK parameters between the two formulations. The values for the terminal half-life should also be treated with caution for the reasons given above.

The PK parameters of the subclasses of IgG were similar to those of IgG for IgG1 and IgG2, but the low concentrations of IgG3 and IgG4 made their PK estimates less reliable.

Conclusion

It was concluded that the two formulations, Intragam P and Intragam 10 NF are biosimilar as shown by comparable results for trough concentrations of IgG and for the PK parameters of each.

Efficacy in ITP

The clinical efficacy of Intragam 10 NF was based on a single study (CSLCT-ITP-05-21) in patients with Idiopathic Thrombocytopenic Purpura (ITP), since this indication is presently approved in Australia for Intragam P. No comparison with Intragam P was made in the study. Efficacy for the other requested indications that are not presently approved in Australia was based on a literature based submission. The first patient was enrolled in the ITP study on 2nd July 2007 and the last on 31st October 2008 at six sites in Australia. Features of the study are shown in Table 5.

Table 5. Details of Study ITP-05-21.

Type of Study	Study number	Objectives of study	Design	Test product/ dose	Number of patients	Disease	Duration of treatment
Safety and Efficacy	CSLCT-ITP-05-21	Efficacy and safety of Intragam 10 NF	Phase III, single arm, open label	Intragam 10 NF Single IV infusion at 1g/kg for 2 days	19	ITP	2 days

Trial Design

Inclusion criteria

1. Male or female patients who were 18 years of age or older.

2. Patients with a clinical diagnosis of ITP and who required treatment with IVIg.

3. Patients with a platelet count of < 50 x 10^9/L who fell into one of the three following categories:

- Patients with a platelet count of < 20 x 10^9/L who were bleeding or were at risk of bleeding.
- Patients with a platelet count of 20-50 x 10^9/L who were bleeding.
- Patients with a platelet count of < 50 x 10^9/L for whom it was desirable to increase the platelet count prior to an elective surgical procedure.

4. Patients and/or their legal representative or guardian who had given written informed consent to participate in the study, understood the nature of the study and were willing to comply with all protocol requirements.

Exclusion criteria

1. Patients with a splenectomy planned during their participation in the study.
2. Patients who had previously been non responders to IVIg treatment.
3. Patients with known or suspected hypersensitivity or previous evidence of severe side effects to immunoglobulin therapy.
4. Patients who had received treatment with IVIg or anti-D immunoglobulin within 3 weeks prior to the first day of Intragam 10NF administration.
5. Patients who had received treatment with an immunosuppressive, any other immunomodulatory medication or other active treatment(s) for ITP within 3 weeks prior to the first date of Intragam 10NF administration.
6. Patients who had received IV administration of steroids within 15 days prior to the first day of Intragam 10NF administration.
7. Patients who had had a change of oral corticosteroid treatment or danazol within 15 days prior to the first day of the Intragam 10NF administration.
8. Female patients who were pregnant, breast feeding or planning a pregnancy during the course of the study. Female patients had to have a negative pregnancy test result at screening.
9. Patients with any of the following abnormal laboratory results at screening: - total bilirubin >1.5x upper normal limit; - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x upper normal limit; - creatinine >1.5x upper normal limit; or - urea >1.5x upper normal limit.
10. Patients who were suffering from an acute or chronic medical condition other than ITP which may have in the opinion of the investigator affected the conduct of the study.
11. Patients who had been involved in a clinical trial and/or had been administered with any investigational agent within 30 days prior to participation in the study (that is, from the signing of the informed consent form).
12. Patients who were not willing or were unable to comply with the protocol.

Treatment administered

The dosing regimen in the study was the approved dose regimen for Intragam P. Investigators determined the dose based on the patient's medical condition, their weight and platelet count on Day 1 and individual treatment requirements. Although the approved dosing regimen for Intragam P is either over 2 days or 5 days, all patients in this study were given a cumulative dose of Intragam 10 NF 2 g/kg body weight IV over 2 days. The IV infusion was to be completed in 6 hours after commencement. A platelet count and haematology assessment was performed and the results obtained before each dose of Intragam 10 NF was adminsitered. If the patient's platelet count was 300 x 10^9/L or more, no further doses of Intragam 10 NF were administered.

The first dose of Intragam 10 NF was administered within 7 days of the Screening Visit.

Duration of Study

If on Day 29 the platelet count was $50x10^9$/L or more with a minimum increment of $30x10^9$/L over the baseline platelet count, the patient attended on Day 57. A third and last visit occurred on Day 85 if the same platelet count requirement was fulfilled.

Evaluator's comment: This schedule allowed a determination of the duration of the platelet response and a follow up time for adverse events of 28 days for most patients. Of the 11 patients who completed the study, 7 did so on or before Day 28, none between Days 28 and 56, and 4 between Days 56 and 85.

Concomitant medications

Concomitant therapies for ITP during the study were restricted to treatment with oral corticosteroid danazol and transfusion with blood products (that is, platelets or red blood cell infusions).

Prohibited medication included the following:

- other immunoglobulins including anti-D preparations.
- IV steroids.
- immunosuppressant medications.
- herbal medicine and tonic preparations that contained quinine.

Efficacy assessment

The study followed the recommendation that the efficacy of IVIg be evaluated in at least 15 patients with chronic ITP in the acute phase. The endpoints in the study were consistent with those recommended and were as follows: the proportion of patients achieving a platelet count response (an increase to 50 x 10^9/L with a minimum platelet count increase of 30 x 10^9/L within 7 days [up to and including Day 8] of the first infusion of Intragam 10 NF), magnitude (maximum platelet levels reached) and duration of the platelet count response rate (days of platelet count response and time taken to reach the first platelet count response) and the number and severity of bleeding events.

Platelet Counts

Platelet counts were measured at the Screening Visit and on Days 1, 2, 4, 6, 8, 15, 22 and 29 and also on Days 57 and 85 if the platelet count at the previous assessment (Day 29 and Day 57, respectively) continued to meet the primary endpoint criteria (that is, an increase to $50x10^9$/L or more with a minimum increment of $30x10^9$/L over the baseline platelet count). The sponsor added the comment that the last day of platelet response was measured by interpolation.

Bleeding Status

At the Screening Visit, a history of bleeding events within the previous 30 days was collected and the current status of bleeding symptoms was assessed. The bleeding status was evaluated at each study visit by the investigators.

Populations analysed

Three populations as follows were analysed:

- Safety Population. This included all patients who had received at least one dose (partial or complete) of Intragam 10 NF.

- Intent-to-Treat (ITT) Population. All patients that had received at least one dose (partial or complete) of Intragam 10 NF and had at least one post-treatment platelet count assessment.

- Per-Protocol (PP) Population. This included all patients who completed the study without any major protocol violations or deviations and who had attended all study visits (that is, all visits until the patient completed the study).

In the analysis, two patients were excluded from the PP Population, one in whom the diagnosis was changed from ITP to quinine-induced thrombocytopenia, and one who received a large dose of prednisolone. The report stated that for this reason, "the evaluation of the efficacy results has placed more emphasis on the PP Population". Nineteen patients were analysed in the ITT and Safety Populations and 17 in the PP Population.

Evaluator's comment: The sponsor's Statistical Analysis Plan (SAP) defined the platelet increase required to be classed as a response for the primary end point but did not define in which patient population. The use of the ITT population is to select a trial population that best resembles the population to be treated in clinical practice outside the trial setting, in which mistakes in diagnosis may occur, similar to those in the two patients described above. The ITT population analysis would therefore give results that are more realistic for medical practice. In the present case, the problem is theoretical only, as both analyses were done (ITT and PP) and the results were similar.

Results

Two patients had major protocol violations (as described above) in the patient populations to be analysed; one with the wrong diagnosis and one who had had prohibited medication. Minor violations that would not affect data analysis included visits occurring outside protocol-specified windows, blood tests not analysed within the specified windows or not collected at all, and study procedures not occurring as required by the protocol. Two minor protocol deviations were not discovered during the monitoring of the study; one of which was that the eight patients considered to have withdrawn (above) did not have a Final Study Visit 30 days after the last dose of Intragam 10NF to assess possible adverse events (AEs).

Demographics and Patient Characteristics

The mean age of participants was 44 years, and 6 of the 19 patients (32%) enrolled were male. The mean time since diagnosis was 11 years. Some 89.5% were White.

Baseline bleeding events were assessed by organ class (skin, nose, oral cavity, genitourinary tract and internal) according to criteria defined previously. Skin was the most frequently affected with 16 (84.2%) patients with mild or moderate bleeding of the skin at screening. Smaller numbers of patients had bleeding of the nose (three [15.8%] patients), oral cavity (six [31.6%] patients) and genitourinary tract (four [21.1%] patients). One patient had severe bleeding of the nose at screening (repeated or continuous bleeding requiring nasal packing) and one patient had severe bleeding of the genitourinary tract (major menorrhagia; and/or metrorrhagia; gross haematuria). No internal bleeding events were recorded for any patient at screening.

Concomitant Medication

A total of thirteen (68.4%) patients used concomitant medications before the first dose of Intragam 10NF. The two most common medications were paracetamol and thyroxine (three [15.8%] patients each). All 19 patients used at least one concomitant medication which they started on or after the first dose of Intragam 10NF. The most commonly used

medications were paracetamol (17 [89.5%] patients) and metoclopramide (seven [36.85] patients) and these were generally administered for headache and nausea. One patient was administered paracetamol and promethazine before each infusion of Intragam 10NF.

Efficacy

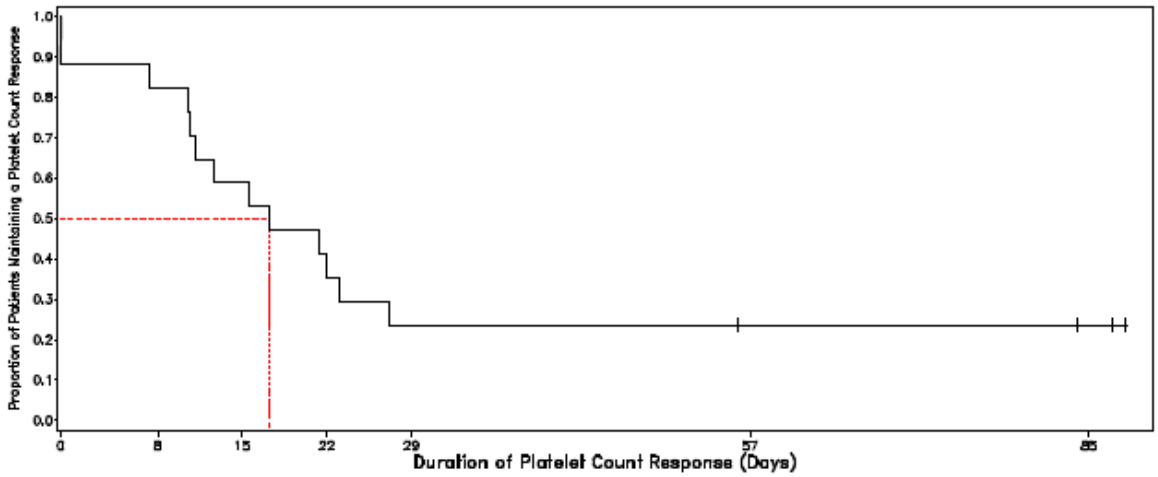
1. *Platelet Response*

The primary efficacy analysis was the proportion of patients with a platelet count response, defined as a platelet count that increased to ≥50 x 10^9/L with a minimum increment of 30 x 10^9/L over baseline within 7 days (up to and including Day 8) after the first infusion of Intragam 10 NF. The proportions of patients with a platelet count response in the PP and ITT Populations were similar: 88.2% (15 patients, 95% CI: 63.6%, 98.5%) in the PP Population and 89.5% (17 patients, 95% CI: 66.9%, 98.7%) in the ITT Population.

2. *Duration of Platelet Response*

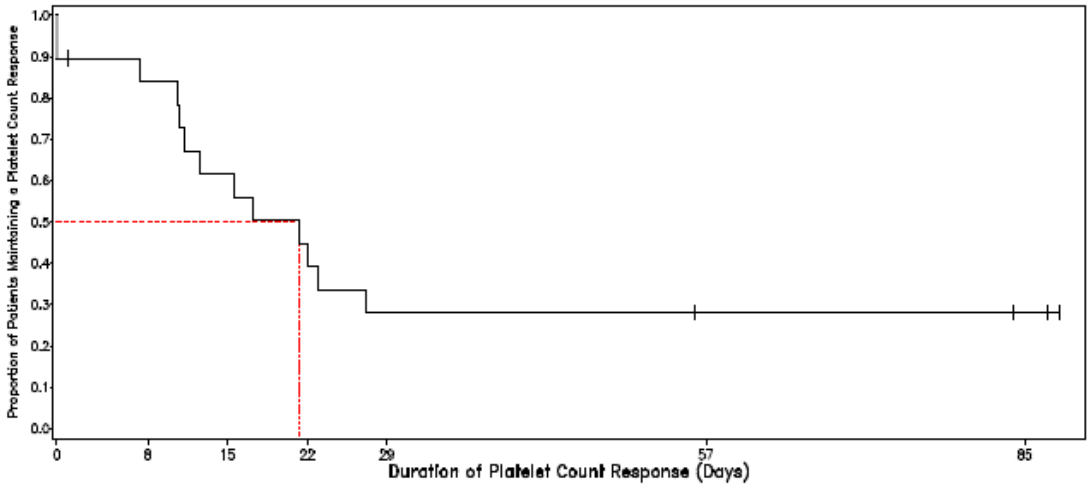
Kaplan-Meier estimates of the duration of platelet count response are presented graphically in Figure 3 (PP Population) and Figure 4 (ITT Population). The median duration of the platelet count response (specified above) in the PP and ITT Populations were 17.2 days and 21.3 days, respectively. The duration of the platelet count response was more than 8 days in 82% of patients (84% in the ITT Population), more than 15 days in 59% of patients (62% in the ITT Population) and more than 29 days in 24% of patients (28% in the ITT Population). The platelet count response was maintained in these remaining 24% of patients until their last follow up study visit, which occurred on or before Day 85.

Figure 3. Days of platelet count response, Kaplan-Meier plot, PP Population.



Note: The red line represents the median days of platelet count response. Durations of platelet response were considered censored if the platelet count remained above response levels at the last follow-up study visit. Censored times are indicated by a vertical line across the horizontal. Patients without a platelet count response had a 'days of response' of 0.

Figure 4. Days of platelet count response, Kaplan-Meier plot, ITT Population.



Note: The red line represents the median days of platelet count response. Durations of platelet response were considered censored if the platelet count remained above response levels at the last follow-up study visit. Censored times are indicated by a vertical line across the horizontal. Patients without a platelet count response had a 'days of response' of 0.

3. Time to First Platelet Count Response

The median time to the first platelet count response (defined above) in both the PP and ITT populations was four days. The time to first platelet count response in the PP Population was more than two days in 71% of patients (68% in the ITT Population) and more than four days in 29% of patients (26% in the ITT Population); therefore 42% of patients in both populations had their first platelet count response on Day 3 or Day 4.

4. Maximum Platelet Level Reached

For the PP Population, the median maximum platelet count reached during the study was 148 (range 46-874) x 10^9/L which can be compared to 178 (range 46-874) x 10^9/L for the ITT Population.

5. Time to Maximum Platelet Count

The median time to reach the maximum platelet count in both the PP and ITT populations was eight days. The time to reach the maximum platelet count in the PP Population was more than 4 days in 88% of patients (84% in the ITT Population), more than 6 days in 76% of patients (74% in the ITT Population) and more than 8 days in 12% of patients (11% in the ITT Population). Therefore, 64% of patients (63% in the ITT Population) reached their maximum platelet count on either Day 7 or Day 8.

6. Time Course of Platelet Count Effects

A platelet count time course from screening to end of study is presented by boxplots in Figure 5 (PP population) and Figure 6 (ITT population). The trend in mean platelet counts from screening to end of study was similar in both populations.

The mean screening platelet count was 19.9 x 10^9/L (PP Population) and it had begun to increase by Day 2 (that is, following one infusion of Intragam 10 NF), peaking on Day 8 at 202.4 x 10^9/L before steadily decreasing until Day 29 (last value). The results beyond Day 29 (that is, Days 57 and 85) are to be interpreted with caution because of the small number of patients who fulfilled the criterion for sampling at those time points.

Figure 5. Platelet time course (screening to the end of the study), Box Plot, Per-Protocol Population.

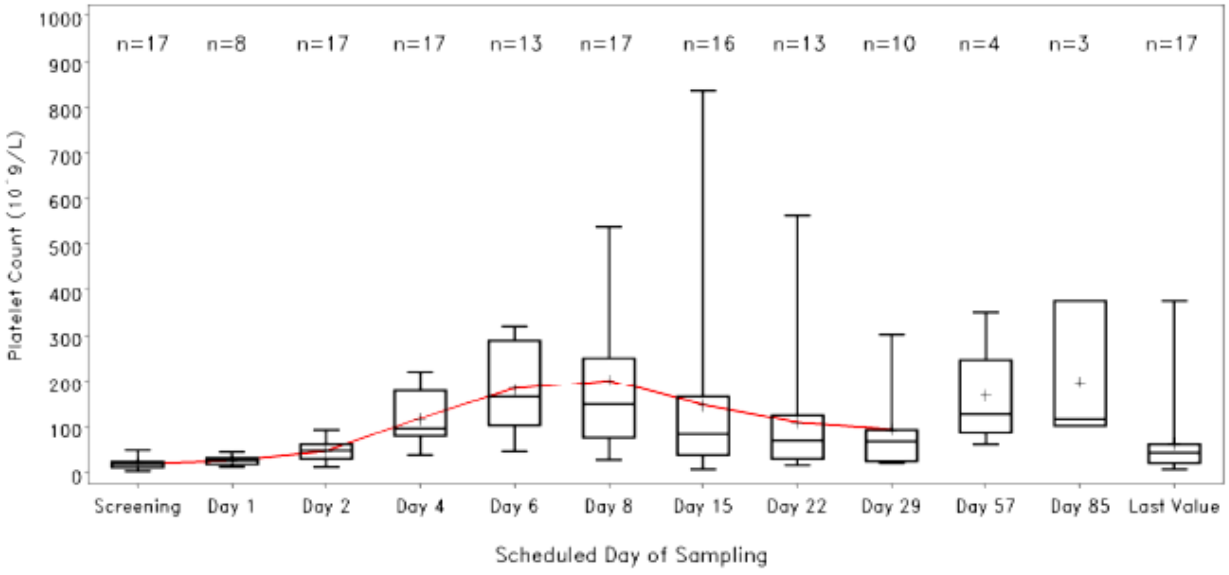
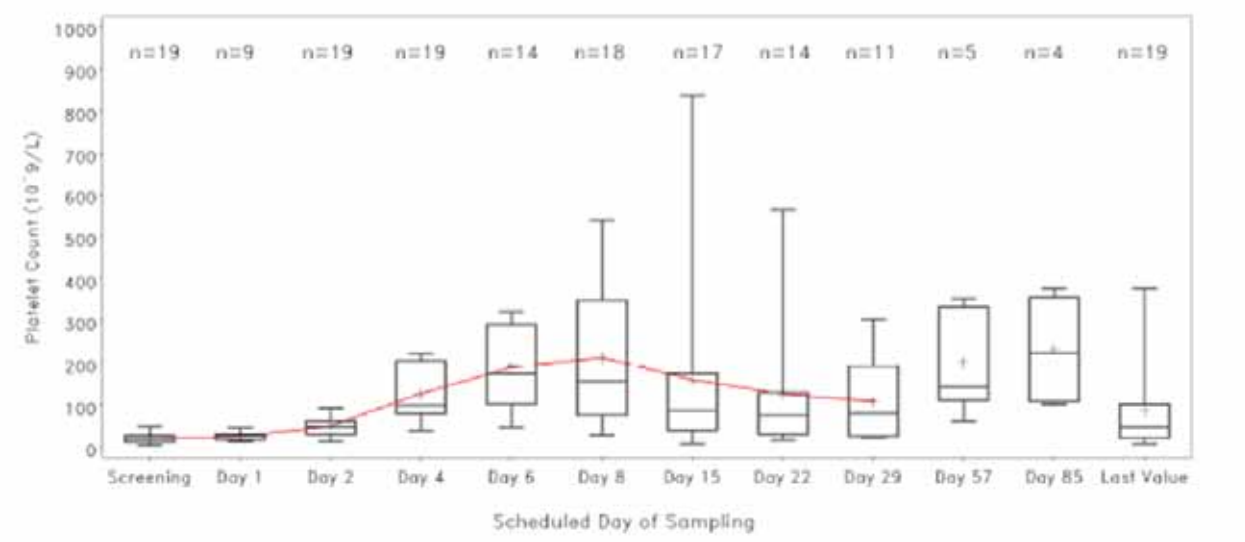


Figure 6. Platelet time course (screening to the end of the study), Boxplot, Intent-To-Treat Population.



Abbreviations: Last Value = the final platelet count for each patient, including those collected on an unscheduled visit day; n = number of patients with a response within the Intent-to-Treat Population.
Note: At each time point, the vertical line represents the minimum and maximum platelet count, the box represents the 25% and 75% quartiles, the cross within the box represents the mean platelet count and the horizontal line within the box represents the median.
Note: The trend in mean values (shown by the line drawn from box to box) is only presented up to Day 29 due to lower patient numbers at subsequent visits.

7. Bleeding Status

A summary of bleeding events over time for the PP Population is presented in Table 6. Bleeding events were classified as mild, moderate or severe and assessed by organ class (skin, nose, oral cavity, genitourinary tract and internal) according to criteria as defined previously. A comparison of the results below for the PP population with those for the ITT population showed no significant differences.

Table 6. Summary of bleeding status over time. Per-Protocol Population.

Body System Criteria	Screening	Day 4	Day 8	Day 15[a]	Day 22[a]	Day 29[a]
Skin	N=17	N=17	N=17	N=16	N=13	N=10
None	3 (17.6%)	8 (47.1%)	13 (76.5%)	8 (50.0%)	10 (76.9%)	6 (60.0%)
Mild	7 (41.2%)	7 (41.2%)	4 (23.5%)	7 (43.8%)	3 (23.1%)	3 (30.0%)
Moderate	7 (41.2%)	2 (11.8%)	0	1 (6.3%)	0	1 (10.0%)
Severe	0	0	0	0	0	0
Nose	N=17	N=17	N=17	N=16	N=13	N=10
None	14 (82.4%)	15 (88.2%)	16 (94.1%)	13 (81.3%)	12 (92.3%)	10 (100.0%)
Mild	1 (5.9%)	1 (5.9%)	1 (5.9%)	3 (18.8%)	1 (7.7%)	0
Moderate	1 (5.9%)	1 (5.9%)	0	0	0	0
Severe	1 (5.9%)	0	0	0	0	0
Oral cavity	N=17	N=17	N=17	N=16	N=13	N=10
None	11 (64.7%)	16 (94.1%)	17 (100.0%)	15 (93.8%)	13 (100.0%)	10 (100.0%)
Mild	5 (29.4%)	1 (5.9%)	0	1 (6.3%)	0	0
Moderate	1 (5.9%)	0	0	0	0	0
Severe	0	0	0	0	0	0
Genitourinary tract	N=17	N=16	N=17	N=16	N=13	N=10
None	14 (82.4%)	13 (81.3%)	14 (82.4%)	15 (93.8%)	13 (100.0%)	10 (100.0%)
Mild	1 (5.9%)	2 (12.5%)	2 (11.8%)	0	0	0
Moderate	2 (11.8%)	1 (6.3%)	1 (5.9%)	1 (6.3%)	0	0
Severe	0	0	0	0	0	0
Internal	N=17	N=16	N=17	N=16	N=13	N=10
None	17 (100.0%)	16 (100.0%)	17 (100.0%)	16 (100.0%)	13 (100.0%)	10 (100.0%)
Severe	0	0	0	0	0	0

Abbreviations: N = number of patients with non-missing results at each visit.

[a] If a patient's bleeding status was recorded on the CRF at the last study visit and duplicated on the Day 29 CRF page, the data are included at the last study visit only. If a patient's bleeding status was recorded on the Day 29 CRF page but the actual date of the data was within an earlier visit window, the data are included at the earlier visit. If a patient's bleeding status was recorded outside all visit windows, it is not included in this table.

Summary and Conclusions of Efficacy in ITP

Platelet Response

A large proportion of patients, 88.2% (95% CI: 63.6%, 98.5%, 15 patients) in the PP population and 89.5% (95% CI: 66.9%, 98.7%, 17 patients) in the ITT population achieved a platelet response of $50x10^9$/L or more, a comparable efficacy to Intragam P, which had a response of 76.5% (Australian PI), and Privigen (a 10% IVIg product recently approved in the USA and Europe as well as Australia) that had an 80.7% response rate. The time to achieve this response was similar (within 7 days) for the three products, as was the median duration of the response (17.2 days in the PP population and 21.3 days in the ITT Population for Intragam 10 NF and 17.2 and 15.4 days for Intragam P and Privigen, respectively). The median maximum platelet count reached during the study was 148 x 10^9/L for the PP Population and 178 x 10^9/L for the ITT Population (range 46-874 for both populations). The median time to reach the maximum platelet count was 8 days in both the PP and ITT Populations, and 64% of patients in the PP Population and 63% in the ITT Population reached their maximum platelet count on either Day 7 or Day 8.

Bleeding events

The results show that any bleeding that occurred after treatment with Intragam 10 NF was mild and infrequent by Day 8. This is a valid assessment of efficacy if pre-treatment bleeding had been significantly greater in frequency and severity. The data for the screening period shows this to be the case for skin bleeding, and GU bleeding (because of its nature), and less so for nose and oral cavity bleeding, except for one severe nose bleed. However, the duration of the study was short, which limited the number of bleeding events that might have occurred.

Conclusion

The demonstration of efficacy of Intragam 10 NF based on bleeding events in treating ITP is therefore limited. However, in conjunction with the increased platelet count described above, the efficacy of the product can be accepted for this indication. An increase in bleeding events was seen on Day 15 compared to Day 8, but it had decreased again around Day 22-29. This result is difficult to interpret due to the small number of events that occurred.

Efficacy for other indications

For products such as Intragam 10 NF that are modifications of an approved product (Intragam P), the EU guidelines only require clinical efficacy to be shown in ITP. If this is demonstrated, the use in Guillain Barré Syndrome, Kawasaki disease and allogeneic bone marrow transplantation can be accepted. The Guidelines do not discuss PID. Study CSLCT-PID-05-22 did not evaluate the efficacy of Intragam 10NF in that condition and the number of infections seen in patients so treated raises a question about its efficacy compared to that of Intragam P for this indication. This issue is discussed in the *Safety* section of this evaluation (see below).

Evaluation of a literature based submission to support the addition of five indications to those approved for Intragam P.

The proposed, additional indications are;

- chronic inflammatory demyelinating polyneuropathy (CIDP)
- multifocal motor neuropathy (MMN), myasthenia gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects
- short term treatment for severely affected non-paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients
- the treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome (SPS).

Overview of data

The literature based submission (LBS) complies with the TGA Guidelines for Literature Based Submissions that require a product to have been on the market for 10 or more years. The LBS was based on a systematic review of the literature, and the TGA reviewed the search strategy (see below) and suggested some changes and additions that were adopted by the sponsor and were documented in the application. The exceptions are noted below.

Seven randomised, controlled trials (RCTs) were submitted for CIDP, four for MMN, five for MG, and one each for LEMS and SPS, giving a total of 18 RCTs. Only the key reference to

support the indication is provided. Additional supportive material are included and described, such as Cochrane Reviews, where relevant.

Search Strategy

The literature search strategy was conducted in consultation with TGA as per guideline requirements. The search terms used were related to the indications sought and were presented in detail in the application with acceptable reasons given for not adopting the TGA suggestions on a small number of terms. Appropriate electronic and manual cross-checks were used. The results of this check indicated that no significant publications had been missed.

Evaluator's comment: The search strategy and its results were acceptable for evaluation.

Evaluation of Efficacy

The following standards (set out in Table 7) are used to classify the level of the evidence of the submitted references, and are based on the National Health & Medical Research Council (NH&MRC) consultation document to June 2009 (*see* Guidelines and Consensus Documents Relating to treatment of CIDP with IVIG *below*), with Level 5 added from the grades of the Oxford Centre for Evidence-Based Medicine.

Table 7. Level of evidence of published references.

Level of evidence	Type of evidence
I	Evidence from a systematic review of all relevant randomised controlled trials.
II	Evidence from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed controlled trials without randomisation.
III-2	Evidence from well designed cohort or case control studies preferably from more than one centre or research group.
III-3	Evidence from comparative studies without concurrent controls, such as historical control studies, two or more single arm studies.
IV	Case series with either post-test or pre-test/post-test outcomes
V	Expert opinion, and guidelines

Chronic Inflammatory demyelinating polyneuropathy (CIDP)

Most studies included nerve conduction measurements, but because of technical problems with the technique and inconsistent results these results have not been reviewed. The first 5 RCTs compared IVIg with placebo and the last two with plasma exchange or treatment with oral prednisolone.

RCTs with placebo for comparison

Reference 1: Level II Hughes R.A., Donofrio P., Bril V., *et al*. *Lancet Neurol*. 2008 7:2 (136 - 144): The study, the largest in treating CIDP with IVIg, is known as the IVIg CIDP Efficacy (ICE) trial. One hundred and seventeen patients with CIDP were randomised; 58 to receive 2.0 g/kg of IVIg IV for 2-4 days followed by 1.0 g/kg for 1-2 days every 3 weeks for 24 weeks, and 59 patients to receive placebo. The trial was a double-blind, controlled, cross-over multicenter study, with a first period, a response conditional cross-over (rescue) period and an extension phase.

The primary efficacy measure was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score (see below Table 8) of 1 point or more through to Week 24. The trial included a blinded extension phase of 24 weeks for responders. During the first period, 32 of 59 (54%) patients treated with IVIg and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to Week 24 (treatment difference 33·5%, 95% CI 15·4–51·7; p=0·0002). The results are shown in the following figure (Figure 7).

Figure 7. Improvement in INCAT disability score through to Week 24.

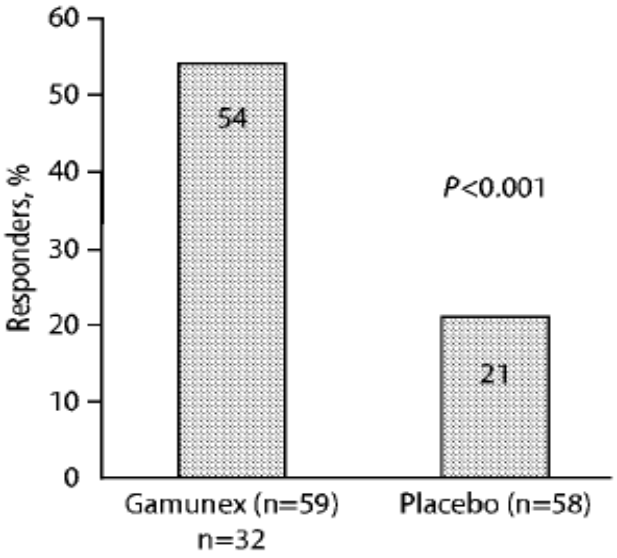


Table 8. INCAT Disability Scale.

Level	***Arm Disability***
0	*No upper limb problems*
1	*Symptoms in 1 arm or both arms, not affecting ability to perform any of the following functions: doing all zippers and buttons, washing or brushing hair, using knife and fork together, handling small coins*
2	*Symptoms in 1 arm or both arms, affecting but not preventing any functions listed above*
3	*Symptoms in 1 arm or both arms, preventing 1 or 2 of the functions listed above*
4	*Symptoms in 1 arm or both arms, preventing 3 or all of the functions listed above, but some purposeful movement still possible*
5	*Inability to use either arm for any purposeful movement*
Level	***Leg disability***
0	*Walking not affected*
1	*Walking affected but walks independently outdoors*
2	*Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors*
3	*Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors*
4	*Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps*
5	*Restricted to wheelchair, unable to stand and walk a few steps without help*

Evaluator's comment: The level of evidence and the quality of the trial were both high. The conclusion was convincing. One anomaly in the result was the failure to show a difference between the two groups in a secondary end point, the compound muscle action potential (CMAP) amplitude, and a separate report was published (Bril, 2009) of more detailed electrophysiological results obtained during the ICE trial, with variable results. This type of assessment appears technically difficult and subject to considerable variation, and the lack of a significant difference should therefore not detract from the positive result. Further positive results were a similar benefit in responding patients continuing in the extension phase who received IVIg compared to those who received placebo. A further publication from the ICE study (Merkies, 2009) found an improvement in quality of life (QOL) measured by the Short-Form 36 and the Rotterdam Handicap Scales in patients treated with IVIg compared to placebo. This effect continued in the extension phase for the former but not for the latter.

Conclusion: This high quality study demonstrated that IVIg at the doses used was effective in treating CIDP.

Reference 2: Level II. Hahn AF, Bolton CF, Zochodne D *et al*; *Brain* 1996; 119(Pt 4):1067-1077: The study was a double-blind, placebo controlled, cross-over study in which 16 patients with chronic progressive CIDP and 14 with relapsing CIDP were randomised to receive 0.4g/kg 5% IVIg, on Days 1 to 5 or placebo for 28 days before cross-over. The concern whether the period before cross-over (maximum 28 days) was sufficient for wash-out was addressed by analysing the results after the first period and those from the study overall.

The measure of efficacy differed from those in the previous study and was based on

(1) a neurological disability scale (NDS) comprised of the summed score of strength in 26 muscle groups; the summed score of sensation; assessment of the tendon reflexes (0 = normal, 1 = reduced, 2 = absent) and of tremor (0 = absent, 1 = present); (2) dynamometer measurements of maximal hand grip (best of three) [Grip Strength, GS]; and (3) a functional Clinical Grading (CG).

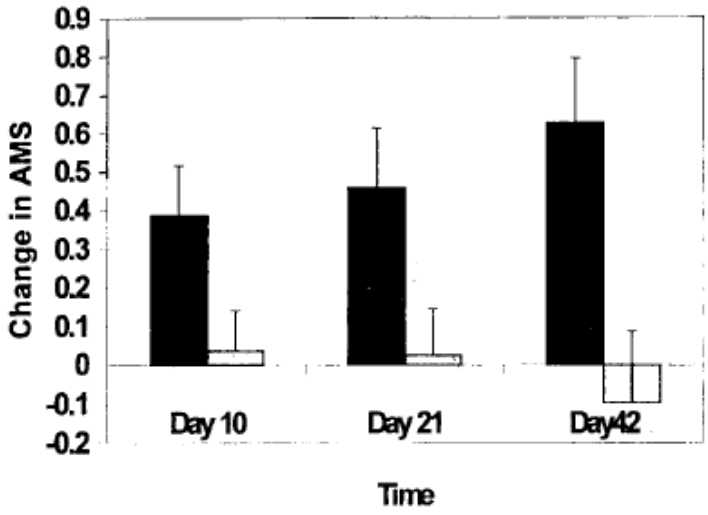
The results showed a significant improvement in the first treatment period for 63% patients (19 of 30) receiving IVIg compared to a transient response in 5 patients receiving placebo. The benefit for the two forms of CIDP was not significantly different.

Evaluator's comment: The design of the study qualified it for a Level II rating but the numbers of patients were small and the assessment different from the more stringent INCAT disability scale of the previous study. Nevertheless, the results show that IVIg was an effective treatment.

Reference 3. Level II. Mendell JR, Barohn RJ, Freimer ML *et al*; *Neurology* 2001;56:445-449: The study was a double-blind, randomised, multi centred study in which 30 patients with CIDP received IVIg. Another 23 patients were given placebo. The IVIg dose was 1g/kg on Days 1, 2 and 21. The primary outcome was the change in muscle strength from baseline to Day 42, using the average muscle score (AMS) and a secondary outcome, the Hughes Functional Disability Scale (HDFS).

The results are shown in the following figure (Figure 8), in which the filled boxes are for patients who received IVIg.

Figure 8. Primary outcome: Change in muscle strength (average muscle score; AMS)



The difference was significant with a p value of 0.006 on Day 42. Eleven patients treated with IVIg improved and none worsened on the HDFS. This can be compared to two improvements and two that worsened in the placebo group (p value of 0.019).

Evaluator's comment: Although a Level II study, the results is less convincing than the previous studies because the assessment was less rigorous from those described above. The IVIg was also given at a different dose from that requested in this application and no cross-over was included to allow for patient variability. Nevertheless, the trial shows that IVIg was effective by both measures used.

Reference 4. Level not rated. Thompson N, Choudhary P, Hughes Ra *et al*; *J Neurol* 1996; 243:280-285. p9

In this double-blind, placebo controlled, cross-over study, patients with CIDP received randomly either IVIg or placebo. After seven patients had been entered, the trial was

terminated due to the publication by Hahn *et al* (1996) showing that IVIg was more effective than placebo which made the trial unethical.

Evaluator's comment: This study will not be evaluated further. It is of interest that the reason the trial was terminated did not prevent later trials using placebo from proceeding (see above).

Reference 5. Level II. M Vermeulen, P A van Doorn, A Brand, *et al*. *J Neurol Neurosurg Psychiatry* 1993; 56:36-39: The study was a randomised, double-blind, placebo controlled, multicentre trial in which 15 patients were randomised to receive IVIg and thirteen were given placebo. The IVIg dose was 0.4g/kg/day for 5 days as a single course of treatment followed by open label IVIg for non responders at Day 16-21. Assessment was by the Rankin scale and MRC sum score. The Rankin scale was a six-point scale ranging from 0 for no symptoms to 5 for severely disabled, totally dependent and requiring constant attention day and night. The MRC scale assessed the weakness of three arm and three leg muscles on both sides.

The degree of improvement of the patients in the IVIg treatment group was no different from the patients in the placebo group.

Evaluator's comment: Although the trial was Level II in design, the patient numbers were small and the methods of assessment less rigorous than the INCAT Disability Scale in the ICE study. The study did not show a benefit of IVIg treatment and the authors attributed this to the methods used for assessment.

RCTs using comparators other than placebo

Reference 1. Level II. Dyck PJ, Litchy WJ, Kratz KM *et al*; *Ann Neurol* 1994; 36:838-845

This was a cross-over study in which 20 patients with CIDP were randomly assigned to receive either of two treatments for 6 weeks, followed by a washout period: treatment was either IVIg infusion (0.4 gm/kg once a week for 3 weeks, then 0.2 gm/kg once a week for the next 3 weeks) or plasma exchange (twice a week for 3 weeks then once a week for 3 weeks). The clinical assessment was blinded and the endpoints were the Neuropathy Disability Score (NDS), weakness subset of this score (NDS-W) and summated muscle action potential (CMAP) of ulnar, media and peroneal nerves together with "vibratory detection threshold (VDT) of the great toe, using CASE IV".

Both treatments were effective with statistically significant improvement over baseline measurements and no statistical difference between the two treatment groups.

Evaluator's comment: The study used endpoint measurements as described, but the authors gave no validation for their use in this setting. The IVIg schedule also differed from other trials. The wash-out period was variable although originally intended to be 6 weeks. Blinding would have been hard to enforce when the patients were aware of the treatment they received. No estimate was made of the sample size required to show a clinically significant difference between the two treatment groups. For these reasons, this study was not rated highly.

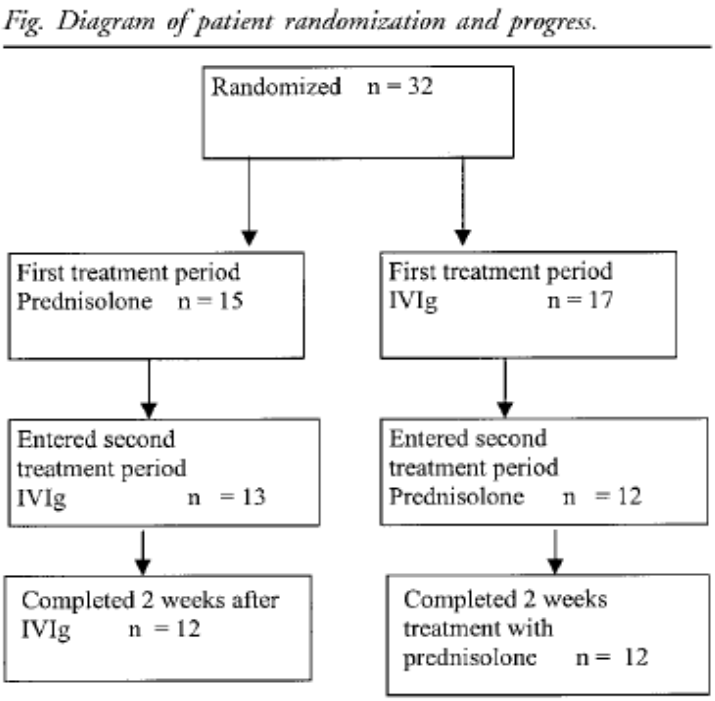
The study found no statistical difference between the treatments. Both treatments were effective.

Reference 2. Level II. Hughes R, Bensa S, Willison H *et al*; Ann Neurol 2001; 50:195-201

This multicenter, randomised, double-blind, crossover trial compared a six week course of oral prednisolone tapering from 60 mg to 10 mg daily with IVIg 2.0 g/kg given over one to two days to treat CIDP. The study was designed for 32 patients but 8 did not complete the

second treatment phase due to the expiration of investigational product as a result of delays in study start-up. Patient randomisation and progress are shown in the following diagram (Figure 9):

Figure 9. Patient randomisation and progress.



Assessment was by what was then a new scale, the INCAT Disability Scale. This scale was also used in the subsequent, pivotal study in this section (Hughes 2008). Eight other assessments were also applied, a number of which were also used in other studies. Both treatments produced statistically significant improvements in the primary outcome measure, both after the first treatment period and at the end of the study. No statistically significant difference was found between the two treatments, but there was a trend in favour of IVIg. The exclusion of eight patients because no IVIg was available may have affected the comparison, although the text of the paper states "The trial was not designed and powered to detect equivalence between oral prednisolone and IVIg. The results allow only the statement that the difference in the overall improvement after two weeks of treatment will lay[9] between 0.35 of a disability grade (for) more improvement with prednisolone to 0.66 of a disability grade with IVIg in 95% of trials."

Evaluator's comment: The trial, because of the number of patients included, the robustness of the primary outcome measure, the doses of IVIg used, and the sound data analysis (with CI limits), can be confidently accepted to show benefit from both treatments. For the reasons stated above, conclusions regarding which treatment is superior cannot be made. The sentence quoted appears to use 0.35 instead of –0.35, the 95%CI being –0.35 to 0.66, including 0 (no difference in treatments).

Supportive studies

Uncontrolled Clinical Studies

Two studies were presented as supporting evidence for the treatment of CIDP with IVIg. The first was intended to be a randomised study but was terminated early with

[9] copied verbatim from paper.

randomisation incomplete and is therefore included in this section of *Supportive studies*. The second study was unacceptable (for ethical reasons) and not evalauted.

Reference 1. Level III-3. L.H. Zinman, D. Sutton, E. Ng, P. Nwe, M. Ngo, V. Bril Transfusion and Apheresis Science 33 (2005) 317–324

Twenty patients consented to the study; nine received high dose IVIg (1g/kg/day on Days 1 and 2), four low dose (0.5g/kg/day on Days 1 and 2), and five were treated with immunoabsorption (IA). The study terminated early because of funding withdrawal, and 8 patients in the IVIg group and 5 in the IA group were analysed for outcomes. Assessment was by Average Muscle Score (AMS), Grip Strength, Median Hughes Score and Toronto Clinical Neuropathy Score (TCNS). Examination of the baseline characteristics revealed that disease duration was longer in the IVIg treated group and was an important effect-modifier that appeared to predict treatment response. When the IVIg group was stratified by treatment response, increased disease duration continued to be an important effect-modifier for predicting treatment response. No comparison of treatments was therefore possible.

Four patients in the IVIg group were classed as responders and four as non responders based on clinical assessments with the assessors blinded with respect to treatment. Electrical conduction studies were also performed.

Evaluator's comments: This was a one-center Level 3 study with a unique assessment instrument (TCNS), although some of the other assessments in the study have been used in other studies. For reasons stated above, this pilot study was considered to be of low quality.

Reference 2. Level not assigned. Study considered unacceptable. van Doorn PA, Vermeulen M, Brand A *et al*; Arch Neurol 1991; 48:217-220

In this study, seven patients with CIDP who were responding to treatment with high dose IVIg were withdrawn from therapy and then randomised to IVIg or placebo in a double-blind cross-over study.

Open label studies

In the three studies cited below, no comparator was used. Since assessments were not blinded, bias was possible.

Reference 3. Level – study not evaluable. Cornblath DR, Chaundry V, Griffin JW. Ann Neurology 1991; 30:104-106

Fifteen patients were treated with IVIg. Six were receiving and continued to receive predisone (4) or prednisone plus azathiprine (2) during the IVIg therapy. Methods of assessment were not described. No improvement was seen in eight of the nine patients who were not receiving concomitant treatment, while five of the six receiving concomitant treatment showed improvement, which was only temporary in two.

Evaluator's comment: The study was not evaluable because of the concomitant medications, the lack of any description of the assessments used and the potential for bias. Even so, the lack of improvement in eight of nine cases is unusual and may indicate unintentional selection of responders (those on other medication) and non responders (those not on other medication). See next study.

Reference 4. Level III-3. R Nemni, S Amadio, R Fazio, *et al*. J. Neurol. Neurosurg. Psychiatry 1994; 57;43-45

Nine patients were treated with IVIg, 0-4 g/kg for five consecutive days. Six patients had been treated previously with prednisone for two months with no effect in four and an

unsatisfactory response in two. Two patients had no beneficial effect from either prednisone and plasma exchange while one experienced a rapid deterioration after plasma exchange. Response to therapy was assessed using the modified Rankin scale at Day 20 after the start of each IVIg course. Improvement was defined as at least a one point decrease on the Rankin scale. Objective improvement in the clinical condition was seen in six patients. One patient became refractory after two treatments and two patients had no response.

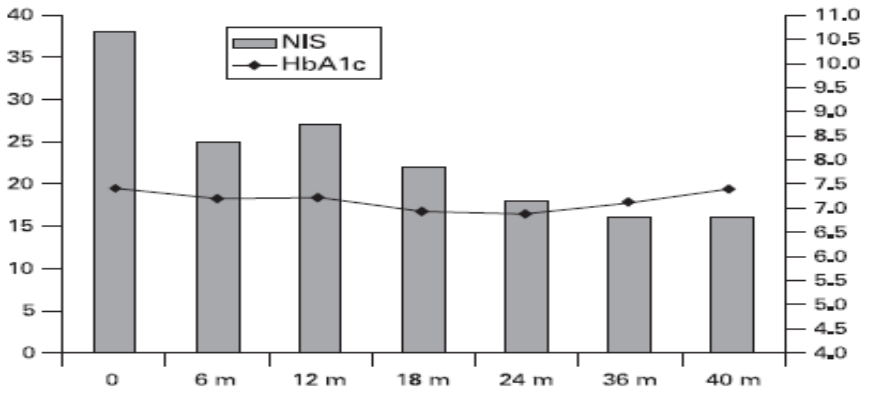
Evaluator's comment: The study supports the conclusion that patients not responding to treatment with prednisone may respond to treatment with IVIg.

Reference 5. Level X. S Jann, M A Bramerio, D Facchetti *et al*. J. Neurol. Neurosurg. Psychiatry 2009; 80; 70-73; originally published online 3 Sep 2008;

Sixteen (8%) of 198 patients referred to the neuromuscular disease unit of the Niguada Hospital, Milan, were diagnosed with both diabetes and CIDP over 18 months. They were treated with at least one course of 2 g/kg IVIg administered over 5 days and classified as treatment responders or non responders on clinical grounds. Improvement was defined as a decrease of 4 points or more in a Neuropathy Improvement Score (NIS). Patients classified as treatment responders were treated again in cases of relapse. All patients were followed for at least 40 months.

The median number of treatments was 4 (range 1 to 6). As described in Figure 10, the NIS score changed from 38 at presentation to 16 at the end of the follow up (after 40 months). The NIS value at Month 40 was found to be significantly less than that at baseline (Student's t test for repeated measures, p = 0.0001).

Figure 10. Neuropathy Impairment Score (NIS) follow up and its correlation with haemoglobin A1c levels.



Neuropathy Impairment Score (NIS) follow-up and its correlation with haemoglobin A1c (HbA1c) levels.

Evaluator's comment: The study provides acceptable evidence that IVIg treatment of CIDP in diabetic patients was effective.

Reports of analyses of data from more than one study

Two systematic analyses were submitted. The more recent Cochrane review (Eftimov, 2009) considered 14 potential studies and excluded seven for valid reasons. Those accepted for analysis were the seven considered above. The earlier systematic analysis (Ferguson, 2005) analysed six trials that were included in the Cochrane review, the Hughes 2008 paper not being available at that time. The evaluation mainly dealt with the Cochrane review with referral to the Ferguson review for any discrepancies.

Reference 1. Level I. Eftimov F, Winer JB, Vermeulen M, de Haan R, van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001797. DOI: 10.1002/14651858.CD001797.pub2.

The total of patients with CIDP in the seven RCTs was 287. Five of the studies compared IVIg therapy with placebo, one compared IVIg therapy with prednisolone and one compared IVIg with plasma exchange. Individual patient data was obtained from four studies (Vermeulen 1993; Thompson 1996; Hughes 2001; Hughes 2008).

Dosage of IVIG: Treatments were IVIg 0.4g/kg/day for 5 days [2.0g/kg total] (3 trials); 0.4g/kg/week for 3 weeks [1.2g/kg total] (1 trial); 1g/kg on Days 1, 2 and 21 [3g/kg total] (1 trial); 1g/kg on Days 1 and 2 or 2g/kg Day 1 [2g/kg] (1 trial); and 2g/kg for 2 to 4 days then 1g/kg for 1 or 2 days every 3 weeks [4 to 8g/kg] (1 trial).

Evaluator's comment: The doses per course of IVIg ranged from 1.2g/kg to 8g/kg. Such a 7-fold range in dosing would not usually be acceptable and would negate any meaningful comparison. No information is available on dose response with IVIg and no comments were provided in the application. The text of the Cochrane report states "We considered any dose of immunoglobulin administered intravenously and compared with placebo, plasma exchange or corticosteroids." No further comment on dosing was made. Sandoglobulin was used in two trials and a different source in the remainder. The report states "The source of IVIg was not considered to be important as long as the preparation was produced according to the guidelines of the WHO".

Assessment of Outcomes

Different disability scales were used in each of the studies. The primary outcome measure in the Cochrane Report itself was defined as the proportion of participants with a significant improvement in disability within six weeks after the onset of treatment as determined and defined by the original authors. In each study the strictest available criteria to define 'significant' improvement were used. Where possible, disability data were transformed to the modified 6 point Rankin disability scale and based on original data where possible. Note that these data were only provided for four of the seven trials. A significant improvement was defined as at least one point improvement on this scale. No change or worsening on the Rankin scale was rated as no improvement.

Outcomes were assessed at 14 days (Thompson 1996), at 16 to 21 days (Vermeulen 1993), at 28 days (Hahn 1996) and at 42 days (Mendell 2001; Hughes 2008).

Appropriate statistical analyses were done on these data and the risk of bias estimated for each study. In five RCTs, the assigned treatment was adequately concealed prior to allocation and they were graded A. Two studies did not contain adequate information to judge concealment and were graded B (Dyck 1994; Thompson 1996).

Results

The results are presented in the following table (Table 9). "Significant improvement" was as assessed by the investigators, while one point improvement in the Rankin Scale could be assessed only in three trials.

Table 9. Study results.

Analysis		N (treatments)	Improvement		Pooled RR (95% CI)	NNT (95% CI)
			IVIg	Placebo		
1.1	Significant improvement in disability within six weeks of treatment onset	235 ex 5 RCT (141 IVIg; 128 placebo)	78 /141	30/128	2.40 (1.72-3.36)	3.03 (2.33-4.55)
		Parallel RCT (104 IVIg; 94 placebo)	57/104	25/94	2.14 (1.48-3.09)	3.33 (2.38-5.88)
1.2		Crossover RCT only			3.52 (1.58-7.87)	
1.3	Improvement of one or more points in Rankin scale	84 3 RCT (50 IVIg; 40 placebo)	16/50	5/40	2.40 (0.98-5.83)	5.26 (2.78-50.00)
		Excluding crossover RCT (44 IVIg; 34 placebo)	15/44	5/34	2.34 (0.92 – 5.94)	5.26 (2.7-100.0)

NNT: number needed to treat

The analyses in the Cochrane Review were extensive, and examined many different groupings of results. The summary of these was as follows "A significantly higher proportion of participants improved in disability within one month after IVIg treatment as compared with placebo (relative risk 2.40, 95% confidence interval 1.72 to 3.36). Whether all these improvements are equally clinically relevant cannot be deduced from this analysis because each trial used different disability scales and definitions of significant improvement. In three trials including 84 participants the disability could be transformed to the modified Rankin score, on which significantly more patients improved one point after IVIg treatment compared to placebo (relative risk 2.40, 95% confidence interval 0.98 to 5.83). Only one study included in this review had a long-term followup. The results of this study suggest that intravenous immunoglobulin improves disability more than placebo over 24 and 48 weeks. The mean disability score revealed no significant difference between IVIg and plasma exchange at six weeks. There was no significant difference in improvement in disability on prednisolone compared with IVIg after two or six weeks."

The Review concluded "The evidence from randomised controlled trials shows that intravenous immunoglobulin improves disability for at least two to six weeks compared with placebo, with a number needed to treat of 3. During this period it has similar efficacy to plasma exchange and oral prednisolone. In one large trial, benefit of IVIg persisted for 24 and possibly 48 weeks."

Evaluator's comment: The above table shows the primary results as (N) "Treatments", whereas "Numbers of Patients Treated" is probably the true meaning, as judged from the numbers used (the number of treatments administered would be much larger). The statement in the text referring to the study by Hughes (2008), "The number of patients (clinical evaluator emphasis) who achieved sufficient improvement by six weeks (and thus were not crossed over by six weeks) was used in the primary outcome of this review.", and the Table "Comparison 1", Eftimov *et al* (2009) has a heading "No of Participants" and shows 269 patients were in the 5 RCTs analysed. The study report also used the term "Treatment", but the text in that report was a verbatim selection from the Eftimov (2009) paper (the Cochrane Review).

The results also show that when the Rankin Scale was used for the 3 RCTs, the improvement seen was not as convincing as when "significant improvement" (investigators' rating) was used for assessment. In these three RCTs, the CI included 1, as it did when the one cross-over RCT was excluded. The results for the RR for the 3 RCTs "just reached significance" (ibid, and the Cochrane Review) for the IVIg treatment. However, the diagram from the Cochrane Review shows a p value of 0.054 that could be described as just not reaching significance. The p value when the cross-over trial was excluded was 0.07 but it was not referred to in the study report. The conclusions of the Cochrane review itself referred to "significantly more patients" who improved on IVIg compared to placebo.

The review used a number of statistical tests for possible heterogeneity of the results from different RCTs. These do not address the heterogeneity of treatment dosage with IVIg. The following table (Table 10) shows the doses used with the response rates reported.

Table 10. Dose of IVIg administered per treatment and Response Rate in 4 of the 5 RCTs*

Trial	Number of Patients		Dose (g/kg)	Response Rate (%)	
	IVIg	Placebo		IVIg	Placebo
Vermeulen 1993	15	13	2	27	23
Hahn 1996	25	25	2	63	16
Mendell 2001	29	21	3	38	6
Hughes 2008	59	58	4-8	54	21

* the trials shown were those with placebo as comparator; the Thompson (1996) trial was not included as it was terminated prematurely.

These data indicate no relationship between dose and response. The only published study in the application that examined dose response of IVIg was the retrospective study (see below).

Evaluator's Conclusions from the Cochrane Review: The methodology of the review was of high quality (although there were some ambiguities), but the trial data used gives rise to a number of reservations as presented above. On balance, it appears that IVIg was effective in treating CIDP in some patients (1 in 3) although the minimum effective dose was not established.

Reference 2. Level 1. Fergusson D., Hutton B., Sharma M., *et al*. *Transfusion* 2005, 45:10 1640 – 1657.

This systematic review preceded the Cochrane Review (above), and was a meta-analysis of randomised controlled trials (RCTs) evaluating IVIg for all neurologic indications for which there had been at least one trial published. CIPD was one of the neurological conditions examined, and included the six RCTs discussed in the Cochrane Review but

excluding Hughes, 2008. The 4 RCTs (Vermeulen, 2001; Hahn, 1996; Thompson, 1996; Mendell, 2001) that were placebo-controlled, treated 125 patients, and were regarded as of high quality in the analysis. Only the first period of the studies could be included. All improvements were assigned a negative value and all deteriorations a positive value.

A significant treatment effect of -0.67 (95% CI, -1.04 to -0.30) in favor of IVIg was found. A pooled analysis of the proportion of patients experiencing clinical improvement, as defined by the investigators, resulted in an OR of 4.43 (95% CI, 2.20-8.91). Mendell and colleagues observed significant changes both from baseline and between groups in mean muscle score at both the 10-day and 21-day examinations in the IVIg and placebo groups (10-day IVIg 0.39 ± 0.13 vs. placebo 0.04 ± 0.09; 21-day IVIg 0.46 ± 0.15 versus placebo 0.02 ± 0.12). The other results were from neurophysiological data and will not be presented here. As with the Cochrane Review, no significant difference was found between the improvement found with IVIg compared to prednisolone or plasma exchange.

Evaluator's comment and conclusion: This review of the best published trials (to 2005) of IVIg treatment in CIDP reached similar conclusions to the Cochrane Review. This was expected since the same data were used in both analyses. The reservations about different doses of IVIg and different methods of assessment also apply to this analysis but the conclusion is acceptable that IVIg is effective in treating some patients with CIDP.

Other Clinical Study Reports. Retrospective Studies

Four retrospective studies were included in the application.

Reference 1. Level III[*]. van Doorn PA, Vermeulen M, Brand A *et al*; Arch Neurol 1991;48:217-220

The authors reviewed 52 patients with CIDP who had been treated for more than eight years with 0.4g/kg/day for 5 days with IVIg. The Rankin Scale was used to assess response. Twenty patients (38%) did not improve after IVIg treatment, two (4%) had a short lasting improvement, nine (17%) reached a spontaneous or therapeutically induced complete remission and 21 (40%) needed intermittent infusions of IVIg to maintain improvement for a mean follow up period of four years.

Reference 2. Level III. Choudhary PP, Hughes RA; QJMed 1995; 88:493-502

The authors studied 105 patients retrospectively by case-notes and follow up to assess long-term treatment of CIDP with plasma exchange (PE) and IVIg. Treatment with IVIg was at a dose of 0.4g/kg/day for 5 days or 1g/kg/day for two days. A modified Rankin Scale was used to assess improvement. Of the patients who were treated with PE, 23 of 33 responded well where of those treated with IVIg, 14 of 22 responded well.

Reference 3. Level III. Vucic S., Black K., Baldassari L.E., Tick Chong P.S. Clin. Neurophysiol. 2007; 118: 9 (1980 - 1984)

This retrospective study measured the neurophysiological changes in 11 CIDP patients who had been treated with IVIg 2 g/kg administered over five consecutive days for three consecutive months with the dose individually changed thereafter. The patients had been treated for 12 months or longer. The results suggested that long-term IVIg maintenance therapy improved neurophysiological parameters in CIDP. However, CIDP patients remained IVIg dependent and new conduction blocks may develop.

[*] This level is based on the simpler and more intuitive scale of Categories used by the FDA rather than the more difficult NHMRC Scale.

Reference 4. Level IIb (FDA Category). Rajabally YA, Seow H, Wilson P: J Periph Nerv System 2006 11: 325-329

The authors retrospectively reviewed data related to IVIg therapy in 15 patients with CIDP to determine the lowest effective dose and treatment frequency. Results are shown in Table 11. The lowest effective IVIg dose per course and treatment frequency were both variable (18 - 108g and 2 - 17 weeks respectively).

Table 11. Characteristics of 15 patients with CIDP receiving regular IV immunoglobulins.

Patient number	Sex	Age at onset (years)	Disease duration (years)	Current weight (kg)	Pre-treatment disability (Modified Rankin Score)	First dose per course (g)	Final dose per course (g)	Dose reductions (g)	Dose reduction (%)	Frequency of infusions (interval in weeks)
1	F	60	7	77	2	135	50	85	63	6
2	M	53	3	74	5	125	36	89	71.2	4
3	M	52	13	75	4	162.5	54	108.5	66.8	3
4	M	64	3	97	2	200	108	92	46	6
5	M	54	4	80	2	150	72	78	52	3
6	M	54	8	97	2	175	24	151	86.3	12
7	F	33	1	63	2	125	25	100	80	17
8	M	49	10	123	2	162.5	72	90.5	55.7	12
9	M	38	7	84	2	150	72	78	52	10
10	M	59	11	73	2	137.5	60	77.5	56.4	8
11	M	48	11	90	4	175	60	115	65.7	4
12	F	59	4	45	4	87.5	25	62.5	71.4	4
13	M	41	5	93	4	150	18	132	88	2
14	F	38	15	71	3	125	72	53	42.4	10
15	M	70	2	47	5	125	54	71	56.8	2

M, male; F, female.

The lowest dose per course did not correlate to weight, frequency of administration, disease duration or pre-treatment degree of disability. Amplitude of dose reduction achieved was independent of disease duration. Treatment frequency could not be lowered in any patient.

These findings show that IVIg target doses should be titrated individually but suggest that infusion frequencies are fixed in each case in relapsing CIDP. Importantly, low dose treatment is not associated with shorter intervals between courses and the lowest effective dose is independent of weight and disease duration. Initial level of disability does not appear to influence the dose required. These results suggest that considerably lower, standardised, initiating and maintenance doses might be effective and they highlight the need for prospective dose comparative trials.

Evaluator's comment: Although this was a retrospective study, the findings are important because this is the only study in this application to address the question of dosing with IVIg for CIDP. Most studies and reviews advise adjusting dosage to suit individual patients but little data was provided on such adjustments for this indication. This paper gives doses as total gram of IVIg rather than per kg body weight and so is not easy to compare with other data. Nevertheless the reduction in dose that is possible ranged from 42% to 88% without loss of efficacy. Also of note is the finding that in any one patient, frequency of treatment should be maintained but the dose can be reduced.

The clinical evaluator calculated the final dose per course as g/kg for each patient and estimated the median dose for maintenance to be 0.67g/kg (range 0.20 to 1.20g/kg) and the mean as 0.69g/kg. The proposed Product Information for Intragam 10 NF to treat CIPD recommends an induction dose of 2g/kg in divided doses over 2 to 5 days, and a maintenance dose of 0.4 to 1.0g/kg every 2 to 6 weeks. The relevant footnote for all treatments states "The optimal dose and frequency of administration of Intragam 10 NF

must be determined for each patient.", and that for CIPD "Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state."

Conclusion: Based on the results of Reference 4, the induction and maintenance doses in the PI are appropriate but a change in frequency of treatment should not be recommended.

Guidelines and Consensus Documents relating to treatment of CIDP with IVIg

A number of guidelines for the clinical use of IVIg have been published worldwide to guide correct clinical usage of IVIg. The published guidelines are listed below. All are Level IV Categories of quality (NHMRC and FDA)

- **Australia**: Australian Health Ministers' Conference (AHMC). Criteria for the Clinical Use of IVIg in Australia (Dec 2007) and Bringing Consensus to the use of IVIg in Neurology (BCIN): The Asia Pacific Immunoglobulins in Neurology Advisory Board 2nd Ed Nov 2008.
- **United Kingdom**: Association of British Neurologists (ABN) 2005.
- **USA**: American Academy of Allergy, Asthma and Immunology (Orange *et al*, 2006).
- **Canada**: National Advisory Committee on Blood and Blood Products with Canadian Blood Services (Feasby *et al*, 2007).
- **European Union**: European Federation of Neurological Societies (EFNS) (Elovaara *et al*, 2008).

Evaluator's comment: The various guidelines used the same published papers, with most reliance on the Cochrane Review (Eftimov, 2009). They arrived at the same conclusion, recommending the first line treatment of CIDP as IVIg. Although such guidelines rate as Level 4 or 5 evidence, each gives the highest rating to the published trials that provided this evidence.

Conclusion: The guidelines recommend use of IVIg for the short-term treatment of CIDP with a high level of evidence cited (Levels 1 or 1a).

Evaluator's Summary on Efficacy of IVIg in the treatment of CIDP

The evidence in the LBS convincingly and consistently supported the efficacy of IVIg in treating CIDP. The strongest evidence was from the two systematic reviews (Eftimov 2009, and Ferguson 2005), in spite of the reservations described above. The Ferguson 2005 review found IVIg treatment effective and this conclusion strengthened by the Eftimov analysis that included in addition the important single study by Hughes 2008 (ICE study). In fact the ICE study alone with supporting evidence may have been sufficient to shown effectiveness. It was important in the conclusions formed by the various consensus groups and in international guidelines.

Little data were available on the minimum effective dose of IVIg, with evidence from a number of trials showing an individual patient response to a variety of doses. The doses requested in this application (an induction dose of 2g/kg in divided doses over 2 to 5 days, and a maintenance dose of 0.4 to 1.0g/kg every 2 to 6 weeks) are consistent with published data, with emphasis on frequent assessment of response and dose reduction where possible. Evidence suggests that while the dose should be reduced, the frequency of treatment should be held constant in any one patient. The duration of effective treatment was from 4 to 6 weeks, with one trial showing benefit persisting for 24 weeks and possibly up to 48 weeks.

Multifocal Motor Neuropathy (MMN)

RCTs with placebo for comparison

Three methods of assessment disability were used in four randomised clinical trials (RCTs);- the Rankin scale to assess general function; the MRC scale for assessing muscle strength and a Neurological Disability scale.

Reference 1: Level II. Azulay J-P, Blin O, Pouget J *et al*. Neurology 1994; 44:429-432.

Twelve patients, five with MMN and seven with lower motor neuron syndrome (LMNS) were randomised in a blinded fashion to either treatment with IVIg (0.4g/kg/day for 5 days) or placebo and crossed over after 8 weeks. The MMN patients had nerve conduction blocks, unlike those with LMNS. Four types of assessments (muscle strength, Norris disability scale, motor nerve conduction, and immunological markers) were done before treatment and on Days 5, 28 and 56. Two patients improved during the time of infusions and showed a clear increase in measurement of strength at Day 5. The other three patients improved only at Day 28. As compared with placebo, overall improvement was obvious with IVIg at Days 28 and 56 but only the evaluation at Day 28 reached statistical significance. No change in disability was observed, conduction studies did not show an increase and no significant change occurred in immunological parameters.

Evaluator's comment: Although the study design was acceptable, the patient numbers were small. However, the number of endpoints for each patient for each of the two treatments were 16 (4 endpoints for 4 different time points) and 80 in total for the five patients. Of these, only one of the four endpoints for one time point showed significant improvement for the IVIg treatment. This study was regarded as exploratory only.

Reference 2. Level II. L H Van den Berg, H Kerkhoff, P L Oey, *et al*. J Neurol Neurosurg Psychiatry 1995; 59:248-252:

The IVIg treatment protocol included an open trial and a single patient double blind placebo controlled designed trial. In the open trial, six patients with MMN were treated with IVIg 0 4 g/kg for five consecutive days. Patients who responded entered the double blind placebo controlled trial, which was started when the patient had returned clinically to the pretreatment state. In this trial, the effect of IVIg treatment was studied in each patient. Four patients received two IVIg treatments (0.4 g/kg for five consecutive days) and two placebo treatments (pasteurized plasma solution for five consecutive days) in a randomised order. Two patients received only one IVIg and one placebo treatment for "practical reasons". Treatments were blinded for both patients and physicians. Patients were examined before and after each treatment (Days 1 and 6 of admission) and then weekly by the same physician . The interval between each treatment was determined by the time it took for the patient to return clinically to the pretreatment state. To prevent cumulative dose effects, the shortest time interval between two treatment courses was kept at one month. Assessments were by muscle strength (by dynamometer and MRC Scale), disability (Rankin scale), and neurophysiological studies before treatment and on Days 6 and 14 of treatment.

In the open trial, muscle strength improved in at least two muscles groups for all six patients, and three patients showed improvement of the Rankin scale (from 2 to 1). All six were regarded as having responded to IVIg and when their performance had returned to baseline, they were entered in the double blind randomised trial. In this part, muscle strength in five patients improved after IVIg but remained stationary or became worse after placebo infusion. Improvement in the sixth patient occurred once after placebo and once after IVIg, but remained stationary after the two other treatment courses. Electroneurographic follow up showed an effect of IVIg treatment in only one patient with

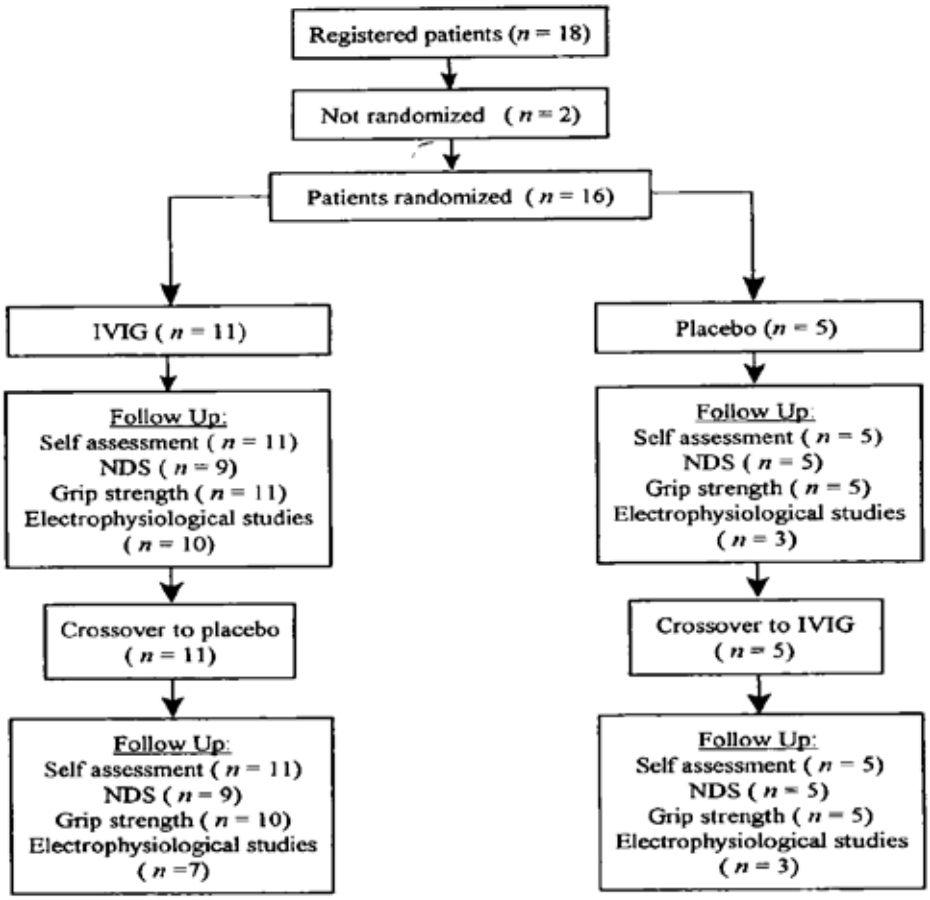
conduction block disappearing in the lower arm segment of the right median nerve. The authors did not mention the results of the disability assessment using the Rankin scale. The duration of the effect on muscle strength was 4 wks (3 patients), 12 weeks (2 patients), and 26 weeks (1 patient).

Evaluator's comment: The design of the study was unusual in the way the subjects were selected as being responders to initial treatment with IVIg. Also unusual was that all (six) patients were initial responders. The real question asked was whether responders to IVIg responded to the same treatment after relapse. The non-surprising answer was that most did. A caveat however remains that response was shown by only one measure, muscle strength, and not by disability score which has been used successfully as a tool in other studies. Overall the study did not inspire confidence in demonstrating the efficacy of IVIg in MMN, rather it indicating that better methods of assessment are needed in this disease.

Reference 3. Level II. Federico P, Zochodne DW, Hahn AF *et al*. Neurology 2000; 55: 1256-1262.

This study investigated the effect of IVIg on neurologic function and applied electrophysiologic studies in MMN patients with conduction block. All subjects (n=16) were given one of two treatments (IVIg [0.4 g/kg/day for 5 consecutive days] or placebo and were assigned according to a randomised, cross-over design under double-blind conditions. The disposition of patients is shown in the following diagram (Figure 11):

Figure 11. Trial profile. NDS=neurologic disability scale.



Because of the variable clinical course of MMN, the cross-over period was varied. Patients who remained unchanged or deteriorated on the measures below were crossed over into

the second arm on Day 28. Patients who improved on Day 26 did not enter the second arm until the above measures returned to baseline levels.

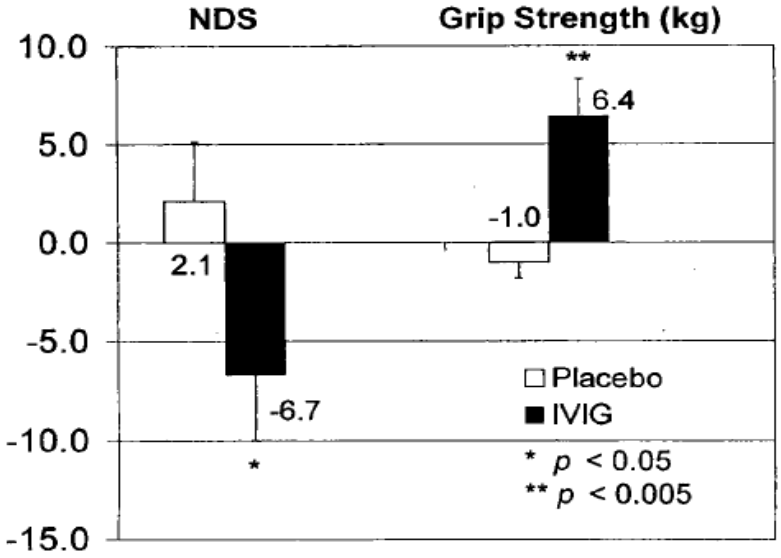
Patients were evaluated before and about 28 days after trial treatment. The primary outcome was change in the neurologic disability score (NDS) at 28 days. Secondary outcomes included subjective functional improvement, grip strength, distal and proximal compound muscle action potential amplitude and conduction block. [Evaluator: The NDS was a summed score of strength in 26 muscle groups].

The primary outcome, the neurologic disability score, improved by 6.7 ± 3.3 points with IVIg treatment but decreased by 2.1 ± 3.0 with placebo (p = 0.038) [Figure 12 following]

The secondary outcomes were that subjective functional improvement with IVIg treatment was rated as dramatic or very good in nine patients, moderate in one, mild in one, and absent in five patients. This improvement was absent after placebo; grip strength on the weaker side was increased by 6.4 ± 1.9 kg with IVIg treatment; it decreased by 1.0 ± 0.8 kg with placebo (p = 0.0021) [Figure 12]; conduction block worsened by 13.46 ± 5.62% with placebo, but improved by 12.68 ± 5.62% with IVIg treatment (p = 0.037). Conduction block was reversed in five patients with IVIg but not with placebo. No changes in distal M-wave amplitude, distal motor latencies or conduction velocity were seen with either treatment.

A comparison of NDS scores and grip strength of the IVIg and the placebo group is show in Figure 12.

Figure 12. Comparison of neurologic disability scale (NDS) and grip strength between the start and end of the treatment arm.



IVIg significantly reduced the NDS and increased grip strength over the course of the treatment arm (n=14 for NDS and n=15 for grip strength).

Evaluator's comment: The primary outcome of the study showed the efficacy of IVIg treatment compared to placebo in improving the muscle strength of 11 of 16 patients with MMN. The grip-strength, a secondary outcome, also supported this. The study had no objective assessment of patient disability (as measured by scales such as the Rankin scale) that is, a measure functional improvement rather than muscle strength.

Reference 4. Level II. Leger JM, Chassande B, Musset L *et al*. Brain 2001; 124:145-153.

In this double-blind, placebo-controlled, study, 19 patients who fulfilled the eligibility criteria for MMN with persistent conduction block were enrolled and divided into two groups: those who had never been treated previously with IVIg (Group 1: 10 patients) and those who presented recurrent symptoms after previous successful treatment with IVIg (Group 2: nine patients).

Patients were randomised prospectively to receive either IVIg or placebo at a dose of 0.5 g/kg/day for 5 consecutive days, once a month for 3 months. At Month 4, patients found to be responders remained on the same treatment for the following 3 months, while non responders were switched to the alternative study drug for the following 3 months.

The primary outcome was the MRC score comparing patients treated with IVIg and those treated with placebo. This assessment was conducted with the Medical Research Council (MRC) score in 28 muscles and a self-evaluation scale (five daily motor activities scored from 0 to 5). Assessments were done every month for 7 months. (Note**:** The MRC scale shows the score was for 20 muscles whereas in this study it was for 28 muscles. This changed the maximum possible score from 100 to 140 in the present study.]

The secondary outcome was the response rate. The responders were defined by combining the MRC score and the patient's subjective evaluation as follows: "At 4 months patients were considered responders if they had at least one more MRC point in two affected muscles plus one point less in two activities of daily life compared to baseline". The latter "was a self-evaluation scale, scored from 0 (normal) to 5 (impossible) for five motor activities of daily life, chosen for each patient together with the examiner at the baseline".

Results.

MRC Score. Primary Outcome

There was no significant difference in MRC score comparing the differences in the median values for the group treated with placebo and the group treated with IVIg. The mean change at 4 months in the two groups was 2 points with a CI of minus 2 to plus 9 (not significant as it included 0).

Response Rate

Group 1: (not previously treated with IVIg): 9 out of 10 patients completed the study.

- First treatment of 4 patients with IVIg: 2 responded; 2 were non responders
- First treatment of 5 patients with placebo: 2 responded; 3 were non responders.
- Cross-over treatment: 3 non responders after placebo were then treated with IVIg and 2 responded
- Cross-over treatment: 2 non responders after IVIg were then treated with placebo and did not respond.

Overall result for Group 1: Four out of 9 patients responded to IVIg treatment.

Group 2: (previous responders to IVIg treatment)

- First treatment of 5 patients with IVIg: 5 responded
- First treatment of 4 patients with placebo: none responded

- Cross-over treatment: 4 non responders after placebo were then treated with IVIg and 3 responded and one remained stable.

Overall result for Group 2: Eight patients 9 responded to treatment.

When the 18 patients were considered together, seven out of the nine patients who received IVIg first were responders at Month 4. Only two of the nine patients who received placebo first were responders. This difference between IVIg and placebo was statistically significant (p= 0.03).

A significant difference was found in the self-evaluation score, at month 4, between IVIg patients and placebo patients. Electrophysiological studies did not show significant differences at month 4 in motor parameters between IVIg patients and placebo patients.

Evaluator's comment: The usefulness of combining the two groups is questionable since previous responders to IVIg would be expected to respond to a second course. This has been shown in other studies. The combined data therefore inflates the overall response rate. Group 1 is best considered alone, with a response rate of 4 of 9 treated patients, a figure consistent with other studies. Assessment of response was problematic. In the IVIg group, the mean change of 3 points at 4 months was considered statistically significant, with a CI of 2 to 13 points. The p value was not given in the paper although the study report states this as <0.05. For comparison, the mean change in the placebo group at 4 months was also 3 points, but the CI was –1 to 10, and so included 0 (not significantly different). The median MRC score at baseline for the IVIg group (n=9) was 118 ± 11.2. It is difficult to accept that with such a SD, an increase of the mean difference by 3 points could be clinically significant, especially when the increase in the placebo group was also 3 points (mean 112.9 ± 19.2).

Conclusion

Because of the complicated criterion used to define a responder (including subjective assessments) and because the primary outcome of the study was negative and the clinical significance as distinct from the statistical significance of the treatment difference is unclear, this study cannot be taken to support the efficacy of IVIg treatment in MMN.

Reference 5. Level II. Harbo T., Andersen H., Hess A., *et al*. Eur. J. Neurol. 2009; 16:5 (631 - 638)

This randomised single-blinded cross-over study was too recent to have been part of the Cochrane Review (Van Schaik, 2005) and was included in the application "as additional evidence from a randomised cross-over study to confirm the efficacy of IVIg in MMN".

Nine IVIg responsive patients were allocated to receive either IVIg or an equivalent dose of self-administered, subcutaneous immunoglobulin (SCIG) for a period equivalent to three IVIg treatment intervals and, subsequently, crossed over to the other treatment. Although the study report states that the primary end points were (i) dynamometric strength of affected muscles and (ii) the SF-36 quality of life questionnaire, the paper states that only the former was the primary outcome.

The design of the study was to compare the two treatments. No statistically significant difference was found between them. Since the SC route is not part of this submission, it will not be considered further. At baseline, the patients in the IVIg group had a muscle strength score of 69.9 ± 18% of normal and this improved by 4.3% (95% CI, -1.3% to 10.0%) following treatment.

Evaluator's comment: The improvement of 4.3% found with IVIg treatment was claimed in both the published paper and in the study report as confirmation of the efficacy of IVIg in MMN. However the CI for the improvement value of 4.3% contained 0 and no other

statistic for significance was given in the paper. As all patients had been responders to IVIg previously, the 4.3% increase in muscle strength seems small compared to the mean score of 69.9% and a SD of 18% and of doubtful clinical significance. No objective ranking of general improvement and disability was made. The clinical evaluator therefore found that this paper does not contribute to evidence for efficacy of IVIg in MMN.

Uncontrolled Clinical Studies (Level III)

Three *Long term open* studies and seven other *Open studies* were presented in the application. As these studies were not included in either the sponsor's Clinical Summary for this LBS or in the Cochrane Overview for MMN they were considered in brief. One study was not included in the long-term studies in spite of the median duration of IVIg treatment being 3 years. The clinical evaluator has therefore included this study in the long-term studies.

Long term studies

(1) Azulay, 1997, found in a study with a median duration of 25.3months (range 9-48 months) that the 12 of 18 patients who improved on IVIg needed repeated courses to maintain their improvement. However, in two patients, IVIg infusions were stopped without signs of relapse after one year. The authors concluded "These results show the long term benefits and safety of IVIg in multifocal motor neuropathy but also the transient effect of this expensive treatment in most patients."

(2) van den Berg, 1998, reported longer follow up of the patients reported previously (van den Berg, 1995). The latter paper was reviewed in this evaluation. Although five patients showed improvement in the earlier study, six are described in the second study as improved and continued treatment for between 2 to 4 years (no median value given, but this was 2.5 years from the table provided). All received the usual dose of 0.4g/kg/day for 5 days.

In all the patients, IVIg treatment had a beneficial effect on most muscle groups during the follow up period. However, in three of the seven patients muscle strength deteriorated during IVIg maintenance treatment in four of the 28 muscle groups that had initially shown an improvement of muscle strength after the start of IVIg treatment and in two muscle groups with normal strength at the start of IVIg treatment. The electrophysiological follow up studies indicated that there was an improvement of conduction block but also that there were new sites of conduction block and ongoing axonal degeneration during IVIg maintenance treatment.

(3) van den Berg, 2002, reported long-term follow up of another group of 11patients with MMN treated with one full course of IVIg (0.4g/kg/day for 5 days) then one IVIg infusion of 0.4g/kg per week, depending on the patient's clinical condition. The second treatment ranged from one infusion everyone to seven weeks, with an average dose of 7 to 48g/week.

Muscle strength improved significantly within 3 weeks of the start of IVIg treatment and was still significantly better at the last follow up examination than before treatment even though it decreased slightly and significantly during the follow up period. The mean MRC sumscore of all patients was 92 ± 7 before and 95 ± 6 after the first full course of IVIg ($p < 0.001$). The mean MRC score at the last follow up examination was 94 ± 7 which was also significantly higher than the pre-treatment MRC score ($p < 0.001$).

The authors concluded that IVIg maintenance treatment had a beneficial long-term effect on muscle strength and upper limb disability but may not prevent a slight decrease in muscle strength. The electrophysiological findings implied that IVIg treatment favourably

influenced the mechanisms of remyelination or reinnervation but that axon loss cannot be prevented.

(4) Bouche, 1995, treated 19 patients who had persistent multifocal conduction blocks in motor fibres with IVIg over 5 days, repeated monthly for at least 6 months. All patients were followed for at least 2 years and evaluated every 3 months. At the end of the 6 month period, IVIg was repeated every 2 or 3 months if there was improvement. Improvement was correlated with at least one point gain in muscle strength (MRC scale) and one point gain in the score of the functional activity scale (Modified Rankin Score). Fifteen patients with amyotrophy formed Group 1 and 9 patients without amyotrophy formed Group 2.

As shown in the following table (Table 12), a higher response rate was seen in the group without amyotrophy (5/9, 56%) compared to those with amyotrophy (1/15, 6.7%). The table also indicates the transitory nature of the improvements in Group 1 in which 10 of 15 patients had less than 6 months improvement. Only one more patient had more than 6 months improvement, even though the median duration of treatment was 3 years.

Table 12. Response to treatment.

	All patients (n = 24)	*Group 1 (n = 15)*	*Group 2 (n = 9)*
Treatment:			
None	5	2	3
Intravenous IVIg	19	13	6
Response to IVIg treatment (19/24):			
Absent	2	2	—
Transient	11	10	1
Sustained	6	1	5
Follow up study:			
Without treatment:			
Improvement	1	—	1
Stabilisation	4	2	2
IVIg treatment:			
Improvement	6	1	5
Stabilisation	12	12	—
Worsened	1	—	1

Group 1 = patients with amyotrophy; group 2 = patients without amyotrophy; transient = transient response to IVIg lasting no longer than six months; sustained = response to IVIg lasting longer than six months; follow up study = follow-up study after six months (mean duration = three years).

Evaluator's comments on long term follow up studies: Overall the studies showed that an initial response was seen in about 60% of patients with MMN treated with IVIg in the studies (one study proved an exception), but re-treatment was required at intervals from between one to seven weeks to maintain the improvement. The response in any one patient appeared to be mixed with some muscles improving in strength and other losing strength, while nerve conduction also varied. Both however continued a downward course. Patients therefore rarely had a true remission, where no treatment was needed and no deterioration occurred. The clinical state appeared to be determined by a balance between improvement in some nerves and muscles and deterioration in others. The role administered immunoglobulin plays in these processes is unknown.

Open label (Shorter term) studies

Seven shorter term studies (up to 12 months in duration) were included in this section of the current application In four studies the usual dose of 0.4g/kg/day for 5 days was used, in one study a dose of 1.6-2.4g/kg over 2-5 days was given. In another study an increasing dose from a base line of 0.5g/kg/month whilst in another study, the patients' regular dose

(not stated) was administered. The following are the evaluator's summaries of these papers:

Cats *et al* (2008): A 5% and a 10% formulation of IVIg was administered to 20 patients at their regular dose. It found that the mean transfusion time with 10% IVIg was 2.5 h compared to 4.5 h with 5% IVIg. Evaluator: As the 20 patients were probably those participating in a previously evaluated study (above) they were not be counted again.

Comi G *et al* (1994): IVIg was administered to five patients with MMN all of whom improved but in three the clinical benefits "declined after three to eight weeks".

Nobile-Orazio E *et al* (1992): Five patients with MMN were treated twice at a 2-month interval. Four of the five patients improved their Rankin and MRC scores. One patient maintained improvement for a year without treatment but in the three other patients, improvement only lasted 20 to 30 days.

Nobile-Orazio E *et al* (2002): This paper attempted to correlate response to IVIg treatment in MMN patients with definite (14), probable (6) or no conduction block (3). The trial did not mention sample size or statistical power and showed no statistically significant difference in the response rates.

Chaundry V *et al* (1993): Nine patients with MMN were treated with 1.6 to 2.4g/kg IVIg over 2-5 days. The authors found strength improvement in all patients after 3 to 10 days, with peak improvement at 2 weeks, lasting on average 2 months. No other information was given on dosing.

Evaluator's comment: It is possible that a higher than usual dose was used in this study and if so it indicates that a higher dose does not improve the outcome (however see next study).

Baumann A *et al* (2009): A prospective, non randomised 6 month observational study, included nine patients who were receiving treatment with a stable dose of IVIg for MMN. Individual IVIg dose given over the last six months was retrospectively analysed. Stable average IVIg dose over the 6 months before entry into the study was 0.5 g/kg per month [range: 0.1–1.1 g/kg/month], given at variable intervals [4–12 weeks]. In Step 1, the dose was increased to 1.2 g/kg per month given over three consecutive days planned for 6 cycles. If patients' motor function did not improve after 2 cycles they entered Step 2 in which the dose was increased to 2 g/kg per month given over 5 consecutive days. The increased dose was maintained for 6 months.

Assessments were performed after 2 and 6 months. The primary clinical outcome measure was change in motor function from baseline to 6 months scored according to the Medical Research Council (MRC) rating scale in 40 muscles or muscle groups with a maximum score of 200 for a normal strength. Functional outcome was assessed using a) the Guy's Neurological Disability Scale where 0 means no disability and 10 means no motor function in arms and legs and b) according to our own non-validated Individual Disability Score where three motor activities of daily life (for example, tying shoe laces) were defined individually for each patient at baseline. A score of 0 indicated no symptoms; 1 = function slightly slowed but qualitatively unimpaired, 2 = function severely slowed, 3 = function qualitatively severely impaired, 4 = function impossible, giving a total score of 0 with normal motor function and 12 if none of the three functions could be performed. To the authors' knowledge, there is no validated individual disability score. In addition, muscle atrophy was assessed and nerve conduction and electromyogram (EMG) measurements made. Response was defined clinically as improvement by at least 2 points in MRC paresis sum score and (in addition) by at least one point either in the Guy's Neurological Disability Scale or the Individual Disability Score.

Following Step 1, six out of nine patients improved, two out of three 3 non responders entered Step 2 and the third non-responder withdrew due to absent efficacy and stopped IVIg treatment but consented to follow up. In this patient disease course was stable despite suspension of therapy. The two patients entering Step 2 did not improve. One out of six responders (Step 1) stopped after 4 months due to side effects (nausea). One patient required hospitalization due to infection of IV line with septicemia (serious adverse event). Seven patients completed the 6 months (5 responders at 2 months and 2 non responders after 2 and 6 months). Mean MRC paresis sum score improved from 28.57 [range: 6–47] to 26.29 [range: 3–46] (p = 0.048), mean Guy's Neurological Disability Scale improved from 3.86 [range: 2–6] to 3.14 [range: 0–6] (p = 0.030), mean Individual Disability Score improved from 9.00 [range: 7–11] to 7.14 [range: 4–9] (p = 0.014). Improvement was best reflected in the Individual Disability Score (6), and less in MRC paresis sum score (5) or Guy's Neurological Disability scale (4). One responder reported marked improvement at Month 2 but had deteriorated again at stable dose of IVIg at Month 6, but was still better than at baseline.

Evaluator's comment: This study has been presented in some detail because, as the authors state, "The dose-response relationship in MMN has not been explored, neither in the short- nor in the long term", a point the clinical evaluator made in reference to CIDP, in the previous section of this evaluation.

One strange result was that one patient had a MRC paresis sum score at 6 months of 278. Since complete paresis had a score of 200 (above), this may be a misprint. On this scale, the table classed the patient as a non-responder. He was also a non-responder on the Guy disability score, but a responder on the Individual Disability score. This is not in accordance with the definition of responder (above) and therefore the number of responders was reduced from the claimed 6 to 5.

In spite of this, the results showed that improvement occurred with the higher dose of IVIg in Step 1 of the study in five patients previously stabilized on a lower dose of IVIg. The authors suggest that it might be more successful to find the highest and most effective dose tolerated and the shortest interval with the highest gain of motor function, but add "Considering side effects and also economic aspects, more and better designed multicenter studies with larger patient samples are necessary before such an expensive and burdensome treatment strategy can be widely recommended." Interestingly, this last conclusion of the study was omitted from the study report.

Analyses of data from more than one study

1. The 2005 Cochrane Review, to be cited as "van Schaik IN, van den Berg LH, de Haan R, VermeulenM. Intravenous immunoglobulin for multifocal motor neuropathy. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004429. DOI: 10.1002/14651858.CD004429.pub2." Level 1.

It should be noted that this version was first published online on 20 April 2005 in Issue 2, 2005 of *The Cochrane Library*. The most recent substantive amendment was made on 27 January 2005, over five years ago.

The objective was to review systematically the evidence from randomised controlled trials concerning the efficacy and safety of intravenous immunoglobulin in MMN. The review identified 16 possible studies and excluded 12 of these.

Evaluator's comment: An author of one of the four studies included was also one of the Cochrane Review Panel itself (Van den Berg). Problems with this study (Van den Berg, 1995) arose because patients entering the open phase of that trial were unselected and all responded to IVIg, and were then entered in the second phase. This led the review group

to analyze separately the data that included and excluded the Van den Berg study (1995). In addition, some trials did not contain data that could be evaluated meaning that the evaluation relied mostly on data from three trials. This number was further reduced by one (to two trials) when the Van den Berg trial was excluded.

IVIG versus placebo.

Primary Outcome: Improvement in Disability.

The analysis of three trials (Azulay 1994, Van den Berg 1995 and Leger 2000) showed no statistically significant improvement in disability. The pooled relative risk of IVIg treatment compared to placebo had a 95% CI of 0.89-10.12; p=0.40). Without the Van den Berg study, the result was still not significant (CI 0.53-7.60; p value not given).

Secondary Outcome: Muscle Strength.

Muscle score was assessed in each of three trials in a different way – summed strength in two selected muscles (Azulay 1994); readings from a handheld dynamometer from 11 different muscles (Van den Berg 1995), and patients rating subjectively their strength (Federico 2000). Overall, a significant improvement of muscle strength was reported in 21 out of 27 (78%) patients receiving IVIg treatments and in one out of 27 (4%) placebo treatments. A significantly higher proportion of patients improved after IVIg therapy as compared with placebo with a pooled relative risk of 11.00 (95% CI 2.86 to 42.25). The study results were homogeneous (chi-square 0.99, P value = 0.61). Analysing this comparison without the study of van den Berg, 1995 resulted in a relative risk of 17.00 (95% CI 2.48 to 116.59).

Mean change in muscle strength was expressed as effect size defined as the mean change in score of the placebo group minus mean change in score of the treatment group, divided by the pooled standard deviation of the change in scores of the two groups. The weighted pooled effect size for all the studies was 1.12 (95% CI -0.71 to 2.95). The review states "This indicates that the mean change in muscle strength on IVIg was approximately one standard deviation higher than the mean on placebo, but this effect is not significant."

Evaluator's comment: The pooling of muscle scores is problematic, since each method was different and one was subjective. An improvement in muscle score was the only significant positive finding in the review. The mean change in muscle strength was not improved, and interestingly the above conclusion was omitted in the study report, as was the conclusion of the Baumann 2009 paper. The Review concludes "Limited evidence from randomised controlled trials shows a non-significant trend towards improvement in disability after IV immunoglobulin compared with placebo. There was a significant improvement in muscle strength." However, the last conclusion should be treated with caution because of the problems referred to above in assessing muscle strength. It was therefore concluded that the analysis of the randomised controlled trials done by the Cochrane Review was not convincing in showing that IVIg treatment of MMN led to significant clinical improvement compared to placebo.

2. Fergusson D., Hutton B., Sharma M., *et al* *Transfusion* 2005 45:10 (1640 – 1657). Level 1.

A systematic review by Fergusson, 2005 provided a meta-analysis of three of the four studies from the clinical dataset included by Van Schaik, 2005, namely Federico, 2000, Leger, 2001, Van den Berg, 1995, from 37 trials representing 14 conditions, one of which was MMN. The review concludes "There is also potential benefit for treatment of multifocal motor neuropathy….".

Evaluator's comment: The analysis adds nothing to the Cochrane Review and to the earlier assessments except in defining the problems of conducting trials in the conditions requested in this application, and so have relevance to the whole of the present LBS application.

Retrospective Studies

Two retrospective studies were presented.

1. Léger J-M, Viala K, Maisonobe T *et al*. J Neurol Neurosurg and Psychiatry 2008;79: (93-96). Level III.

A retrospective study was conducted in 40 patients with MMN and treated with periodic IVIg infusions between 1995 and 2003. The short-term response was defined as improvement of at least 1 point on the MRC score in at least two affected muscles at 6 months. The population comprised 22 treatment-naive patients (who had never received IVIg before inclusion), and 18 previously treated patients. For the long-term evaluation (>6 months), the patients were classified into three groups according to the dependency or not on periodic IVIg. In addition, changes in conduction block (CB) and predictive criteria for response to IVIg were explored.

The MRC score significantly improved ($p<0.0001$) in 14 (70%; 95% CI 0.46 to 0.88) of the 20 treatment-naive patients (missing data for 2 patients). None of the predictive criteria studied were found to be significant. At the end of follow up (mean of 2.2 ± 2.0 years), only 8 of the 40 patients (22%) had significant remission, whereas 25 patients (68%) were dependent on periodic IVIg infusions. The number of CBs decreased or remained unchanged in 12 treatment-naive patients and increased in 2 such patients

The authors conclude "..MMN should merit further prospective studies for the better knowledge of its natural history and of the potential beneficial effects of additional long-term effects of additional immunomodulating therapy".

Evaluator's comment: This paper further confirmed the short period of effective response of MMN to IVIg, with only 22% of patients having a long-term remission. As above, the study report omitted the authors' conclusions.

2. Vucic S, Black KR, Chong PS *et al*; Neurology 2004;63:1264-1269. Level III

The authors reviewed medical records of 10 patients with MMN who had been treated with IVIg at a dose of 0.4g/kg/day for 5 days given monthly for 3 consecutive months followed by monthly maintenance therapy in which the dose was reduced if the patient maintained improvement, and increased up to the original dose if there was deterioration.

There was significant and sustained improvement in muscle strength and functional disability while on IVIg therapy with a significant improvement in CB, decrease in axonal degeneration (AD) and evidence of reinnervation by the end of the follow up period (average of 7.2 years; range 3.5 to 12 years).

Evaluator's comment: The results differed from most other studies in showing such improvement long term. The authors attribute this to a higher dose (not quantitated),

presumably because the treatment period was maintained at 4 weekly whereas in most studies the period was lengthened.

Guidelines for the Use of IVIG in MMN

The application included one Australian and a number of national guidelines for the use of IVIg. Most reviewed MMN with other neurological conditions, and one (Van Schail 2006) reviewed MMN alone.

Evaluator's comment: Some guidelines rated the clinical studies on which the guidelines were based but the scales for quality differed for each, for example those used by the European Federation of Neurological Societies (EFNS; Elovaara 2008), the FDA (online), the American Academy of Allergy, Asthma and Immunology (Orange 2006), the IVIg Hematology and Neurology Expert Panel, Canada, (Freasby 2007), and the Australian Health Ministers' Conference, AHMC (2007). An earlier Australian overview was that by Biotext, Science Information Consultants, whom The National Blood Authority of Australia commissioned to undertake a systematic literature review of the efficacy and risks of IVIg. All scales of quality however in all guidelines placed consensus documents and guidelines at the bottom of their scales (NHMRC Level IV, Canadian Level 5).

The guidelines may have been formulated after careful evaluation of the results in each of the papers cited, but some, such as that of the Association of British Neurologists, give no indication of this, instead simply quoting for MMN the results of the Cochrane Review. The AHMC (2007) quoted both the Biotext conclusions and the Cochrane Review. Only a summary of the Biotext report (2004) was provided in the application so the details of the Biotext review of MMN treatment with IVIg could not cross-checked. At the time of the Biotext review, 2004, some important studies had yet to be performed. The best-documented consensus was the Canadian (Freasy 2007), which included a number of cautions about the interpretation of the relevant RCT data, and the Conchrane Review itself.

All consensus statements and guidelines supported the use of IVIg as first treatment of MMN because it was safe and effective but without defining effective although sometimes stating that muscle strength alone improved but not disability performance as the Cochrane review had concluded previously.

Evaluator's overall conclusion on efficacy of IVIG in treating MMN

Studies of efficacy in the treatment of MMN were difficult for the reasons given above and well summarized by Ferguson, 2005. The comments still apply, although more studies have been published since the Ferguson review. The surrogate end point in most studies was muscle strength which had not been validated in any study as representing significant clinical improvement. Different numbers of muscles in different muscle groups were used in different studies to assess muscle strength. Similarly, none of the many ratings used to assess disability had been validated. Even more surprising, no tested Quality of Life measure was used in any study.

Based on the RCTs and supporting trials, the clinical evaluator conclude that initial treatment of MMN with IVIg produced in some patients an increase in muscle strength. However, the studies have not shown that this was accompanied by a statistically significant clinical improvement in disability. Those patients in who muscle strength improved required ongoing treatment with IVIg at varying intervals and doses to maintain that improvement and showed steady deterioration with time.

Myasthenia Gravis (MG)

Two scores or scales of muscle strength, the Quantitative Myasthenia Gravis (QMG) Score and the Myasthenic Muscle Score (MMS), as well as classes of severity (Osserman) and functional status (Oosterhuis) were used to assess the clinical state of trial patients with MG in the studies submitted.

RCTs in MG

Five RCTs of IVIg in the treatment of MG were included with the current Australian application. As comparators for IVIg, two of the trials used placebo, three used plasma exchange (PLEX) and one compared the efficacy of two doses of IVIg.

Reference 1: Level II Gajdos P, Chevret S, Clair B *et al*. Ann Neurol 1997; 41: 789-796

Aim: The aim of this study was to compare the efficacy and tolerance of IVIg and of plasma exchange in MG exacerbation and to compare two doses of IVIg.

Treatments: In the plasma exchange group, participants received three plasma exchanges of 1.5 plasma volumes performed once every two days. The IVIg group had two arms: in one arm participants received IVIg 0.4 g/kg for three days (total 1.2 g/kg) and in the other arm participants received 0.4 g/kg for five days (total 2 g/kg).

Endpoints: The main endpoint was the variation of a myasthenic muscle score (MMS) between randomisation and Day 15. The MMS used was the sum of nine independent observations of trunk, limbs, neck and cranial muscles which when added yield an overall numerical rating between 0 for a maximum deficit and 100 for normal strength.

Sample Size: A sample size of 86 participants was calculated to be sufficient to detect a 50% difference in the change in the mean MMS between the plasma exchange and the IVIg group with 85% power and p = 0.05.

Study participants: Eighty-seven participants were included: 41 in the plasma exchange group and 46 in the IVIg group (23 in the 3-day group and 23 in the 5-day group). Participants' characteristics at the time of randomisation were well balanced without any significant differences.

Results:

1. Changes in the MMS score: At day 15, the mean change in the MMS score was 16.6 (95% CI 11.6 to 21.6) in the plasma exchange group and 15.6 (95% CI 10.9 to 20.3) in the IVIg group (p= 0.65 Wilcoxon test). In the IVIg group, the mean change was 18.9 (95% CI 13.1 to 24.7) in the 3-day IVIg group and 12.4 (95% CI 5 to 19.8) in the 5-day IVIg group (p= 0.14 Wilcoxon test).

2. Responses: Response was defined as an improvement of 20 points in the MMS score over the baseline assessment. The score was from 0 (major weakness) to 100 (no weakness). Of the 87 participants included, 48 treatment responses were observed, 26 in the plasma exchange group and 22 in the IVIg group (14 in the 3-day and 8 in the 5-day group).

3. Changes in Anti-ChR antibodies: Among the 63 participants with detectable anti-acetylcholine receptor (AChR) antibodies, 39 (62 %) exhibited a decrease in concentration on Day 15 compared with that measured at randomisation: 19 of 41 participants in the plasma exchange group and 20 of 46 participants in the IVIg group. The mean change in anti-AChR antibodies titre was a 13.8% (95% CI -40.8 to +13.2) decrease in the plasma exchange group and a 16.8% (95% CI -24.9% to +58.5%) increase in the IVIg group (p= 0.36 Wilcoxon test). The mean change in anti-AChR antibodies titre was not significantly different between the 3-day and 5-day IVIg groups.

Evaluator's comment: Exacerbation of MG. In the trial neither the participants nor observers were blinded, while the power of the study detected only a 50% difference in the two treatments. As the later Cochrane report concluded, within these limits there was no significant difference between the treatments. Plasma exchange resulted in 26 (30%) of 87 patients in the plasma exchange group responding, and 22 (25%) of 87 in the IVIg group. Results from the comparison of 3-day versus 5-day dosing were inconclusive due to the low power of this comparison.

Reference 2. Level II. Ronager J, Ravnborg M, Hermanen I *et al*; Artificial Organs 2001; 25:967-973

Aim: The purpose of the study was to compare the efficacy of IVIg versus plasma exchange in people with moderate to severe MG in a stable phase.

Randomisation and Treatment: Participants were randomly assigned to receive either IVIg 0.4 g/kg on five subsequent days and 16 weeks later five plasma exchanges every other day, or five plasma exchanges and 16 weeks later IVIg.

Endpoints: The main endpoint was the clinical improvement measured before and seven days after each treatment using the quantified MG score (QMGS). The QMGS was performed by only one observer who was blinded to the treatment given. Secondary endpoints were decrease in anti-AChR antibodies titre, change in decrement and the clinical effect assessed four, eight and 16 weeks after each treatment. Clinical relevant differences were pre-defined as 0.3 decrease in the QGMS or a 20% response rate.

Sample size: A sample size of 20 participants was calculated as sufficient to identify a range of improvement in MG score of 0.0 to 0 2.0 and the clinically relevant difference in QMGS of 0.3 or 20% in response with a power of 80% and p= 0.05.

Results: Twelve participants were included. The mean fall in QMGS was 0.23 ($p < 0.05$) after plasma exchange and 0.10 (NS) after IVIg, from baseline to one week. From baseline to four weeks, the mean fall in QMGS, both after plasma exchange and after IVIg was significant ($p < 0.05$, mean values not published). The change from baseline to eight or 16 weeks was not significant for either plasma exchange or for IVIg. Comparing the clinical effect of the two different regimens (that is the change from baseline to one and four weeks after either treatment); no significant difference between IVIg and PE could be detected.

Evaluator's comment: Stable MG, moderate or severe: The results of the study are difficult to interpret. The primary endpoint (at one week) did not show a positive response for IVIg treatment. However, improvement was seen at Week 4, a secondary endpoint. As well, although both treatments produced a statistically significant fall in the MG score compared to the pre-treatment values, the fall did not reach the 0.3 figure required for clinical relevance. As no individual patient results were given, the number of responders could not be estimated, and so it is unknown if the other clinically relevant figure of 20% response rate (using the 0.3 fall in MG score) was achieved. Overall, the study was so poorly reported that it can only be classed as preliminary

Reference 3. Level II. Wolfe GI, Barohn RJ, Foster Bm *et al*; Muscle Nerve 2002;26:549-552

In the trial, IVIg was compared to 5% albumin as placebo. Participants were randomised to receive either IVIg 1g/kg or 5% albumin placebo on Days 1 and 2. A 1g/kg infusion of IVIg or placebo was repeated on Day 22.

A sample size of 88 participants had a power of 80% to detect a difference of 3.5 units on the QMGS of five per cent level of significance.

The authors comment that after 15 patients were enrolled (six give IVIg and nine given placebo) the study was terminated "because of insufficient IVIg inventories". In their discussion they further states "Due to early termination, the randomised study was under-powdered to determine whether IVIg is effective in MG.", and "At Day 42, several patients who received placebo demonstrated improvement in outcome measures, including on electrophysiologic testing. Perhaps this observation is not surprising for a disease characterized by spontaneous fluctuations, but underscores the value of placebo-controlled trials to evaluate treatment efficacy in MG."

Evaluator's comment: It was noted that the authors' comments were not mentioned in the study report in the current application.

Reference 4. Level II. Gajdos P, Tranchant C, Clair B *et al*; Arch Neurol 2005; 62:1689-1693

Aim: To compare on Day 15 the effectiveness of two doses of IVIg - 1g/kg and 2g/kg, in treating the acute exacerbation of MG.

Patients' randomisation and treatment: In total, 173 patients, aged 15 to 85 years, with acute exacerbation of MG were randomised. Acute exacerbation was defined as development within the last month of at least one of the following symptoms: difficulty swallowing, acute respiratory failure, and major functional disability precluding physical activity. Eighty-four patients were randomised to Group 1 (1g/kg dose) and 89 to Group 2 (2g/kg dose). Five patients (three in Group 1 and two in Group 2) were excluded from the analysis, leaving 168 patients for the intention-to-treat efficacy analysis, 81 in Group 1 and 87 in Group 2. Patients were randomly assigned to receive 1 g/kg of IVIg on Day 1 and placebo on Day 2 (Group 1) versus 1 g/kg of IVIg on each of two consecutive days (Group 2).

Endpoint: The main endpoint was the change of MMS between randomisation and day 15. Other endpoints were the time to the occurrence of a treatment response within the first two weeks, defined as an increase in MMS of at least 20 points compared with the initial value; and the change of anti-AChR antibody titres between Day 0 and Day 15.

Sample size: A sample size of 170 participants was calculated to be sufficient to detect a 50% difference in the change in the mean MMS between the 1 g/kg IVIg group and the 2 g/kg IVIg group with 90% power and p= 0.05.

Results: At baseline, the mean (SD) MMS was 50.47 (15.62) in Group 1 and 49.56 (16.56) in Group 2. On Day 15, the mean MMS change from baseline was 15.49 points (95% CI 12.09 to 18.90, P < 0.0001, Wilcoxon signed rank test) in Group 1 and 19.33 points (95% CI 15.82 to 22.85, P < 0.0001, Wilcoxon signed rank test) in Group 2. The mean MMS change in each groups was similar (difference = 3.84 (95% CI -1.03 to 8.71); p= 0.12).

Similar numbers of participants responded at least once within the first 2 weeks (44 [54%] of 81 patients in Group 1, and 52 [59%] of 87 in Group 2 respectively). The median time needed to response was similar in the two groups (13.5 days and 12 days in the 2 groups respectively p= 0.48). No significant differences were found for the other secondary efficacy criteria.

Evaluator's comment: Acute exacerbation of MG: The study was well designed and conducted, although the sought-for difference in the two groups was high at 50%. The authors commented, without giving reasons, that any smaller difference would have been clinically unimportant. We can accept that the higher dose may have been up to 50% more effective than the lower dose, but not more than 50%, so that the response rate at the lower dose could have been increased by a higher dose up to, but not more than, 80%

from 54%. The important point for the present application is that the lower dose of 1g/kg was effective in a two week period in 54% of patients with acute exacerbation of MG.

Reference 5. Level II. Zinman L, Ng E, Bril V. 2007; 58:837-841

Aim: The aim of the study was to compare IVIg and placebo in the treatment of patients with MG and worsening weakness. Worsening weakness was defined as increasing symptoms or signs severe enough as judged by both patient and physician to warrant a change in therapy. (People were excluded if they had respiratory distress requiring intensive care, a vital capacity less than 1L, severe swallowing difficulties, a change in corticosteroid dosage in the two weeks prior to screening or other disorders causing weakness.)

Randomisation and Treatment: Patients were allocated to receive either IVIg 2g/kg or the equivalent volume of dextrose 5% over two days. The main endpoint was the change in QMGS from baseline (Day 0) to Day 14. Other end points were the change in QMGS from Day 0 to Day 28 and from Day 14 to day 28; the change in single fibre electromyogram (SFEMG) and repetitive nerve stimulation (RNS) from Day 0 to day 14; and the Post-Intervention status on Day 14 and 28.

Sample size: A sample of 22 participants per treatment arm was calculated to be sufficient to detect a change of 3.5 units in the QMGS. An analysis of the IVIg treatment effect was performed stratifying participants by baseline severity: mild MG (QMGS <10.5) and moderate to severe MG (QMGS > 10.5).

Results (Table 13 and Figure 13 below): Primary end point: On Day 14, the mean (SD) change in QMGS was -2.5 (3.4) in the IVIg group and -0.9 (2.4) in the placebo group (p= 0.047), and this difference was statistically significant.

Secondary endpoints: On Day 28 these values were -3 (3.7) in the IVIg group and -1.2 (2.9) in the placebo group, (p= 0.055), not statistically significant. For the mild MG patients the mean change in QMGS on Day 14 was similar in the two groups: -0.7 (2.3) in the IVIg group and -1.1 (1.9) in the placebo group. For the moderate to severe MG these values were -4.1 (3.5) in the IVIg group and -0.7 (2.7) in the placebo group (p= 0.01) and the treatment effect was maintained at Day 28. The Post-Intervention status on Day 14 demonstrated that 25% of participants on IVIg improved compared with 6% on placebo (p < 0.004 χ^2 test). None of the electrophysiological measures showed a significant improvement with IVIg.

Table 13. Mean change in QMG score for disease severity at Days 14 and 28.

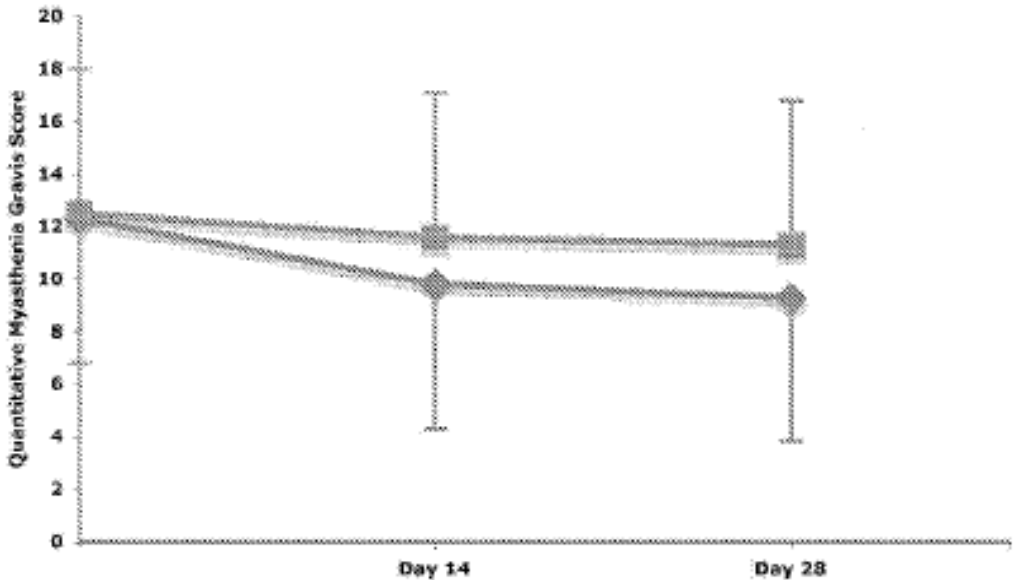
	IVIG, n = 24	D5W = 27	*p* Value
Baseline QMG Score (mean)	12.3 ± 4.9	12.5 ± 5.5	0.897
ΔQMG			
Day 0–14	−2.54	−0.89	0.047*
Day 0–28	−3.00	−1.19	0.055
Day 14–28	−0.46	−0.30	0.823

This table demonstrates a modest and significant treatment effect of IV immunoglobulin (IVIG) compared with placebo. IVIG treatment produced 2.5 U of improvement in the Quantitative Myasthenia Gravis (QMG) Score for Disease Severity at day 14 (an additional 1.6 U compared with placebo) and 3.0 U of improvement at day 28 (an additional 1.8 U compared with placebo).

* Significant by analysis of covariance.

D5W = IV dextrose 5% in water.

Figure 13. Mean change in Quantitative Myasthenia Gravis (QMG) score for disease severity in all patients treated with IV immunoglobulin (IVIg) and placebo.



t =IVIG (24) and ■=placebo (27)

There was a small decrease in the QMG score for disease severity with IVIg treatment observed at Day 14 (2.5 U; p<0.047).

Evaluator's comment: MG with worsening weakness**:** The study was well designed, conducted, analysed and reported. Following IVIg treatment, patients demonstrated statistically significant improvement at Day 14 but not at Day 28. The latter result may have been because of the greater improvement in placebo treated patients at that time in the study compared to Day 14, thus reducing the power of the statistic. Importantly the improvement in IVIg treated patients was maintained at Day 28. There is a good case then to say improvement was maintained for 28 days. The authors acknowledge that overall

the observed benefit was small, but patients with more severe disease did show greater benefit.

Uncontrolled Clinical Studies

Four publications were cited for evaluation. The clinical evaluator made the following comments regarding these papers:

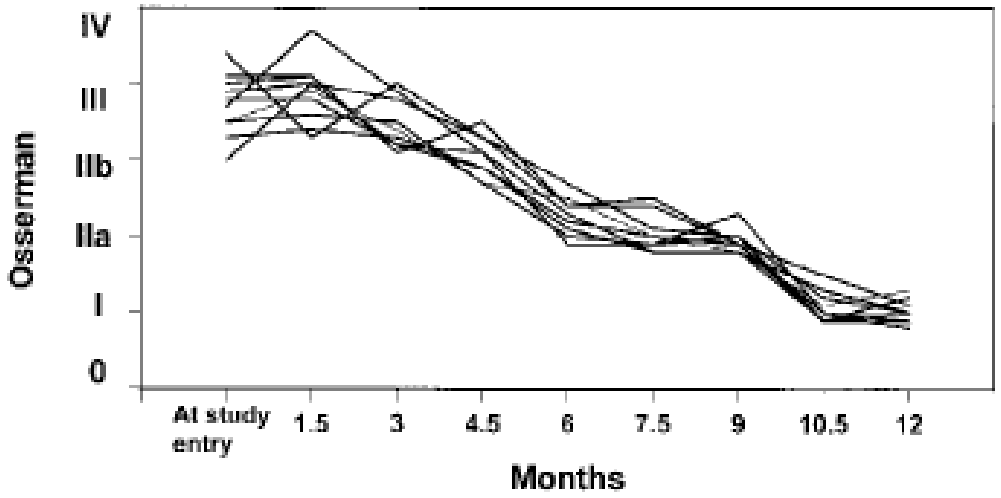
Reference 1. Level III-2. Achiron A, Barak Y, Miron S *et al*; Muscle Nerve 2000;23:551-555

Aim: To evaluate the efficacy of IVIg in an open study of 10 people with severe generalised MG and with acute deterioration unresponsive to conventional treatment with corticosteroids and immunosuppressive drugs.

Treatment: Intravenous immunoglobulin was administered at a loading dose of 2 g/kg over five days and maintenance IVIg at 0.4 g/kg once every six weeks.

Results: Significant improvement occurred in all patients, as measured by the Osserman scale, fatigue variables, muscle strength, and respiratory function tests. Initial improvement was observed at 6.4 ± 2.2 days after the start of IVIg treatment and became maximal at 10.5 ± l.6 days. Severity of disease decreased from a mean score of 3.7 ± 0.5 (severe generalized weakness) to 2.2 ± 0.7 (mild to moderate disease) (p= 0.001). Further IVlg treatments were highly efficacious in maintaining the remission. The severity of the disease decreased by 2.5 ± 0.8 grades of the Osserman scale over a period of 1 year (p<0.001) [Figure 14], in parallel with reduction of immunosuppressive therapy as well as a decrease in acetylcholine receptor antibody titers (p< 0.01). The authors concluded that IVIg therapy seems to be highly potent for inducing rapid improvement in refractory myasthenia during acute deterioration as well as for maintaining remission.

Figure 14. Individual Osserman scores for the 10 patients throughout the study.



Evaluator's comment: The weaknesses of the study were the small number of patients, the open design, and a scale that may lack sensitivity and may be subject to bias in assessment. However the maintenance treatment with IVIg was administered 6 weekly for 12 months and the end result indicated improvement over the whole time period, especially for refractory disease with acute deterioration.

Reference 2. Level III-2 Hilkevich O, Drory VE, Chapman J *et al*; Clin Neuropharmacol 2001; 24:173-176

Aim: The aim of the study was to study the efficacy of IVIg administered as maintenance treatment for MG.

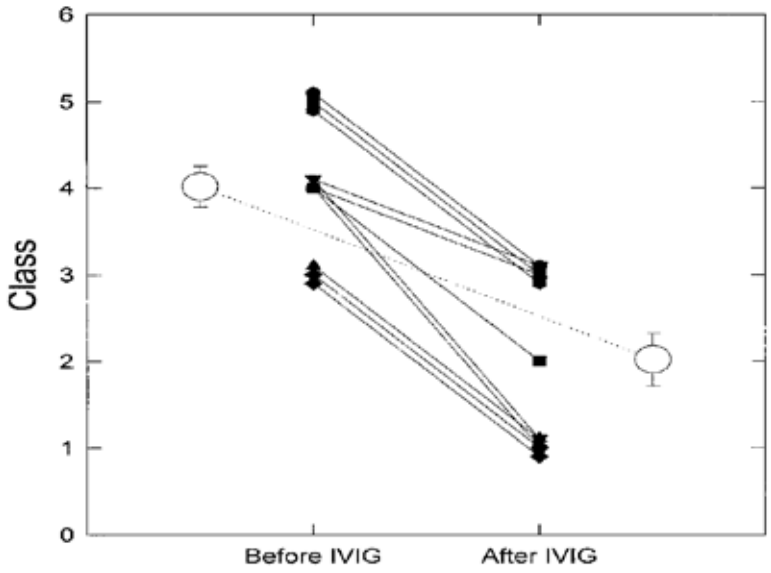
Study design: Eleven people with severe bulbar involvement were treated with IVIg initiated at a dose of 2 g/kg over five days followed by 0.4 g/kg once monthly for a mean period of 20.3 (8.3) months. Regular medications were continued as necessary.

Assessment: Neuromuscular function was measured by the Oosterhuis global clinical classification of myasthenia severity using a six-point scale. Note: This scale had six points because Class 0, asymptomatic, was included with the 5 classes.

Results: All patients improved during IVIg treatment as evidenced by their clinical score (Figure 15). The mean clinical score improved in all patients from 4.0 ± 0.7 (moderate to severe generalized weakness) to 2.0 ± 0.8 (p = 0.0000005 [sic] by paired Student *t* test). One-point improvement was seen in only two patients, two-point improvement in seven patients, and three-point improvement in two patients at the end of the follow up period.

In the eight patients who were treated with prednisone, IVIg had a marked steroid-sparing effect, and in two of the patients steroid treatment was discontinued. In three patients with generalized myasthenia with bulbar involvement treatment was initiated with IVIg, pyridostigmine and azathioprine (in one patient) simultaneously with no steroids administered at any stage. The mean steroid dosage at the beginning of IVIg treatment was 60 mg prednisone or its equivalent dose on alternate days (range of 0-100 mg), whereas at the last follow up It was 9.25 mg on alternate days (range, 0-40 mg) (p = 0.0004 by paired Student *t* test). The pyridostigmine daily dose was also reduced in response to IVIg treatment *(p* = 0.0004, paired Student t test). There was no attempt to reduce the azathioprine dose. During the study, none of the patients required mechanical ventilation or plasma exchange.

Figure 15. Oosterhius global clinical classification.



The individual clinical scores of 11 patients before and during IVIg treatment are indicated by full symbols together with the mean scores ±standard error (SE) indicated by the circles.

The authors concluded that IVIg demonstrated a beneficial long-term effect on the clinical course of generalized MG that was apparent both in the clinical severity and in the need

for additional therapy. Moreover, the patients who never received steroids also improved significantly compared with baseline.

Evaluator's comment: The results of this study were better than one would expect from the literature. The authors acknowledge problems with the study including the unblinded and non-randomised design, the possibility of spontaneous clinical improvement in MG and the fact that gradual improvement is the rule in steroid treated patients but point to the unlikelihood that the observed improvement was due to chance and was seen in all patients, including those who did not receive steroid treatment.

Reference 3. Level III-3. Wegner B, Ahmed I. Clin Neurol Neurosurg 2002; 105:3-8

Aim: To investigate the effectiveness of long-term treatment of myasthenia gravis (MG) with IVIg.

Study Design: Six patients on relapse were treated on a long-term basis with initial infusion of IVIg for five days at a dose of 0.4g/kg/day followed by maintenance therapy of 0.4g/kg for one day every 3 - 4 months and were then followed for 2 years. All had positive acetylcholine receptor antibody titers and had previously received steroids / anticholinergic drugs.

Results: The paper presented a case report for each patient with the clinical outcome. All patients showed improvement within days to a week, with resolution of diplopia and improvement in the neuromuscular strength. Subsequently, they were given 400 mg/kg/day on a 1 day treatment every 3-4 months. For the last 2 years, each of these patients maintained better than functional Class 2 on an average of 1.5-2.2 ± 0.5[*] grades on the University of Virginia modification of Ossermann's classification scale for MG while the prednisone and anticholinergic drugs were gradually withdrawn.

Evaluator's comment: The study is one of a series of case reports and so does not have high quality of evidence. The caveats in the previous study apply here also.

Reference 4. Level III-3. Selcen D., Dabrowski E.R., Michon A.M., Nigro M.A; Pediatr. Neurol. 2000 22:1 (40 - 43)

Aim: The aim was to prospectively evaluate the clinical response and complications of high dose IVIg therapy over a 5-year period in 10 children with juvenile myasthenia gravis (JMG).

Patient selection: The patients were selected on the basis of refractoriness to cholinesterase inhibitors, complications from or failure of steroids or incomplete response or inability to effectively use plasmapheresis.

Treatment: The IVIg dosage was 2g/kg body weight, infused at variable rates of 2g/kg for 1 day, 0.66g/kg daily for 3 day, and 0.5g/kg daily for 4 days. All children but one tolerated IVIg without complications.

Results: All the patients had Grade 4 or 5 functional status with acute relapse at the first infusion of IVIg. Three patients required mechanical ventilatory assistance. During the repeated infusions, the functional status of the patients was Grade 2 or 3. The results of IVIg therapy are listed in Table 14. Eight of nine patients demonstrated positive functional status improvement during acute relapse. The clinical change was evident 1-7 days after

[*] It is not clear what the figures 1.5-2.2 represent and no explanation of the statistic was given.

the infusion but a decreasing response to IVIg was evident after multiple monthly treatments, warranting the additional use of corticosteroids in two patients.

Table 14. Clinical parameters.

Pt. No.	MG Functional Status (First Episode) Before HDIVIG	Maximal Improvement	Artificial Ventilation	Repeat HDIVIG
1	4	3	−	0
2	3	2	−	1
3	5	1	+	0
4	4	2	−	5
5	3	2	−	2
6	5	2	+	4
7	5	3	+	2
8	4	2	−	2
9	4	4	−	0

Abbreviations:
HDIVIG = High-dose intravenous immunoglobulin
MG = Myasthenia gravis
Pt. No. = Patient number

Conclusions: The authors concluded that IVIg was safe and effective in most patients for short-term management of juvenile myasthenia gravis, in myasthenic crises and in preparing patients for surgery but appears to be of limited long-term benefit.

Reports of Analysis of Data from More than One Study

Reference 1. Level 1. Gajdos P, Chevret S, Toyka K. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD002277. DOI: 10.1002/14651858.CD002277.pub3.

This analysis reviewed the 5 RCTs above and in addition an unpublished RCT (by Schuchardt2002) in which a comparison of IVIg and methylprednisolone treatments of patients with moderate exacerbations of MG showed no significant differences between the two groups. As the data from the 5 RCTs could not be pooled in the review, the studies were reviewed much as above and will not be repeated here.

The analysis was thorough and also reviewed reports of uncontrolled studies. The conclusions were similar to those above (Evaluator's comments) as follows:

In severe myasthenia gravis exacerbation, one randomised controlled trial of IVIg versus placebo demonstrated the efficacy of IVIg. Another did not show a significant difference between IVIg and plasma exchange in severe myasthenia gravis exacerbation. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIg. A further, yet underpowered, trial showed no significant difference between IVIg and oral methylprednisolone. [Evaluator comment: However, in the three trials without placebo, the improvements above baseline assessments seen with IVIg were significant]

In chronic myasthenia gravis, there is insufficient evidence from randomised trials to determine whether IVIg is efficacious. More research is needed to determine whether IVIg reduces the need for corticosteroids as suggested by two case series.

Reference 2. Level 1. Fergusson D., Hutton B., Sharma M., *et al* Transfusion 2005 45:10 (1640 – 1657). This early meta-analysis analysed three of the five RCTs that were included in the Cochrane review above and discussed above. Again, these data could not be pooled because of differences in the studies. The analyses and conclusions were as above and will therefore not be repeated here.

Other Clinical Study Reports. Retrospective studies.

The sponsor cited four publications in this section. All these references were considered as Level III evidence.

Reference 1. Level III-3. Jongen JLM J Neurol 1998 245:26-431

Some 56% of 11 patients with generalised MG showed an improvement in functional status after a median of 3 days, reaching a peak after 7 days, following treatment with 0.4g/kg/day IVIg for 5 days.

Reference 2. Level III-3. Qureshi AI, Choudhry MA, Akbar MS *et al* Neurology 1999;52:629-632

This chart review found that the mean severity score of patients in MG crisis following IVIg treatment improved from 7.5 to 10.3. Improvement in the plasma exchange group was from 6.9 to 11.1. The study claimed to show superiority for plasma exchange group but a number of methodological flaws made this conclusion uncertain.

Reference 3. Level III-2. Perez Neller J, Dominguez AM, Llorens-Figueroa JA *et al*; Rev Neurol 2001;33:413-416

This paper compared prospectively a group of 33 patients with MG treated with IVIg with a historical group of 38 people with MG treated with plasma exchange during the peri-operative period of thymectomy. In the prospective group, participants received IVIg 2 g/kg (two-thirds of the dose before and one third after thymectomy). In the retrospective group, participants were treated with three plasma exchanges on alternate days before and two plasma exchanges on alternate days after thymectomy.

The duration of mechanical ventilation was not different between the two treatment groups: 14.1 hours (95% CI 10.71 to 17.31) in the IVIg group and 17.24 hours (95% CI 12.54 to 21.94) in the plasma exchange group (mean difference -3.23 (95% CI -8.71 to 2.31). The time in the intensive care unit was shorter in the IVIg group: 3.36 days (95% CI 2.9 to 3.82) in the IVIg group compared with 4.34 days (95%CI 3.76 to 4.92) in the plasma exchange group; mean difference - 0.98 (95% CI -1.72 to -0.24).

Reference 4. Level III-3. Wood A., Sutcliffe A. Care Crit. Ill 2004 20:4 (107 - 110)

This retrospective study reviewed case notes for 13 patients with MG who required ventilation and received IVIg at a dose of 0.4g/kg/day for 5 days for myasthenic crisis. If no improvement was noted by the end of this course, plasma exchange was commenced within 48 hours of the last IVIg dose. If improvement occurred, plasma exchange was delayed to 5 days post IVIg treatment. The endpoint for this audit was unassisted breathing. Three patients (23%) reached this endpoint after IVIg alone and a further three patients (23%) showed some improvement at the end of their course. These data confirm that not all patients with myasthenic crisis requiring ventilation will respond to IVIg, and of those that do, only a small proportion will do so in the timescale that facilitates early

weaning from the ventilator. The authors suggest that IVIg is not the appropriate first-line treatment for this group of patients.

Consensus Documents and International Guidelines

The consensus documents and international guidelines that refer to MG are those discussed above in for CIPD and MMN sections and were published in 2004, 2005, 2006, 2007 [two], and 2008 [two]. The dates of the publications of the RCTs reviewed for MG were 1997, 2001, 2002, 2005, and 2007. The earlier consensus documents and international guidelines would not have considered the later RCTs and only the consensus documents and guidelines published in 2007 and 2008 were evaluated.

1. *Australian Health Ministers' Conference (2007) Communique*

The indication for IVIg use is given as

a. As an alternative treatment to plasma exchange in acute exacerbation [myasthenia crisis] or prior to surgery and/or thymectomy and

b. As maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects.

Evaluator's comment: The document incorrectly states that the level of evidence for both indications is Level 1. However, that is true for the first indication only, as the document refrences when discussing the Cochrane Review. The second recommended indication was not in agreement with the recommendations of the Asia-Pacific Group.

2. *Expert Consensus Statements on the Use of IVIG in Neurology. Second edition 2008. Prepared by the Asia Pacific Immunoglobulins in Neurology Advisory Board*

The Expert Consensus was as follows: 1. IVIg is recommended for myasthenia gravis exacerbations, myasthenic crisis and in patients with severe weakness poorly controlled with other agents or in lieu of PE. 2. A dose of IVIg of 1g/kg for 1 day can be used in the treatment of MG exacerbations.

3. *Feasby T., Banwell B., Benstead T., et al (2007). Guidelines on the Use of Intravenous ImmuneGlobulin for Neurologic Conditions. Transfus. Med. Rev. 21:Suppl 1 .*

In these guidelines, from the IVIG Hematology and Neurology Expert Panels Canada all important studies in MG to date were summarised and the text drew balanced conclusions from them based on the quality of the trials and the clinical evidence presented.

The recommendations were as follows:

Adult and Juvenile Myasthenia Gravis – Intravenous immune globulin is recommended as a treatment option for patients with severe exacerbations of myasthenia gravis or myasthenic crises.

Based on consensus by the expert panel, IVIG may be considered as an option to stabilize patients with myasthenia gravis before surgery.

Intravenous immune globulin is not recommended as maintenance for patients with chronic myasthenia gravis.

Neonatal Myasthenia Gravis – Based on consensus by the expert panel, IVIG may be considered among the treatment options for neonates severely affected with myasthenia gravis.

Dose and duration of therapy were based on consensus by the expert panel, a total dose of 2g/kg given over 2 to 5 days is a reasonable option. If additional therapy is required, the

dose should be adjusted depending upon response and titrated to the minimum effective dose.

Evaluator's comments: These guidelines were thorough, clearly presented and well balanced.

4. *Elovaara I., Apostolski S., Van Doorn P., et al (2008). European Federation of Neurological Societies (EFNS) guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases Eur. J. Neurol. 15:9 (893 - 908)*

The Joint Task Force of the European Federation of Neurological Societies in its recommendations concluded that "Intravenous immunoglobulin is an effective treatment for acute exacerbations of MG and for short term treatment of severe MG (Level A). IVIg is similar to plasma exchange regarding effect. This treatment is safe also for children, during pregnancy and for elderly patients with complicating disorders. There is not sufficient evidence to recommend IVIg for chronic maintenance therapy in MG alone or in combination with other immuno-active drugs."

Evaluator's Overall Conclusions on Efficacy of IVIG in MG

The clinical evaluator's conclusions agree with those of the Cochrane Review (Gajdos, 2008) that there is convincing evidence that treatment with IVIg is effective in acute exacerbations of MG (myasthenic crisis), but that significant benefit of IVIg treatment in chronic MG has not been convincingly demonstrated. There is some uncertainty about the efficacy of IVIg in myasthenia crisis, as stated in the Review:

> "It is noteworthy that in the trial conducted by Zinman (Zinman 2007) people were excluded if they developed MG crisis or severe swallowing impairment and in the other RCTs (Gajdos 1997; Schuchardt 2002) dealing with exacerbation the number of MG crisis included was small. So it is still not clear whether the conclusion concerning the efficacy of IVIg in the treatment of MG exacerbation is also valid if the patient is in MG crisis".

Although there is only weak evidence the use of IVIg in MG crisis and to stabilise patients prior to surgery, these indications can be accepted.

Lambert-Eaton Myasthenic Syndrome (LEMS)

About 50% of cases of Lambert-Eaton Myasthenic Syndrome suffer from the paraneoplastic form while the remainder suffer from the non-paraneoplastic form.

RCT with placebo control

One study (Level II evidence) was cited by the sponsor as follows:

Reference 1. Level II. Bain PG, Motomura M, Newsom-Davis J *et al*; Neurology 1996; 47:678-683

Aim: This study investigated the effects of IVIg on muscle strength and on the serum titre of the autoantibodies that are likely to be pathogenic in the LEMS

Trial design: In this randomised, double-blind, placebo controlled crossover trial, serial indices of limb, respiratory, and bulbar muscle strength and the serum titer of antibodies in nine patients with non-paraneoplastic (NP)-LEMS were compared over an 8 week period. The period of 8 weeks was chosen to allow washout of the IVIg, and cross-over occurred at this time, although in the case of four patients this was delayed due to a supply problem of IVIg. Blinding in randomisation was considered adequate by the Cochrane Review, 2005.

Treatment: IVIg at 1g/kg/day on two consecutive days or placebo (0.3% albumen) were infused in the same volume and over the same time (8 to12 h/day).

Power of the Study: The power of study to detect a 15% improvement in muscle strength with a significance level (p value) of 0.05 was calculated to be approximately 90%.

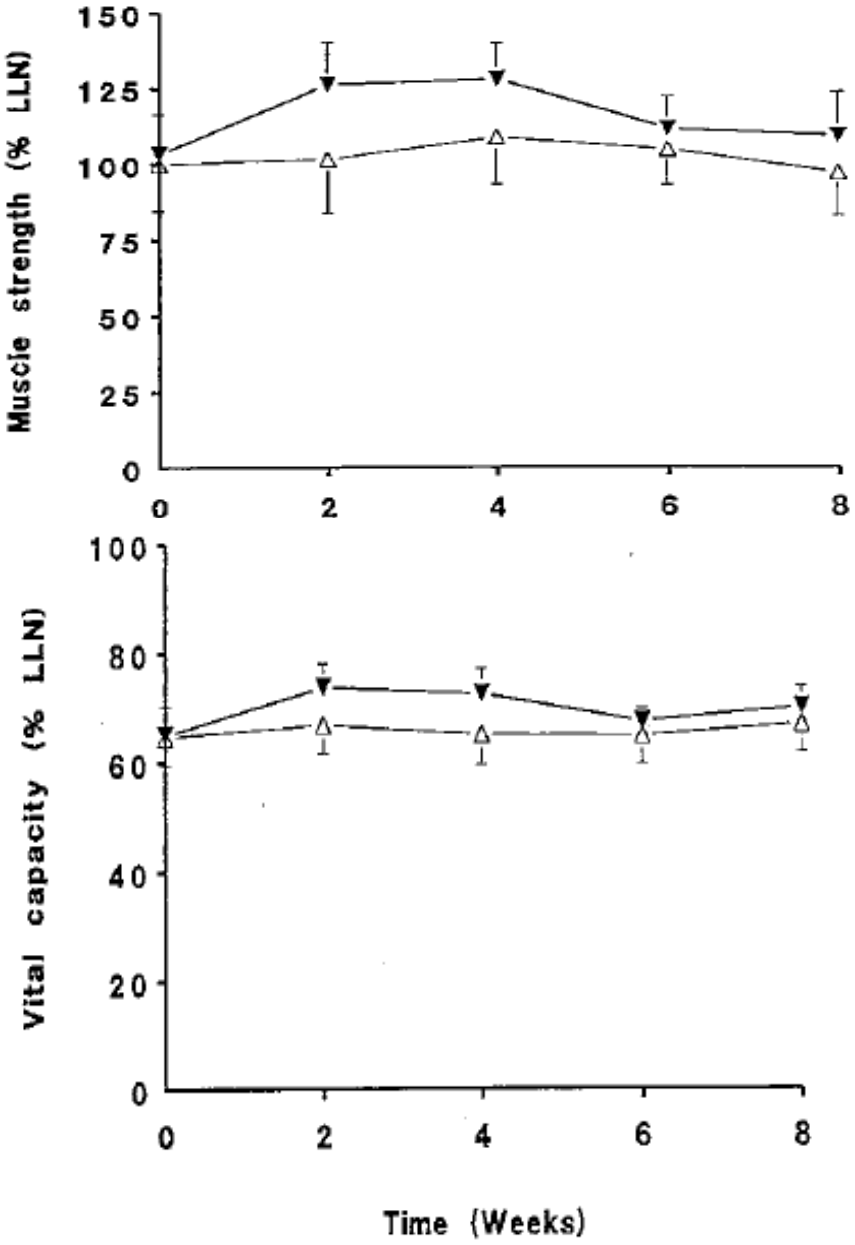
Results: Analysis of the mean intensity of response to the treatments revealed significant improvements in each of the three strength measures following IG infusion compared with placebo infusion (Table 15). The profiles of the mean values for muscle strength and vital capacity (expressed as a percentage of the lower limit of normal) showed maximum improvement at two weeks through four weeks with subsequent decline (Figure 16). The peak effects on overall muscle strength, vital capacity, and drinking time showed median improvements of 20%, 8% and 15% of the respective lower limits of normal [See also comments below]

Table 15. Intensity of response, evaluated over an 8 week period following infusion of Ig or albumin (placebo) on Days 1 and 2, using the area-under-the-time-curve approach.

	Mean ±SD	n	Median	P value*
Limb strength†				
Immunoglobulin	118.2±33.4	9	124.3	0.038
Albumin	101.8±43.9		101.8	
Vital capacity†				
Immunoglobulin	69.5±13.6	9	69.3	0.028
Albumin	64.8±15.3		67.0	
Drinking Time †				
Immunoglobulin	132.6±174.9	9	60.5	0.017
Albumin	170.8±241.3		58.8	
Antibody Titre‡				
Immunoglobulin	264.6±242.8	7	197.7	0.028
Albumin	369.0±204.9		347.9	
CMAP amplitude§				
Immunoglobulin	5.46±2.71	9	4.98	0.066
Albumin	4.55±2.64		3.78	

Note that a lower value for antibody titer and drinking time indicates an improvement.
* Values for two-tailed *p* obtained by pairwise comparison of the results by the Wilcoxon signed-rank test.
† The data for limb muscle strength, vital capacity, and drinking time are expressed as a percentage of the respective lower limits of normal.
‡ In pM.
§ Compound muscle action potential amplitude in abductor digiti minimi (mV).

Figure 16. Mean values for muscle strength and vital capacity.



Time course of the effects of immunoglobulin and albumin (placebo) infusion on indices of limb and respiratory muscle strength. The mean ± SEM values for limb muscle strength and for vital capacity are compared over an 8-week period following infusions of immunoglobulin (filled symbols) or albumin (open symbols) on days 1 and 2 (n = 9). Results are expressed as a percentage of the respective lower limits of normal.

Evaluator's comment: In this trial, assessment and data analysis require comment. Changes in vital capacity, drinking time and myometry measurements were expressed as a percentage of the lower limit of normal rather than as a percentage of the actual values of individual patients. This avoided a skewing effect that would otherwise occur if the latter were initially very low. The normal lower limits for vital capacity corrected for an individual's sex, height and age were calculated using standard formulae. Also to avoid

making multiple statistical comparisons, the results of myometry from individual muscles were averaged to give an overall value for the muscle strength of each patient.

This would appear to understate the improvement observed. For example if a patient's performance was 25 units and his or her lower normal was 50 units, a performance after treatment of 75 units would rate as a 50% improvement (compared to 50 units) rather than 200%, based on the patient's initial score of 25.

The statistical analysis used the non-parametric Wilcoxon Matched-Pairs Signed Ranks Test (W), and this was considered appropriate since a value for the mean drinking time (albumen) of 170.8% with a SD of 241.9%, and a median of half the mean, indicates Non-Normal distribution of individual values. As these individual values were not provided in the paper, some statistics cannot be confirmed; for example that for drinking time, where the median values for IVIg and placebo were 60.5% and 58.8%, respectively, and yet the p value was 0.017 when comparing the difference (n=9).

In spite of the significant p values for each parameter, the actual improvement as shown in percentages below appears small, and seems doubtful clinical significance. However, for reasons given above, the improvement may have been under stated. In the case of limb strength, treatment with placebo resulted in 101.8% of lower normal strength, when the pre-treatment strength was described as "below the lower limit of normal in 8 patients" but with no values given.

Because of these considerations, the clinical evaluator was unable to interpret the results in this paper.

Case Study Reports

Four reports (Pterlin BL *et al* 2002; Muchnik S *et al.,* 1997; Takano H *et al* 1997; Bird SJ *et al.,* 1992), described one patient each, and were included as support for the one RCT above. Two patients had a small cell lung cancer. No malignancies were detected in the other two patients. Three patients received a dose of 0.4g/kg/day of IVIg for 5 days and one patient received 2g/kg over 2 days. All were reported as showing improvement, which was maintained for 24 months in the patient with non-paraneoplastic (NP) LEMS.

Reports of Analyses of Data from more than One Study

Reference 1. Level X. Maddison P, Newsom-Davis J. Treatment for Lambert-Eaton myasthenic syndrome. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD003279. DOI: 10.1002/14651858.CD003279.pub2.

The review analysed three trials, two with the approved treatment, 3,4-diaminopyridine (3,4 DAP), and one RCT comparing IVIg and placebo (Bain, 1996 – see above). The review concluded that limited evidence from RCTs showed that either 3,4 DAP or IVIg improved muscle strength scores and compound muscle action potential amplitudes in patients with LEMS. However, there are insufficient data available in the published literature to quantify this treatment effect.

Evaluator's comment: The Cochrane review did not consider the problems of the Bain trial but reached the same conclusion that the degree of improvement seen with IVIg could not be estimated from that trial. The review further states that "… it is likely that people with LEMS who have not responded favorably to IVIg have not been reported widely in the literature."

Retrospective Studies

One publication was cited by the sponsor.

Reference 1. Level III-3. Rich MM, Teener JW, Bird SJ; Muscle Nerve 1997; 20:614-615

This paper reviewed 6 patients with LEMS treated with IVIg from 1991 to 1996. The group comprised three men and three women with clinical and electrophysiological findings characteristic of LEMS. All three men had small cell lung carcinoma and one woman had breast carcinoma. No malignancy was noted in the other two women. In all patients the total dose of IVIg administered at each treatment was 2g/kg given over 1-5 days.

Five of the six patients had subjective and objective improvement following their first treatment with IVIg. All five responding patients were re-treated when weakness later worsened and 4 of the 5 responded again to treatment. Of this group, 3 patients continued to receive IVIg as chronic therapy and all responded to repeat treatment with duration of improvement of 4-10 weeks. All patients who responded had improvement in proximal leg strength and functional status.

Consensus documents and International Clinical Guidelines

- The Associations of British Neurologists (2005) concluded "The short term use of IVIg may be appropriate in non-cancer LEMS patients where 3,4-diaminopyridine (3,4-DAP) has not been successful, but there is insufficient evidence to justify long term use".

- The Asia Pacific Advisory Board (2008) in a number of recommendations included the need to treat the underlying tumour in paraneoplastic (P)-LEMS, 3,4-DAP is first line treatment. IVIg or PE produces temporary improvement so each has a role as second line therapy.

- The Australian Health Ministers' Conference stated that IVIg was indicated for short term therapy for severely affected non-paraneoplastic LEMS patients.

- The Biotext review concluded there was possible benefit of IVIg in treating LEMS and that research was needed.

- The American Academy of Allergy, Asthma and Immunology (Orange 2006) concluded that IGIV might be used as an alternative treatment in patients who do not respond to or tolerate other treatments of LEMS.

- The IVIg Hematology and Neurology Expert Panel (Feasby 2007) recommends IVIg as an option for treatment of LEMS, noting that objective evidence of clinical improvement is needed for sustained use.

- The European Federation of Neurological Societies (EFNS) guidelines (Elovaara 2008) recommend IVIg "may be tried in paraneoplastic LEMS …."

Evaluator's conclusion on efficacy in LEMS

Some of the studies discussed above found that IVIg treatment of some patients with non-paraneoplastic LEMS produced a small and transient benefit, but they did not demonstrate convincingly that this effect was clinically significant. It is therefore concluded that efficacy of IVIg treatment in patients with LEMS has not been demonstrated at this time.

Stiff Person Syndrome (SPS)

SPS is a rare disorder and clinical trials of its treatment have been difficult to conduct because of small patient numbers, publication bias and the difficulty in evaluating disease

activity. One randomised controlled study and several open studies and case reports formed the basis of this section of the application.

RCT with placebo control

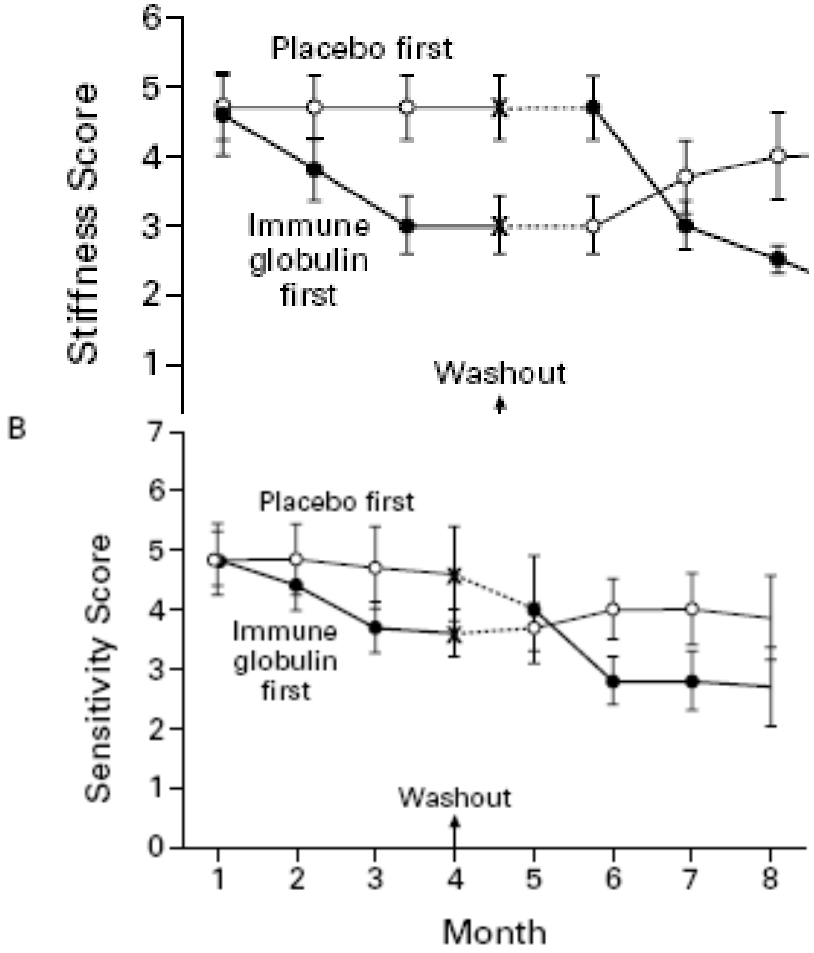
Reference 1. Level II. Dalakas MC, Fujii M, Li M, *et al*. N Eng J Med 2001; 345:1870–1876

Trial Design: Dalakas *et al* assigned 16 patients who had stiff person syndrome and anti-GAD65 antibodies in random order to receive IVIg or placebo for three months. This was followed by a one month washout period and then by three months of therapy with the alternative agent. Efficacy was judged by improvements in scores on the distribution-of-stiffness index and heightened-sensitivity scale from baseline (Month 1) to the second and third month of each treatment phase. Direct and carry-over effects of treatment were compared in the two groups.

Assessment methods and statistical analysis: The statistical analysis of the distribution-of-stiffness index, the heightened sensitivity scale and patients' own assessments was elaborate and appeared thorough, but was beyond this evaluator's expertise.

Results: In the group that received placebo first, the mean distribution-of-stiffness scores did not change significantly during the three months of placebo administration but decreased significantly during the three months of immune globulin therapy ($p=0.01$) (Figure 17). (In contrast, the scores in the group assigned to receive immune globulin first dropped significantly ($p=0.02$) during the three months of immune globulin therapy, remained constant during the washout period and then increased during placebo administration but did not return to base-line values. The differences in scores between placebo and immune globulin were significant at Months 3, 4, 5, 7, and 8. When the overall changes were compared between the two groups, immune globulin therapy was found to have a significant direct treatment effect ($p=0.01$) and first-order carryover effect ($p<0.001$). Changes in scores on the heightened-sensitivity scale were similar to those for stiffness scores but less striking.

Figure 17. Mean distribution of stiffness and sensitivity scores



Mean (±SE) Distribution-of-Stiffness Scores (Panel A) and Heightened-Sensitivity Scores (Panel B), According to Whether Patients Were Assigned to Receive Immune Globulin or Placebo First.

In each scale, higher scores indicate greater impairment. Differences between placebo and immune globulin were significant at months 3, 4, 5, 7, and 8 with respect to stiffness scores (Panel A) and at months 6 and 7 with respect to heightened-sensitivity scores (Panel B). Open symbols indicate placebo administration, and solid symbols immune globulin administration.

Eleven patients who received Ig were able to walk more easily or without assistance, their frequency of falls decreased, and they were able to perform work-related or household tasks. The duration of the beneficial effects of immune globulin varied from six weeks to one year. Anti-GAD65 antibody titers declined after immune globulin therapy but not after placebo administration.

Of 14 patients who were contacted after the results were analysed (the spouses of 2 patients who died were contacted), 12 readily identified the treatment phase on the basis of the unequivocal improvement in their condition during that time. One patient, who received immune globulin first, had a slight improvement that was maintained throughout the study, presumably owing to a sustained carry-over effect, and could not

distinguish one phase from the other. Of the patients who successfully pursued continued immune globulin treatment, seven required infusions every 5 to 12 weeks and one required them every 4 months in order to engage in routine daily activities. Two patients did not need any additional treatment for up to a year. One patient was unable to obtain approval for immune globulin therapy from the medical insurance company. **Authors' conclusion:** IVIg is a well-tolerated and effective, albeit costly, therapy for patients with stiff-person syndrome and anti-GAD65 antibodies.

Evaluator's conclusion: This study from the National Institutes of Health (NIH), USA, was of high quality, and convincingly showed the efficacy of IVIg in this rare condition.

Reports of Uncontrolled Clinical Studies

Four publications (Level IV evidence) were cited.

Reference 1. Level IV. Amato AA, Corman EW, Kissel JT Neurology 1994; 44: 1652–1654

This was an uncontrolled pilot study on three patients who were treated with IVIg 0.4g/kg/day for 5 days followed by two additional infusions of 0.5 to 2,0g/kg at 3 to 4 week intervals. All three patients showed subjective (overall disease rating on a 1 to 10 scale) and objective improvement (time taken to walk 30 feet with or without ambulatory aids). Two patients had been treated previously with other therapies (including plasmapheresis in one patient) without a therapeutic response.

Reference 2. Level IV. Karlson EW, Sudarsky L, Ruderman E, *et al*. Arthritis and Rheumatism 1994; 37: 915–918

This was an open, unblinded study of three patients with active disease and/or disease refractory to treatment with diazepam and/or corticosteroids. All three bedridden patients improved substantially shortly after infusion with IVIg at doses of 0.4g/kg/day for 5 days with repeat cycles, and regained function in terms of both gait and mobility.

Reference 3. Level IV. Gerschlager W, Brown P. Movement Disorders 2002; 17: 590–593

Gerschlager *et al* 2002 investigated whether IVIg improves quality of life (QoL) in SPS. Six patients with the classic form of SPS completed a generic QoL instrument, the SF-36 and a Visual Analogue Scale (VAS) before treatment as well as 2 weeks after completion of a course of IVIg. There was significant improvement in the SF-36 sub-scores for pain, social functioning, general mental health and energy-vitality with treatment. The VAS also improved significantly.

Reference 4. Level IV. Cantiniaux S, Asulay JP, Boucraut J, Poget J, Attarian S Revista de Neurologia (Paris) 2006; 162: 832–839

Cantiniaux *et al* 2006 presented three case reports concerning three women suffering from different forms of SPS, giving the main clinical features, their associations with other diseases and the biological and electrophysiological findings. The first patient presented asymmetric axial muscle rigidity, painful spasms and contractions of the trunk and limbs associated with anti-GAD antibodies. The common form of SPS was diagnosed and the patient was improved by IVIg. The second patient suffered from contractions and spasms localised to the lower limbs. In this patient, anti-GAD antibodies were absent. The Stiff-Leg syndrome was diagnosed and the patient was improved by intrathecal baclofen.

The third patient presented rigidity of limb and trunk muscles associated with signs of encephalitis. This patient only had anti-amphiphysin antibodies. A progressive

encephalomyelitis with rigidity was diagnosed and the patient improved following IVIg together with corticosteroid treatment.

The authors conclude that identifying patients with SPS makes it possible to propose appropriate medical management. There are several forms of the disease, and the severity of the evolution differs in each case. Treatment with GABA-ergic[10] inhibitory drugs, IVIg and corticosteroids improves both the symptomatology and the quality of life of these patients.

Reports of Analyses of Data from More Than One Study

The literature search retrieved no publications related to a meta-analysis across studies. This was expected given that only one randomised controlled study has been reported in the SPS indication.

Case Reports

Six publications reported single cases of SPS treated with IVIg. All were given IVIg mostly at a dose of 2g/kg over 2 to 5 days, repeated sometimes at a lower dose twice weekly (one case) and monthly in the remainder of patients. Improvement in rigidity and spasms was reported for all patients except the four patients who improved on clonazepam. Trials of intermittent high-dose methylprednisolone administration gave relief from rigidity in one patient and permitted reduction of the dose of clonazepam in another. IVIg had no effect in one patient.

Evaluator's comment: The abstract does not say if all four patients received IVIg or only the one referred to. The main difficulty with the case reports presented is publication bias since a negative result in a single case would most likely not be published.

Consensus Documents and International Guidelines

The recommendations from these sources for the use of IVIg to treat stiff person syndrome were as follows:

1. The Association of British Neurologists Guidelines (2005) recommended that where other measures have failed, IVIg may be considered.
2. The Expert Consensus of the Asia Pacific Immunoglobulins in Neurology Advisory Board (2008) was "Considering the disabling progressive course of the stiff person syndrome, IVIg should be offered as the first line treatment. Though periodic infusions would be required in the majority, further studies are needed to determine optimal dosage and duration."
3. The Australian Health Ministers' Conference (2007) Communiqué recommended IVIg for "treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome"
4. The Biotext review (2004) concluded IVIg was of possible benefit and that research was needed.
5. The American Academy of Allergy, Asthma and Immunology (Orange *et al* 2006) found IVIg was "probably beneficial" in Stiff-man syndrome.
6. The Canadian IVIg Hematology and Neurology Expert Panels (Feasby, 2007) recommended IVIg as an option for treatment of stiff person syndrome if GABA-ergic medications fail or for patients who have contraindication to GABA-ergic medications.

[10] The GABA receptors are a class of receptors that respond to the neurotransmitter gamma-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the vertebrate central nervous system.

7. The EFNS task force (Elovarra *et al* 2008) recommended IVIg (2g/kg in 2-5 days) in patients with SPS who responded incompletely to diazepam and/or baclofen and with significant disability requiring a cane or a walker due to truncal stiffness and frequent falls.

Evaluator's conclusion on Efficacy in SPS

The single RCT was of high quality and convincingly showed the efficacy of IVIg in this rare condition.

Evaluator's Conclusions on the Efficacy of IVIg for the Indications Requested

The question addressed here is whether the clinical data have demonstrated the effectiveness of IVIg in treating the neurological conditions requested in the application, rather than possible benefit, or the need for treatment of a particular condition, or the advantages or disadvantages of IVIg when no direct comparison was made. The primary endpoint of the studies has been given more weight than secondary endpoints, clinically significant improvement considered rather than a surrogate measure and the quality of the trial taken into account.

1. Chronic Inflammatory Demyelinating Polyraduculoneuropathy (CIDP)

There is strong evidence of high quality from the large RCT of Hughes (2008) indicating the effectiveness of IVIg. Additional support was provided by the Cochrane Review and the meta-analysis of Ferguson (2005), although each had some problems in data analysis as described. Two other RCTs were supportive and one RCT found no effect of IVIg treatment, but this difference may have resulted from the method of assessment used.

2. Multifocal Motor Neuropathy (MMN)

Although all five RCTs claimed to show efficacy of IVIg, only one (Frederico 2000) was of acceptable quality, and showed an improvement in both muscle strength and disability. The other RCTs had serious methodological problems. The Cochrane Review concluded only muscle strength and not disability was improved. As the Cochrane Review states "In clinical Phase III trials the primary outcome should be disability and not impairment as the primary question to be answered is whether a patient benefits from a particular treatment". The clinical evaluator concluded that overall the published studies have not established that IVIg significantly improves the disability of treated patients, the primary endpoint, as distinct from muscle strength, as tested by a variety of methods.

3. Myasthenia Gravis (MG)

One quality RCT showed efficacy of IVIg over placebo in severe exacerbation of MG. Evidence for efficacy in treating myasthenia crisis and to stabilize patients with MG prior to surgery was weaker but can be accepted. There was insufficient evidence of efficacy in chronic MG.

4. Lambert-Eaton Myasthenia Syndrome (LEMS)

The clinical trial evidence provided in this application was not of sufficient quality to conclude that IVIg has clinically significant efficacy in LEMS.

5. Stiff Person Syndrome (SPS)

The single RCT was of high quality and convincingly showed the efficacy of IVIg in this rare condition.

Safety

Intragam P and Intragam 10 NF are similar biological products and their clinical safety should be similar. The TGA raised concerns with CSL about the cases of infection in the PID trial, and a case of Aseptic Meningitis Syndrome in the ITP trial. TGA requested all information on this issue be presented within three months of the original submission which was done.

The sponsor's Clinical Overview of Safety discussed the safety of different IgG products and the problems of identifying less frequent adverse reactions due to the small numbers of patients treated in most trials. More information has come from postmarketing data. Such reactions may be early onset, during infusion and up to 72 h post infusion; headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, diarrhoea, blood pressure changes, tachycardia, and hypersensitivity reactions have been reported in the literature. Reactions in IgA-deficient subjects (which were excluded from the present studies) depend on the presence of anti-IgA sensitisation and the presence of significant concentrations of IgA in the IVIg product.

Delayed onset adverse reactions after infusion are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia and haemolytic anaemia, skin reactions, and rare events of arthritis. Headache appeared to be one of the most consistently and frequently reported AEs after IVIg use[11]. Significant osmotic renal injury has been reported but appeared to be related to sucrose as a stabilizing excipient[12].

The sponsor's Overview also referred briefly to the theoretical risk of transmission of infectious agents, including Hepatitis C[13, 14], associated with all blood products, and stated that transmission of infectious agents to humans via IVIg products has never been confirmed for immunoglobulins fractionated in Australia, including Intragam P. This safety aspect was discussed in the sponsor's Australian submission.

The safety of Intragam 10 NF was evaluated in two clinical studies. The data from both the PID study (CSLCT-PID-05-22) and the ITP study (CSLCT-ITP-05-21) have been combined in order to meet the minimum requirement of at least 30 patients or 180 infusions (see comments below). The total number of patients from both studies was 38 and the total number of infusions 171, which therefore meets the patient number requirements recommended in the relevant guideline[15] and complements the safety data already available for the parent product, Intragam P. A summary of the safety data provided from the two clinical studies is shown in Table 20 below.

Evaluator's comment: The Guidelines do not specify that the required 30 patients or 180 infusions be in the same trial: "All adverse events in clinical studies should be

[11]Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfusion Med Rev 2003; 17(4):241-51.

[12]Chapman SA, Gilkerson KL, Davin TD, Pritzker MR. Acute renal failure and IVIg: occurs with sucrose stabilised, but not with D-sorbitol stabilised formulation. *Ann Pharmacother* 2004, 38, 2059-2067.

[13] Asia Pacific Immunoglobulins in Immunology Expert Group Inc (APIIEG 2008). Consensus Recommendations for the Use of Immunoglobulin Replacement Therapy in Immune Deficiency. 1st edition. November 2008.

[14] Yap PL. The viral safety of intravenous immune globulin. *Clin Exp Immunol*. 1996; 104 Suppl 1:35-42.

[15] EU Note For Guidance on the Clinical Investigation of Human Normal Immunoglobulin For Intravenous Administration (IVIg) (CPMP/BPWG/388/95, rev. 1, 29 June 2000.

recorded….and reported in accordance with the ICH[16] Guidelines…. Data from at least 30 patients or 180 infusions are required." The requirement is ambiguous in its wording[17]. Several studies on the same disease may be the intended meaning. When different disease processes have different pathogenesis, as with PID and ITP, the AEs observed in each may differ following administration of the same medicinal product and differ from those seen following administration to healthy volunteers. Safety data such as those from Post-Marketing Reports often come from patients with a variety of clinical conditions, depending on the indications of the product. In this application therefore, the combined safety data can be accepted with reservations stated.

A second problem was that Intragam P was administered in the PID trial on Day 1 of Cycle 0, followed by Intragam 10 NF on Day 1 of Cycles 1 to 7. The AEs observed during Cycle 0 were presented in the report as associated with Intragam P, and separate from those seen with Intragam 10 NF in Cycles 1 to 7. The former would include the early onset events (up to 72 h after transfusion, see above). If, however, the products had adverse effects that occurred after 4 weeks (delayed onset AEs), those due to Intragam P would be classed as due to Intragam 10 NF. The results for the frequency of AEs for Intragam 10 NF could therefore be inaccurate.

The safety data were presented in each study report and in the sponsor's Clinical Overview of Safety. The following table (Table 16) summarises the safety studies conducted.

Table 16. Tabular listing of studies providing safety data on Intragam 10 NF.

Study ID: Protocol No.	Country of study location	Design/ control type	Clinical phase, Dates	Study objective/ patient type	No. of patients	No. /Sex Mean age ± SD (range)	Primary endpoints
CSLCT-PID-05-22	Australia	Comparative crossover, multicentre (4 centres)	III May 2007 to July 2008	Comparative pharmacokinetics, safety and efficacy of Intragam P and Intragam 10 NF in patients with PID	19	8 male 11 female 43.9 ± 17.9 years (18.7 - 69.1)	Steady state serum IgG trough levels in PID patients treated with Intragam P and Intragam 10 NF.
CSLCT-ITP-05-21	Australia	Single arm, open label, multicentre (6 centres)	III June 2007 to October 2008	Safety and efficacy in patients with ITP	19	6 male 13 female 43.9 ± 17.2 years (20.4 - 76.2)	Platelet count response (≥ 50 x 10^9/L) from baseline within seven days of the first infusion in ITP patients.

[16] ICH=International Conference on Harmonization.

[17] The sponsor commented that the guideline requires that clinical studies be undertaken in patients with PID and ITP to demonstrate efficacy and that conducting several studies on the same disease to show safety data from at least 30 patients or 180 infusions however, would not meet the guideline requirement for efficacy. The sponsor conducted studies in PID and ITP to demonstrate both safety and efficacy of the new formulation.

Patient demographics and characteristics

These were presented above in relation to each of the studies. A total of 38 patients comprised the safety population and had a mean age of 44 years. 14 of the 38 were male (37%) and the majority were Caucasian.

Evaluator's comment: It would have been more helpful if "white" patients were identified by their ethnicity, since drug metabolism differs in different ethnic groups and can be an issue in drug safety.

Patient exposure in the two trials

CSLCT-PID-05-22: During Cycle 0, the mean prescribed and mean delivered dose of Intragam P was 29.5 g (SD 5.9, median 30.0 g). During Cycles 1-7, the mean prescribed and delivered dose of Intragam 10 NF increased slightly from 29.5 g (SD 5.9, median 30.0 g) at Cycle 1 to 30.4 g (SD 7.2, median 30.0 g) at Cycle 7.

The total number of infusions of Intragam 10 NF for each PID patient was seven and the overall mean prescribed and mean delivered dose was 209.3 g (SD 44.5, median 210.0 g). The overall mean duration of exposure for Intragam 10 NF was 162.8 days (SD 16.1, range 127-176 days).

Two patients had a change in dose. One patient had an increase in dose at the investigator's discretion. Another patient had an increase in dose (the first one following hospital admission for lobar pneumonia and a second one due to the patient's condition.

The mean time taken to infuse Intragam P was 2.52 h (range 1.9-3.5 h), and the mean time taken to infuse Intragam 10 NF was 1.75 h (range 1.1-2.8 h). Thus, the Intragam 10 NF mean infusion time was shorter by 46 minutes.

***CSLCT-ITP-05-21*:** All ITP patients received two infusions of Intragam 10 NF over two days, receiving a total cumulative dose of 2 g/kg body weight. The overall actual median dose delivered was 140g (range 100-200). The mean average duration of infusion was 3.90 (range 2.4-5.8) h. The mean duration of infusion should be interpreted with caution because it was based on all patients' average infusion durations and two patients had unknown infusion stop times on one of their infusion days.

Evaluator's comment: In the PID study, the median dose of the two products was the same (30.0g). However, patient exposure to Intragam 10NF was 7 times the exposure to Intragam P (see below), so a direct comparison of the frequency and nature of AEs for the two products reported is not valid. However, a comparison could be made (as was done in the sponsor's Clinical Overview on Safety) of the frequency and nature of AEs during one cycle of treatment, Cycle 0 for Intragam P, and Cycle 1 for Intragam 10NF. Reference will also be needed to the results of previous studies of the safety of Intragam P, as stated in the approved PI. The seven treatment cycles with Intragam 10 NF should provide reliable safety data to compare with those for Intragam P in the Australian PI.

In the ITP study, Intragam 10NF was administered for a short time (2 days) compared to the previous study (over 7 months). No Intragam P was given and the median dose of Intragam 10NF was 140g compared to 30g in the previous study. A further difference was in the durations of infusion, which had a mean of 1.75 h in the previous study. In the ITP study, the median and mean durations of the infusions were 3.6 h (range 2.4-5.8 h) and 3.9 h (SD 0.87), respectively. The report cautions that the latter mean and median durations should be interpreted with caution because they are based on all patients' average infusion durations (see discussion above). However, in spite of this, the mean and median values are close together and the SD is only 22% of the mean, so the values can be

accepted as showing that the duration of infusion in the ITP study was about twice that in the PID study

Adverse Events

Treatment emergent adverse events (TEAEs) defined as an adverse event (AE) starting on or after the first dose of the product or an AE starting before the first dose of the product but worsening after the first dose.

AEs were analysed in the following categories:

TEAE, severe TEAE, TEAE possibly, probably or definitely related to Intragam 10NF, serious TEAEs considered related, severe TEAEs considered related, and TEAE leading to discontinuation of treatment.

The number and percentage of patients experiencing any TEAE was summarised by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT), as well as by maximum severity. The number of patients experiencing a treatment-related AE (defined as an AE that is possibly, probably or definitely related to Intragam 10NF, in the opinion of the investigators) was also summarised.

The figures for TEAEs in this analysis refer to the number of patients with a TEAE as a percentage of the total number of patients in the safety population (that is, nineteen). The exception is those frequencies which were calculated from the number of a particular TEAE compared to the total number of infusions across both PID and ITP studies.

Analysis of adverse events (both related and unrelated to the product)

Overall Adverse events in the PID and ITP studies

The majority of patients in both PID and ITP studies experienced at least one TEAE (18 of 19 patients (94.7%) in the PID study; and all 19 patients (100%) in the ITP study. Table 17 shows a summary of the adverse events. The table shows that drug related TEAEs were more frequent with Intragam 10 NF in ITP patients compared to PID patients, an effect that may be dose-related or disease-related.

Table 17. Summary of Adverse Events.

Number of patients with at least one of the following:	PID Patients N=19	ITP Patients N=19	Total Patients N=38
TEAE	18 (94.7%)	19 (100%)	37 (97.4%)
Serious TEAE	3 (15.8%)	3 (15.8%)	6 (15.8%)
Severe TEAE	6 (31.6%)	5 (26.3%)	11 (28.9%)
TEAE possibly, probably or definitely related to Intragam 10 NF	9 (47.4%)	15 (78.9%)	24 (63.2%)
Serious TEAEs considered related	0	1 (5.3%)	1 (2.6%)
Severe TEAEs considered related	0	4 (21.1%)	4 (10.5%)
TEAE with Action Taken of Intragam 10 NF discontinuation	0	0	0

Specific Adverse Events and Drug related Adverse Events in the PID and ITP studies

CSLCT-PID-05-22: The frequency of common upper and lower respiratory tract infections were similar (42%, and 37% respectively). The frequency of headaches was 37%. Other TEAEs occurring in more than 20% of subjects in the PID study included gastroenteritis

(26%), sinusitis (26%), lethargy (21%), osteopenia (21%) and cough (21%). A total of 17 PID patients (90%) had at least one infection or infestation during the seven Cycles of Intragam 10 NF.

Drug-related TEAES (MedDRA SOC) are shown by treatment cycle below (Table 19). Two of 19 (11%) patients had three drug related TEAEs (headache, myalgia, pyrexia) from Intragam P in Cycle 0, and 5 of 19 (26%) patients had eight drug related TEAEs (headache, myalgia, nausea, malaise, pain, pyrexia, pruritus, wheezing) from Intragam 10 NF in Cycle 1. The number of TEAEs related to Intragam 10 NF decreased in subsequent cycles.

Evaluator Comments: As noted by the TGA, the frequency of respiratory tract infections is surprisingly high (90% of patients) even for PID patients at risk for such infections. In the trial, the high frequency was not recorded as a drug related event since Ig would not cause the infections. The cause of the high frequency was not considered to be lack of efficacy of the immunoglobulin treatment because efficacy was not evaluated in the PID study. The PID study used Intragam P for one cycle and Intragam 10NF for the next 7 cycles.

Was the high frequency of respiratory infections in the PID study similar to that in the previously evaluated study of Intragam P in PID?

Unfortunately no comparison was possible since the current PI for Intragam P did not provide this information. Nor was any information available as to what extent Intragam P treatment has been found to reduce infections. The study report and the sponsor's Clinical Overview did not deal directly with the high frequency found in the PID trial and they offer no explanation. This is discussed further below.

How did the frequency of the other AEs in the PID trail compare with those reported previously in the PI for Intragam P?

The approved PI for Intragam P does not indicate whether the AEs shown were drug related or not. Overall, the frequency of AEs was 95% in the PID trial compared to 51% (18 of 35) in the PI. The following is a comparison of individual AEs. The first value is from the PI (0 means not mentioned), the second value represents the frequency of AEs reported in the PID trial and the third value corresponds to the frequency of drug related AEs from the trial: headache 23%, 37%, 37%; gastroenteritis 0, 26%, 26% (gastrointestinal (GI) disorders); sinusitis 0%, 26%, 0; lethargy 3%, 21%; 11%; osteopenia 0%, 21%, 0; and cough 0%, 21%,0.

Except for headache, the frequencies of AEs in the PID study are considerably greater than those given for the use of Intragam P alone in PID patients.

CSLCT-ITP-05-21: Headache was by far the most frequent TEAE in the ITP study, occurring in 14 of the 19 patients (74%). The TEAEs which occurred in more than 20% of patients were headache in 14 patients (74%), nausea in nine patients (47%) and vomiting in six patients (32%), three of which were assessed as unrelated to Intragam 10 NF. A total of four patients (21%) had at least one infection or infestation. No patients discontinued treatment with Intragam 10 NF due to a TEAE.

The frequency of the same TEAEs that were classed as drug related included the following: headache (13, 68%), dizziness (2, 11%), lethargy (2, 11%), migraine (2, 11%), nausea (8, 42%), vomiting (3, 16%), fatigue (2, 11%), infusion site pain (2, 11%), arthralgia (3, 16%), musculoskeletal stiffness (2, 11%), and aseptic meningitis (2, 11%).

Comparison of adverse events seen with Intragam P and Intragam 10 NF used to treat patients with PID (similar dosing)

Although the safety of Intragam P treatment was not compared directly to that of Intragam 10NF since Intragam P was administered in Cycle 0 and Intragam 10NF in Cycle 1, a comparison of the AEs occurring in Cycle 0 with those occurring in the Cycle 1 can be made. Drug-related events are shown by Cycle in Table 18 below.

In Cycle 0, two patients (11%) had at least one TEAE related to Intragam P. In Cycle 1, five had a TEAE related to Intragam 10 NF. This number decreased in subsequent cycles. Since the number of TEAEs due to Intragam P in Cycle 0 totalled three, two TEAEs would have occurred in one of the two patients. The total of TEAEs in the five patients (26%) in Cycle 1 for Intragam 10NF was 10 TEAEs.

Table 18. Number of patients with at least one related TEAE to Intragam P (Cycle 0) or Intragam 10NF (Cycles 1-7). Safety population (n=19).

MedDRA System organ class Preferred term	C0 N=19	C1 N=19	C2 N=19	C3 N=19	C4 N=19	C5 N=19	C6 N=19	C7 N=19
Number of patients with at least one TEAE related to Intragam P (cycle 0) or Ig NextGen 10%[a] (cycle 1-7)	2	5	3	3	2	1	3	2
Nervous system disorder	1	2	1	1	1	-	2	1
Headache	1	2	-	1	-	-	2	1
Lethargy	-	-	1	-	1	-	-	-
Musculoskeletal and connective tissue disorders	1	2	1	-	-	-	-	-
Myalgia	1	2	-	-	-	-	-	-
Arthralgia	-	-	1	-	-	-	-	-
Gastrointestinal disorders	-	1	2	1	1	1	1	-
Nausea	-	1	2	1	1	1	1	-
Constipation	-	-	1	-	-	-	-	-
General disorders and administration site conditions	1	2	-	-	-	-	-	-
Malaise	-	1	-	-	-	-	-	-
Pain	-	1	-	-	-	-	-	-
Pyrexia	1	1	-	-	-	-	-	-
Skin and subcutaneous tissue disorders	-	1	-	1	-	-	-	-
Pruritus	-	1	-	1	-	-	-	-
Cardiac disorders	-	-	-	1	-	-	-	-
Ventricular extrasystoles	-	-	-	1	-	-	-	-
Respiratory, thoracic and mediastinal disorders	-	1	-	-	-	-	-	-
Wheezing	-	1	-	-	-	-	-	-
Vascular disorders	-	-	-	-	-	-	-	1
Hot flush	-	-	-	-	-	-	-	1

Abbreviations: C = cycle; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = Treatment-emergent Adverse Event.
[a] *Related is defined as possibly, probably or definitely related to Intragam P (Cycle 0) or Ig NextGen 10% (Cycles 1-7).*
Note: Adverse events only appear within a cycle if they started on or after the dose of Intragam P or Ig NextGen 10% for that cycle.

At similar doses as used for PID treatment, the Intragam 10NF-related AEs were about twice as frequent as those of Intragam P.

Comparison of adverse events in the PID trial and the ITP trial

The results show that the frequency of overall and drug related TEAEs was more frequent in the ITP trial than in the PID trial. This could be due to more disease-specific events in the ITP trial. For drug related events, the difference may be explained by the higher dose of IVIg used in the ITP trial.

Comparison of adverse events seen with Intragam P and Intragam 10NF used to treat patients with ITP (similar dosing)

No direct comparison of the two products was made. The recommended dose of each product for ITP treatment is higher than that for PID, and only Intragam 10NF was used in the ITP study in the current Australian application. Therefore, a comparison can only be made with the figures given in the approved PI for Intragam P for the treatment of ITP. The figures in the PI for selected adverse events were as follows for Intragam P [those from the ITP study with Intragam 10NF are given in square brackets for comparison]: headache 59% [68%]; positive direct Coombs test 29% [x]; hemolysis 24% [x]; nausea 18% [42%]; rigors 18% [0]; fever 12% [5%]; myalgia 6% [11%]; somnolence 6% [0]; abdominal pain 6% [5%]; arthralgia 0 [16%]; vomiting 0 [16%]; injection site reaction 6% [11%]; aseptic meningitis 0 [11%].

Evaluator's comment: The comparison indicates a similar frequency of adverse events with both preparations at the higher dose except for the AE of aseptic meningitis. The frequency of headache shown for Immunoglobulin 10NF did not include the headaches of migraine and aseptic meningitis[18] (see *Balance* below).

Intensity of Adverse Events

The intensity of AEs was graded by the investigator as mild - symptoms easily tolerated and no interference with daily activities; moderate - discomfort enough to cause some interference with daily activities; and severe - incapacitating with inability to work or do usual activity.

PID Study

If AEs that occurred in 20% or more of subjects are considered, the severity of TEAEs are as below.

Severity of AEs (all) in the PID study:

- Upper respiratory infection (42% of patients): mild 7/19 (37%); moderate 1/19 (5%); severe 0.
- Lower respiratory infection (37%): mild 2/19 (11%); moderate 3/19 (16%); severe 2/19 (11%).
- Headaches (37%): mild 3/19 (16%); moderate 4/19(21%); severe 0.
- Gastroenteritis (26%) – mild 0; moderate 2/19 (11%); severe 3/19 (16%).
- Sinusitis (26%): mild 3/19 (16%); moderate 2/19(11%); severe 0.
- Lethargy (21%): mild 2/19 (11%); moderate 1/19(5%); severe 1/19 (5%).
- Osteopenia (21%): mild 4/19 (21%); moderate 0; severe 0.
- Cough (21%): mild 1/19 (5%); moderate 3/19 (16%); severe 0.

[18] The sponsor added the comment that the frequency of headache does include the headaches of migraine and AMS, as one patient reported headache with AMS and the other patient reported headache with migraine.

Comparison of the severity of AEs associated with Intragam10NF in the two studies

The most striking difference was in the severity of the headaches in the two studies. In the ITP study, headaches were of moderate to severe intensity in 5 of 19 patients (26%), not including the headaches of migraine (2) and aseptic meningitis (2). That adds up to 9/19 (47%) in all, compared to 4/19 (21%) which were all moderate in the PID study. In the ITP study the only other severe AE was aseptic meningitis in two patients (discussed later). In the PID study, severe AEs, not necessarily drug related, included lower inspiratory infections in two patients and lethargy in one patient [these AEs occurred in total in 20% or more of patients], and also gastroenteritis in three patients, nausea and abdominal pain (one each), dehydration in one patient and metabolic and nutrition disorder in one patient.

Rates of AEs per infusion

In the PID study, the overall rate of all AEs per infusion possibly, probably or definitely related to Intragam 10NF was 23% (31 AEs, 133 infusions). In ITP patients, the rate of AEs possibly, probably or definitely related to Intragam 10NF per infusion in ITP patients was much higher at 180% (68 AEs, 38 infusions), on average about 8 times more frequent[19].

Deaths and other Serious Adverse Events (SAEs)

No deaths occurred in either study. In the PID study, three SAEs were recorded which included one helminthic infection (severe), one sepsis (moderate severity) and one lobar pneumonia (moderate severity). All SAEs resolved, the latter with sequelae, and were considered unrelated to Intragam 10 NF administration. In the ITP study, three SAEs were also recorded. One was a decrease in platelet count in a patient whose count was 30 x 10^9/L on screening, 148x10^9/L on Day 8 and 18x10^9/L on Day 29. A second patient had aseptic meningitis and is discussed next. The third patient had a severe cerebrovascular accident (CVA). Only the aseptic meningitis was considered related to Intragam 10 NF treatment.

Aseptic Meningitis

The TGA raised concerns with the sponsor about the occurrence of aseptic meningitis associated with Intragam 10 NF in the ITP trial. These cases were reviewed in detail.

Review by the Safety Review Committee (SRC): The SRC comprised three independent members and CSL representatives and was charged with reviewing safety data available in the study database as of 14 March 2008, in particular two reported cases of aseptic meningitis syndrome were reviewed.

The Minutes of a meeting together with the Committee's recommendations were provided in the study report.

Recommendations of the SRC for Precautions to be taken in the Continuing Study: From its review of the cases, the SRC made a number of recommendations while agreeing that the study should continue. These were to assess each patient on Day 2 prior to treatment to ensure continuing treatment was appropriate; to ensure each patient was adequately hydrated prior to treatment; administer paracetamol prior to treatment if headache was present; avoid an infusion rate above 4ml/min if the patient has any symptoms such as headache; and if an event is "believed" to be serious, the patient should be seen by a physician at the time.

[19] The sponsor added the comment that the two clinical studies were at different doses and for different patient populations and as adverse events of IVIg's are related to dose, a direct comparison of adverse events in patients with different doses etc is inappropriate.

Evaluator's comment: These recommendations are appropriate. The clinical evaluator agreed that the events described should be classed as aseptic meningitis, related to the treatment of the patient with Intragam 10NF, making two such cases in this study. It was the evaluator's opinion that the number of SAEs in the study therefore increases from 3 to 4.

Presentation of the Safety Results in the Proposed Product Information

The safety results are presented in the proposed PI as adverse drug reactions (ADRs) (drug related) per infusion, in categories of very common (1 in 10 infusions or more), common (fewer than 1 in 10 but more than 1 in 100) and uncommon (fewer than 1 in 100 but more than 1 in 1000) (see Table 19 below).

Table 19. Causally related adverse drug reactions (ADRs) observed in clinical studies with Intragam 10 NF.

System organ class	Very common (≥ 10%)	Common (≥ 1% and < 10%)
Nervous system disorders	Headache Lethargy Migraine* Dizziness*	
Gastrointestinal disorders	Nausea Vomiting*	Abdominal pain*
General disorders and administration site reactions	Infusion site pain* Pyrexia Pain	
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Musculoskeletal stiffness*	
Infections and infestations	Meningitis aseptic*	
Skin and subcutaneous tissue disorders	Pruritus	Rash*
Vascular disorders	Hot flush	
Immune system disorders		Hypersensitivity*
Respiratory, thoracic and mediastinal disorders		Dyspnoea*

* These adverse events were only observed in the clinical study for the treatment of ITP.

Adverse events (AEs) reported by two or more patients (>10%) in the studies, *irrespective of causal relationship to the product*, are presented in the following table (Table 20).

Table 20. Adverse events occurring in two or more patients (>10%) in at least one of the clinical studies with Intragam 10 NF, irrespective of causality

MedDRA System organ class Preferred term	PID Patients N=19 n (%)	ITP Patients N=19 n (%)
Infections and infestations		
Upper respiratory tract infection	8 (42.1%)	0
Lower respiratory tract infection	7 (36.8%)	0
Gastroenteritis	5 (26.3%)	0
Sinusitis	5 (26.3%)	0
Viral infection	2 (10.5%)	0
Meningitis aseptic	0	2 (10.5%)
Nervous system disorder		
Headache	7 (36.8%)	14 (73.7%)
Lethargy	4 (21.1%)	2 (10.5%)
Dizziness	0	2 (10.5%)
Migraine	0	2 (10.5%)
Gastrointestinal disorders		
Nausea	3 (15.8%)	9 (47.4%)
Vomiting	0	6 (31.6%)
Diarrhoea	3 (15.8%)	1 (5.3%)
Musculoskeletal and connective tissue disorders		
Osteopenia	4 (21.1%)	0
Arthralgia	2 (10.5%)	3 (15.8%)
Myalgia	2 (10.5%)	0
Osteoporosis	2 (10.5%)	0
Musculoskeletal stiffness	0	2 (10.5%)
Pain in extremity	0	2 (10.5%)
General disorders and administration site conditions	0	3 (15.8%)
Fatigue	2 (10.5%)	1 (5.3%)
Pyrexia	0	2 (10.5%)
Infusion site pain	2 (10.5%)	0
Pain		
Respiratory, thoracic and mediastinal disorders		
Cough	4 (21.1%)	0
Injury, poisoning and procedural complications		
Animal bite	0	2 (10.5%)
Contusion	0	2 (10.5%)
Procedural pain	0	2 (10.5%)
Vascular disorders		
Hot flush	3 (15.8%)	0
Eye disorders		
Conjunctivitis	2 (10.5%)	0
Skin and subcutaneous tissue disorders		
Pruritus	2 (10.5%)	0

Clinical Laboratory Evaluations

CSLCT-PID-05-22

Haematology. Three patients had clinically significant changes in their haematology values reported; one with low haemoglobin, haematocrit and lymphocyte count, one with low neutrophils and high lymphocytes and a third with high platelet count, white cell and neutrophil counts. Laboratory-related TEAEs included these three patients.

Biochemistry. One patient with a history of increased gamma glutamyl transpeptidase (GGT) and ALP due to nodular regenerative hyperplasia of the liver had increased values of both these enzymes throughout the study. Two patients had clinically significant biochemistry values after receiving Intragam 10NF, one with hypokalaemia and another with high glucose at Cycles 0 and 1.

Tests of Haemolysis. None of the tests of haemolysis were considered clinically significant and no cases of haemolysis were reported.

CSLCT-ITP-05-21

Haematology. Two patients had haematology values that were considered by the investigators to be clinically significant; one with low neutrophils and platelets and a second with high white cell and neutrophil count. Laboratory-related TEAEs included neutropenia and thrombocytopenia in one patient (mentioned above) and a decrease in platelet count in another. The first patient also had a serious TEAE of aseptic meningitis on Day 2.

Biochemistry. Two patients had biochemistry values that were considered by the investigator to be clinically significant; one with high ALT, AST and LDH, and a second with high glucose on Day 4. Laboratory-related TEAEs included increased transaminases, abnormal blood glucose levels and decreased potassium levels in the above mentioned patients.

Urinalysis. Two patients had urinalysis values that were considered by the investigators to be clinically significant; one with hematuria at screening and another with protein, blood and leukocyte esterase in his urine at screening and again at Day 29.

Tests of haemolysis. Two patients had values that were considered by the investigator to be clinically significant. The first had high LDH (333 U/L) on Day 8. The parameter was within normal range at all other time points, including at screening. This patient had a serious TEAE of aseptic meningitis on Day 2 as well as clinically significant haematology and biochemistry values. The second patient had a positive Direct Coomb's test[20] at Day 8.

Safety Studies in Special Populations

Since Intragam 10 NF is a modified formulation of Intragam P, the aim of the current application was to establish the biosimilarity of the two products. The safety studies on Intragam 10 NF were therefore similar to those for the approved product Intragam P, for which no special populations (pregnancy, lactation, paediatrics and the elderly) were studied. The PI document has been worded accordingly. The possible attenuation of immunoglobulin infusion on the efficacy of live attenuated vaccines from 6 weeks to 3 months after infusion was not demonstrated for the proposed product but extrapolated from the PI for Intragam P, with the note that other drug interactions of Intragam 10 NF had not been established.

[20] The Coombs' test screens for antibodies that may bind to the red blood cells and cause premature red blood cell destruction (hemolysis).

Immunological events

When pooled immunoglobulins of varied types with specific antibodies are administered to patients with PID and to those with altered immunological reactions such as in ITP, safety issues relating to immunological reactions may be expected. However with the products under review, these were surprisingly few.

True hypersensitivity reactions have been reported but not in the present studies. Reactions in IgA-deficient subjects (which depend on the presence of anti-IgA sensitisation) and the presence of significant concentrations of IgA in the IVIg product were not seen in the present studies as IgA-deficient subjects were excluded. The concentration of IgA in the products is also low. Passively transferred antibodies may cause misleading results with some serological tests as has the transmission of antibodies to erythrocyte antigens. Testing for hemolysis showed two clinically significant events in the ITP study but these were on single testing without adverse clinical outcomes. Advice about the need for pre-infusion blood group determination and the need to monitor haemoglobin after therapy are in the proposed PI, as are the above events.

Drug Drug Interactions and Other Interactions

As the study objective was to establish similarity of the proposed product to the approved product Intragam P, no studies were conducted on this subject. No adverse reactions were attributable to drug drug interaction. The proposed PI contains a warning that immunoglobulin infusion may impair the efficacy of live attenuated vaccine, for as long as one year in the case of measles vaccine.

Discontinuation due to Adverse Events

CSLCT-PID-05-22

No patient withdrew from this study due to adverse events.

CSLCT-ITP-05-21

Two of eight withdrawals were due to TEAEs; one patient suffered a cerebrovascular accident (CVA) at Week 3, five days after Intragam 10 NF administration and the investigator considered withdrawal to be in the patient's best interest; the other patient experienced pain following elective eye surgery and was treated with medication that may have interfered with the study measurements. Neither TEAE (which was followed by withdrawal) was assessed as possibly, probably or definitely related to Intragam 10 NF.

Evaluator's comment: One patient experienced drug related aseptic meningitis that was classed as a SAE. The patient recovered in 5 days and was not withdrawn from the study at that time. However, sixteen days later the patient was withdrawn (on Day 23) due to a low platelet count that necessitated treatment for ITP with a prohibited medication. The patient was therefore not regarded as a withdrawal due to an AE.

Post marketing experience

As the product Intragam 10 NF has not yet been registered, no postmarketing data is available.

Safety (Literature based submission)

The sponsor's Safety Overview of the published literature submitted with this LBS presented a thorough summary and a balanced analysis of a large number of publications. The overview concluded with a comparison of AEs in the current PI document for Intragam P with those reported in the reports of IVIg use for neurological indications.

Adverse Events reported in studies presented for use of IVIg in neurological conditions

The rigor of reporting AEs in the many published papers varied widely, from anecdotes to systematic collection in the better quality studies. The AEs reported from RCTS (Level II evidence) have more credibility than those from small uncontrolled studies.

Studies of the use of IVIG to treat CIDP

The Cochrane Review analysed five of the seven RCTs and noted that only three (Mendell 2001, Hughes 2001, Hughes 2008) reported AEs.

The Cochrane Review found that for any AE, there was a significantly increased risk with IVIg treatment (relative risk (RR) 2.61, 95% CI 1.80 to 3.78). Headache, nausea, chills and fever were most frequent with IVIg treatment, occurring in 82 of 167 (49%) IVIg treated patients, compared to 25 of 141 (18%) placebo treated patients. The RR for the development of a SAE was not significantly different between IVIg and placebo treatment (RR 0.82, 95% CI 0.36 to 1.87). SAEs were encountered in 10 of 172 (6%) IVIg treated patients, in 10 of 143 (7%) placebo treated patients, in two of 27 (7%) prednisolone treated patients and in two of 17 (12%) plasma exchange patients. These differences were not statistically significant.

The number of patients needed to experience any AE with IVIg treatment was 3.3 (95% CI 2.56 to 4.76). The authors of the Cochrane review (Eftimov, 2009) noted that mild and transient AEs were reported in 49% of IVIg treated patients and this is far more than has been reported in the 'non-randomised' literature. Headache was the most frequent AE, and because cumulative percentages of all AEs were not given, Eftimov (2009) used the percentage of headache as an estimate of any AE. The report commented that this figure probably underestimated the AEs of IVIg because "RCTs are recognised as not suitable for determining the frequency of AEs". SAEs were encountered in 6% of IVIg treated patients, which is more consistent with previously published figures, but not significantly different from placebo.

Evaluator's comment: The report's comment about RCTs and their lack of suitability to determine the frequency of AEs did not include a reason but may have been because of the short period of observation and the small number of subjects in most of the RCTs submitted for this indication.

Studies of the use of IVIG to treat MMN

The Cochrane database review by Van Schaik 2005 provided the following analysis of AEs reported in RCTs of IVIg in MMN.

Only mild AEs occurred in three of the RCTs which reported AEs. Cutaneous rash and transient fever were seen in two patients out of five treated with IVIg in the study of Azulay 1994. Federico 2000 noted mild AEs in 13 of 16 patients treated with IVIg: headache (5), headache and rash (3), rash alone (2), headache and malaise (1), anorexia, chills and fever (1), transient hypertension (1), and in one patient after placebo treatment: headache, fever and chills. Non-serious AEs were reported in the study of Léger 2001 but were not attributable to individual patients and could not be included in the analysis of this comparison. In this study, patients treated with IVIg complained of headache three times, flushing once, shivering twice, fever once, visual blur twice and

eczema once. After placebo treatment only one patient had cold feet, which was noted as an AE. The pooled relative risk for the development of AEs was 10.33 (95% CI 2.15 to 49.77), indicating a significantly increased risk with IVIg treatment.

Studies of the use of IVIG to treat MG

Evaluator's comment: The Gajdos study (2005) was the largest with 172 patients with MG receiving either 1g/kg (84) or 2g/kg (88) of IVIg. The figures in brackets in the table represent the frequencies of AEs with the lower and higher doses respectively, not a range of values as written. The cumulative incidence of AEs in the 1g/kg group and 2g/kg group were 40.5±5.4% and 46.6±5.3%, respectively, which is a non-significant difference (p=0.39). The differences for most other AEs were also not statistically significant except for headache where the incidence was 13.1% and 22.7%, respectively (p=0.05).

The Cochrane Review found that AEs related to IVIg were observed in all the trials. One hundred and sixty-two AEs were observed among 251 patients treated with IVIg in the five RCTs: fever (11.2%), headaches (10.7%), nausea (5.6%) and allergic reaction (1.2%).

Studies of the use of IVIG to treat LEMS

Evaluator's comment: As the table shows, few AEs were reported in the small number of patients treated with IVIg. The study report lists a number of AEs occurring in 15% of patients with LEMS, taken from a review paper (Weimer and Wong 2009), which cited another review (Ross, 2007) from which the figure was taken. Ross however quoted this figure (from three other papers) for an incidence figure of AEs from all neurological uses of IVIg, not from LEMS alone.

Studies of the use of IVIG to treat SPS

Evaluator's comment: No safety data were given in the publications provided on the use of IVIg in this condition.

Recent review publication of AEs of IVIG in neurological conditions

Evaluator's comment: Although the study report says these recent reviews are more relevant in providing a profile of AEs in neurological conditions than earlier publications, a number of the reviews were based on earlier publications, while others merely provide data on AEs reported for all uses of IVIg, and not just for neurological conditions. Three of the publications were not reviews at all, but case reports, two of which (Vucic 2004 and Wittstock 2003) dealt with the association of thromboembolic events and IVIg administration.

The best quality review was that by two of the staff of the US FDA (Pierce and Jain 2003[21]). Although the review was published earlier than some others, no additional data were presented in the more recent reviews that would have changed the conclusions made by these authors.

Determination of the incidence of AEs

Two opposite views were given in this application. The first was that in the Cochrane Overview (Eftimov *et al*, 2009). Eftimov *et al* stated "RCTs are recognised as not suitable for determining the frequency of AEs". The sponsor's Clinical Expert (quoted in the Overview of Safety) also supports this position, stating "The overall knowledge on the safety of IVIg obtained from clinical studies has been supplemented by post marketing data. From these studies, a significant number of post marketing serious adverse events

[21] Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfusion Med Rev* 2003;17 (4):241-51.

(SAEs) affecting renal, cardiovascular, central nervous, integumentary and haematological organ systems have been reported (Pierce & Jain 2003)." However Pierce and Jain (2003) do not say this, but state the opposite position; "Unfortunately, passively reported post marketing surveillance data are inadequate to estimate the actual incidence of serious and/or significant AEs, much less give even a crude estimate for the overall incidence of AEs occurring after administration of IVIg products. Post marketing surveillance data are never appropriate for calculating incidence data". The text then gives the reasons for their position.

Evaluator's conclusion: Both positions have merit. The nature and incidence of AEs from RCTs are important in defining those AEs that occur within the defined period of surveillance, usually short, and sometimes medium term. Post marketing surveillance is important in defining AEs that occur long term and more rarely, but the incidence of these will be underestimated. A combination of these data provides the best available safety data for the product in question.

Classification of AEs associated with IVIG usage

In summary, AEs associated with IVIg use can be classified as follows (from the sponsor's Clinical Overview).

1. *Early Onset AEs:* The early onset AEs (that is, during infusion and up to 72 h post infusion) reported in the literature include headache, flushing, malaise, chest tightness, fever, chills, myalgia, fatigue, dyspnoea, back pain, nausea, vomiting, diarrhoea, blood pressure changes, tachycardia, and hypersensitivity reactions. Reactions in IgA-deficient subjects depend on the presence of anti-IgA sensitisation and the presence of significant concentrations of IgA in the IVIg product.

2. *Delayed Onset AEs*: Delayed onset AEs (that is, after infusion) are rare and include acute renal failure, thromboembolic events, aseptic meningitis, neutropenia and haemolytic anaemia, skin reactions, and rare events of arthritis. Headache appears to be one of the most consistently and frequently reported AEs after IVIg use. Significant osmotic renal injury has been reported but appears to be related to sucrose as a stabilizing excipient (Chapman *et al*, 2004).

3. *Risks with Blood Products*: In addition to immediate and delayed treatment related AEs, all blood products carry the theoretical risk of transmission of infectious agents, including Hepatitis C. Transmission of infectious agents to humans via IVIg products has never been confirmed for immunoglobulins fractionated in Australia including Intragam P.

Comparisons of AEs in the studies of IVIG use in neurological conditions with those of IVIG use overall, with those in the current PI document for Intragam P

1. *The types of AEs reported*. If the 16 early onset AEs presented in the sponsor's Clinical Overview are considered with the 14 in the approved PI, there are only four in common. Three of the AEs shown in the PI as being of delayed onset are shown as of early onset in the Clinical Overview. Of those listed in the sponsor's Clinical Overview as being of delayed onset, none except haemolytic anaemia are in the similar list in the PI document. Most of the AEs listed from the sponsor's Clinical Overview and from the PI are included in the first 16 AEs in the FDA MEDWATCH list. The clinical evaluator's review of the AEs reported in the published papers submitted agrees in the main with those of the sponsor's Clinical Overview and indicates that the AEs in the current PI require updating. A comparison of the AEs in the table with those individually reported from the neurological studies shows no unexpected type of adverse event.

2. The incidence of AEs reported. Determining the incidence of these events however is difficult. The incidence in the studies differed for each neurological indication. The clinical

evaluator believes that the difference is most likely due to poor design and reporting of safety outcomes in many studies, in which the emphasis has been on the efficacy of IVIg treatment, rather than the frequency of AEs being truly different for each indication. The results indicates that the most reliable safety data came from the studies of CIDP, and a number of the AEs reported in those studies also occurred in the other neurological studies, in which the reporting on safety was less rigorous. An exception was a rare event such as aseptic meningitis. Also the AEs in the CIDP patients were consistent with those reported for IVIg in the treatment of all conditions.

3. *Seriousness, Prevention, Minimisation and Treatment of AEs Associated with IVIG Treatment.* The more serious AEs reported were not more frequent after IVIg treatment of the neurological conditions than after treatment of all indications. The long history of the use of the product has identified risk factors such as the use of sucrose in the formulation, high rates of infusion of IVIg, and for patients - anti-IgA antibodies, increased blood viscosity (and other risk factors for thromboembolic events), migraine, blood groups A or AB, which are included as Precautions in the current Product Information. When they occur, the AEs are usually self limiting, non-fatal and can be manageable.

Summary: The best safety data from the neurological studies was that from the CIDP studies, in which the type and incidence of AEs were headache 32-67%; fever 13-33%; nausea 0-33%; chills 8-30%; hypotension 3-10%; hypertension 0-9%; indigestion 0-20%; asthenia 0-8%; back pain 0-8%; rash 0-7%; dizziness 0-6%. To these should be added flushing 0-10%, fatigue 14%, and aseptic meningitis 0-11%.

Clinical Summary and Conclusions

Two clinical studies were submitted: a pharmacokinetic study, CSLCT-PID-05-22, and an efficacy study CSLCT-ITP-05-21 in patients with ITP treated with Intragam 10 NF. The former used both Intragam P and Intragam 10 NF to demonstrate the biosimilarity between Intragam P and the new formulation Intragam 10 NF, by an analysis of the plasma trough concentrations during treatment, and from determination of the PK parameters of Intragam 10 NF. Published literature was provided to support additional indications: CIDP, MMN, MG, LEMS and SPS.

Pharmacokinetics

The clinical evaluator concluded that the two formulations, Intragam P and Intragam 10 NF are biosimilar as shown by comparable results for trough concentrations of IgG and for the PK parameters of each product.

Clinical Efficacy

The only trial of efficacy was, as required by the CPMP Guidelines, in patients with ITP. In this study (CSLCT-ITP-05-21), Intragam 10 NF alone was used to treat patients with ITP and efficacy was assessed by the response of the platelet count, its magnitude and duration, and by the number and severity of bleeding events.

ITP: The demonstration of efficacy based on the reduction in bleeding events is therefore limited, but in conjunction with the increased platelet count described above, the efficacy of the product can be accepted. An increase in bleeding events was seen on Day 15 compared to Day 8, but it had decreased again by Days 22 and 29. This result is difficult to interpret, due to the small number of events that occurred.

PID: As stated, efficacy was not tested in this trial. However, the high frequency of infections in these patients who were treated with Intragam 10NF (except for Cycle 0) raises the question of how effective Intragam 10NF was in preventing infections, one of the main outcomes of such treatment (ref 8). The clinical evaluator is unaware of any

published data to indicate immunoglobulins can be effective in a disease such as ITP and not in PID. In theory however the disease processes are different in each case and the action of IgG presumable different also. In ITP the action is classed as immunomodulatory and in PID as replacement of missing or defective antibodies. It is possible therefore that the latter effect may have been reduced in Intragam 10NF.

Until a satisfactory explanation is provided for the high frequency of infection seen in patients with PID treated with Intragam 10NF, on the basis of a precautionary principle, it was concluded that the efficacy of the product is in doubt in treating patients with PID[22].

Clinical Safety

Deaths and Withdrawals

No deaths occurred due to AEs in the two trials. No patients withdrew from the PID trial due to AEs and two withdrew from the ITP trial, one with a CVA, and a second because of the need for a medication that may have interfered with the study measurements. Neither was causally related to Intragam 10 NF.

Serious Adverse Events (SAEs)

In the PID trial, the three SAEs included a severe helminthic infection, a moderately severe case of sepsis and a moderately severe case of case of lobar pneumonia. None were treatment related and all patients recovered, the latter with sequelae. In the ITP trial, the three SAEs included a decrease in platelet count and a CVA, neither were considered related to Intragam 10 NF. The third was an episode of aseptic meningitis which was considered as related to Intragam 10 NF. The SAEs all resolved, but the patient with the CVA was left with a mild left partial hemiplegia, speech impairment and expressive aphasia. In addition, that a fourth patient should be considered a SAE with a diagnosis of drug related aseptic meningitis, from which he fully recovered.

Adverse Events in the PID and ITP trials

PID: Except for headache, the frequencies of AEs in the PID study (mainly Intragam 10NF) were considerably greater than those given in the approved PI for the use of Intragam P in PID patients. The high frequency of infectious respiratory AEs in the PID study was not explained and was discussed above as possibly indicating lack of efficacy of Intragam10NF in this condition.

ITP: Headache was by far the most frequent TEAE in the ITP study occurring in fourteen of the 19 patients (74%). The TEAEs, which occurred in more than 20% of patients, were headache in fourteen patients (74%), nausea in nine patients (47%) and vomiting in six patients (32%), three of which were assessed as unrelated to Intragam 10NF. A total of four patients (21%) had at least one infection or infestation. No patients discontinued treatment with Intragam 10NF due to a TEAE.

The frequency of the same TEAEs that were classed as drug related included the following: headache (13, 68%), dizziness (2, 11%), lethargy (2, 11%), migraine (2, 11%), nausea (8, 42%), vomiting (3, 16%), fatigue (2, 11%), infusion site pain (2, 11%), arthralgia (3, 16%), musculoskeletal stiffness (2, 11%) and aseptic meningitis (2, 11%).

[22] The sponsor added the comment that the frequency of infection seen in clinical studies with Intragam 10 NF is consistent with reported literature on patients with PID and this evidence was provided by the sponsor in the response to the Clinical Evaluation Report. This was also deemed a satisfactory explanation by the Delegate in the Delegates Overview (see below).

Comparison of adverse events seen with Intragam P and Intragam 10NF used to treat patients with PID with similar doses

The frequency of TEAEs for Intragam 10NF that were drug related in Cycle 1 in the treatment of PID was about twice that for Intragam P in Cycle 0.

Therefore, at similar doses for PID, the drug related AEs of Intragam 10NF were about twice as frequent as those of Intragam P.

Comparison of adverse events seen with Intragam P and Intragam 10NF used to treat patients with ITP with similar doses

No direct comparison was made of the two products. The dose of each was higher for ITP than for PID and only Intragam 10NF was used in the ITP study in this application. A comparison can only be made therefore with Intragam P from the figures given in the approved PI for Intragam P in the treatment of ITP. The figures in the PI for selected adverse events were as follows for Intragam P [those from the ITP study with Intragam 10NF are given in square brackets for comparison]: headache 59% [[68%]; positive direct Coombs test 29% [x]; haemolysis 24% [x]; nausea 18% [42%]; rigors 18% [0]; fever 12% [5%]; myalgia 6% [11%]; somnolence 6% [0]; abdominal pain 6% [5%]; arthralgia 0 [16%]; vomiting 0 [16%]; injection site reaction 6% [11%]; and aseptic meningitis 0 [11%].

A similar frequency of adverse events was observed with both Intragam P and Intragam 10 NF at the higher dose except for the AE of aseptic meningitis.

High Frequency of Aseptic Meningitis from Intragam 10NF in Patients with ITP

Because of the TGA's concern about this aseptic meningitis and the high frequency (two of nineteen patients), further review is needed. The Clinical Review included a helpful and balanced discussion. For this reason, this section has been included below.

> "AMS [Acute Meningitis Syndrome] is very distressing for the affected patient. Sekul *et al*. (1994[23]) describe the headache in AMS as "intense and pounding" and to be "associated with meningismus, photophobia, vomiting, fever and cerebrospinal fluid pleocytosis." The onset of symptoms occurs 6 to 48 h after the completion of the infusion then subside spontaneously over 3 to 5 days (Pierce and Jain 2003[24]).
>
> AMS has been reported with high IVIg dosage regimens such as 1 to 2 g/kg over three to five days administered to patients for ITP or idiopathic demyelinating polyneuropathy. In a relatively old study Sekul *et al.* (1994) reported an incidence of AMS in 6 of 54 patients with various neuromuscular diseases on a high dose regimen. In addition, the incidence of AMS is reportedly higher in patients with a history of migraine regardless of the type of commercial preparation or the infusion rate (Sekul *et al.* 1994). More recently an incidence as high as this has not been reported. In a prospective study in 2003 of high dose immunoglobulin there was only one case of aseptic meningitis out of 84 treatment courses (Stangel *et al*. 2003). In a prospective study of 24 patients with ITP there were no cases of AMS (Colovic *et al*. 2003[25]). A review of the literature did not reveal any more recent prospective studies.

[23]Sekul E *et al* (1994). Aseptic Meningitis associated with high-dose intravenous immunoglobulin therapy: Frequency and risk factors. *Ann Intern Med* 121: 259-62.

[24] Pierce LR and Jain N (2003). Risks associated with the use of intravenous immunoglobulin. *Transfusion Med Rev* 17(4):241-51.

[25]Colovic M *et al (*2003). Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. *Hematol J*. 4(5):358-62.[26] The sponsor added the comment that the frequency of respiratory infections seen in clinical studies with Intragam 10 NF is consistent

AMS is a much less common side effect of IVIg administration when a lower dose is used. In a postmarketing observational study reported by Debes *et al*. (2007) doses used were 0.18-0.34 g/kg body weight: of 6,357 patients treated with a 5% IVIg (92,958 infusions) only three cases of AMS were reported (Debes *et al*. 2007). There have also been no reports of AMS in patients receiving a standard replacement dose of IVIg for PID (Hamrock 2006) which is consistent with the findings of the Intragam 10NF PID study. Important determinants of the incidence of AMS appear to be the dose of IVIg and the period over which the dose is given (APIIEG 2008; Eibl 2003; Hamrock 2006; Nydegger & Sturzenegger 1999).

Clinically, a history of migraines was present for the first patient diagnosed with AMS which was assessed as serious. In addition, this patient received Intragam 10NF at rapid infusion rate of 6 mL/min, which was higher than that for any other patient on this study. The patient's state of hydration was not reported. These factors, plus the cumulative dose of 2 g/kg are possible contributors to the specific occurrence of AMS in this patient.

Other possible contributing factors which may play a part in the occurrence of both AMS and other TEAEs in patients taking part in this study could theoretically lie in the differences between the parent product, Intragam P and Intragam 10NF .

These differences are: Intragam 10NF is formulated at a higher concentration of IgG, glycine is used instead of maltose as stabiliser and the extra virus removal step in the Intragam 10NF manufacturing process. Both the higher concentration of IgG and the extra virus removal step are unlikely to be a cause of headache or AMS, however cannot be excluded as possible causes. The safety of glycine has been examined in animal studies: safety pharmacology, single dose toxicity, repeat dose toxicity and reproductive and developmental toxicity were conducted in rats. The results from these studies showed no evidence of toxic effects of glycine when administered at a dose of approximately twice that expected in ITP patients given the maximum recommended dose of Intragam 10NF (2 g/kg/day). Glycine is also used in other IVIg products and CSL has considerable experience with this stabiliser in their manufacturing process for immunoglobulin products. Therefore, it seems unlikely that glycine would be the cause of an increased frequency of TEAEs in this study.

A rate of two cases of AMS in 19 study participants (10.5%) is greater than that would be expected in a study of this size with the following caveats. Firstly, one case of AMS was not clinically verified by the investigators. Secondly, the case of AMS that required hospitalisation occurred in a subject with a history of headaches who received an infusion rate that may have been inappropriately high in the clinical circumstances. Thirdly, the true rate of AMS cannot be determined in a study of this size, and there appear to be no data on large numbers of patients treated with currently marketed IVIgs. Therefore, it is difficult to assess the true frequency of AMS associated with IVIg use. Hence, it would be helpful to perform post market follow up in the form of routine Product Safety Update Reports (PSURs) to determine the incidence of AMS when Intragam 10 NF is used in high dose regimens. These routine Pharmacovigilance practices are discussed in detail in Section 1.13 (Risk Management Plan)."

The clinical evaluator felt that there was an unacceptably high frequency of adverse events in the clinical studies. Taking general information on aseptic meningitis associated with IVIg use into account and the data presented in the report of the study of Intragam 10 NF in ITP, it is possible that the high frequency of aseptic meningitis seen was an unusual combination of the circumstances. However, as this is the only study available of this

with reported literature for patients with PID.

product for this indication, the burden of proof of the sponsor is to demonstrate the safety of Intragam 10NF, and not to justify the unacceptably high frequencies of adverse reactions that occur. The clinical evaluator was not prepared to rely on a plan of post-marketing surveillance for the safe use of the product, mainly because the new formulation is a convenience and not a necessity in the treatment of PID and ITP, for which Intragam P provides a safer alternative, based on the data provided. This is reinforced by concerns about the high frequency of respiratory infections seen in treated patients in the PID study[26]. No post marketing data is available on Intragam 10 NF.

Benefit risk assessment

Benefits

No comparison of the efficacy of Intragam 10NF was made with that of Intragam P and none was claimed. The studies did achieve the stated objectives, namely that the two products are biosimilar, and that Intragam 10NF is effective in treating patients with ITP.

The only clinical benefit claimed for patients treated with Intragam 10NF was given in the sponsor's Clinical Overview: because of the higher concentration of immunoglobulin in the new formulation compared to that in Intragam P (10% compared to 6%), the new formulation to be administered in less time, benefiting the patient by shortening time spent in the clinic. The volume of the dose is also smaller than that with Intragam P which may be of benefit to some patients at risk from fluid overload. Neither of these benefits was assessed in either trial, so no evidence of these benefits was presented. Another theoretical benefit is that the manufacture of Intragam 10NF involved three viral removal steps compared to two for Intragam P.

No benefit was claimed for the treating physician from using the new formulation, although the possible patient benefits above would be relevant. Because of the higher concentration of immunoglobulin in Intragam 10NF, a higher dose could be given at a slower rate than with Intragam P, possibly of importance in reducing the chance of headaches or aseptic meningitis.

The new formulation would be of benefit to the sponsor for reasons given in the sponsor's Clinical Overview, namely that the higher concentration fits in with a global trend and the fact that CSL has considerable experience with glycine in their manufacturing process for immunoglobulin products (for example, Normal intramuscular immunoglobulins).

Chronic inflammatory demyelinating polyneuropathy

The evidence presented for the efficacy of IVIg treatment of CIDP was strong, with the dose determined on an individual basis, and administered for a period of 4 to 6 weeks.

Multifocal motor neuropathy

The evidence presented for the efficacy of IVIg treatment of MMN showed only improvement in the secondary outcome, muscle strength, but not in the primary outcome, disability or overall patient performance, and so IVIg cannot be accepted for this indication.

Myasthenia gravis

The evidence presented is convincing in showing that treatment with IVIg was effective in acute exacerbations of MG, but that significant benefit in chronic MG has not been convincingly demonstrated. For efficacy in treating myasthenic crisis and when given prior to surgery to MG patients, the evidence was weaker, but acceptable.

[26] The sponsor added the comment that the frequency of respiratory infections seen in clinical studies with Intragam 10 NF is consistent with reported literature for patients with PID.

Lambert-Eaton myasthenic syndrome

The evidence provided was not of sufficient quality to conclude that IVIg has clinically significant efficacy in LEMS.

Stiff person syndrome

The efficacy of IVIg in this condition was convincingly demonstrated in one high quality RCT that can be accepted, given the severity and rarity of the condition.

Risks

The adverse events reported for Intragam 10NF were similar to those of Intragam P in treating patients with PID in the first clinical trial, consistent with the biosimilarity shown in that study and of relatively low frequency. A different situation occurred in the second trial, with more frequent and more severe adverse events, probably because of the higher dose of Intragam 10NF used, and the higher rate of infusion in some patients. The adverse reactions (drug related events) that did occur with the new formulation were similar to those for Intragam P in treating the same disease at the same dose, except for the severity of the headaches and the unusually high frequency of aseptic meningitis in two of the 19 patients with ITP treated with Intragam 10NF, a rate that was higher than all recent reports of this complication (see above).

In addition, the duration of treatment in the ITP trial was short and the number of patients too small to assess safety. Only two treatments with the new formulation were administered to most patients (11 of 19), and their follow up was only for 28 days. Although any aseptic meningitis resulting from administration of Intragam 10NF would have occurred in this time, other adverse events may not. No other study has used this product.

The high frequency of respiratory infections in patients with PID treated mainly with the new formulation introduced another risk factor; that Intragam 10NF may have reduced or no efficacy compared to Intragam P in treating this condition, as distinct from ITP.

Safety and the Proposed New Indications

The AEs associated with the use of IVIg in the above neurological conditions were significant, sometimes severe and more rarely serious. All have been reported previously as associated with the use of IVIg. Prescribing advice has included risk factors to be aware of in its use, and the steps to be taken to avoid and reduce the frequency of adverse events. Treatment for many AEs is effective, and the AEs themselves non-fatal and self-limiting.

There are no significant safety concerns with the use of IVIg in the manner described provided the product has met the required standards of manufacture, is administered with care with regard to the risk factors involved, and carefully supervised.

Balance

To determine a balance between the benefits and risks of the new formulation, Intragam 10NF recommendation will be based on the patients' interests, since those of physicians and the sponsor are of secondary importance.

The benefits and risks to patients were presented in the previous section. The benefits arise from an undefined shorter time spent in the clinic receiving treatment, and for a smaller (undefined) percentage of patients, receiving a smaller volume of infusion. In the treatment of patients with PID, the risks have been increased by the occurrence of a high frequency of respiratory infections compared to the approved product, Intragam P. Therefore, on balance, the new formulation is not acceptable for the treatment of PID at this time.

In the comparison of Intragam P and Intragam10NF in the treatment of ITP, the benefits of the new formulation are as stated, but the risks were different because of the occurrence of two cases of aseptic meningitis. The frequency of the adverse reaction of headache for Intragam 10NF was 68% and the severity was mild in 8 patients. However the frequency of moderately severe (2) and severe (5) headaches in the 19 patients was 37%. This did not include the headaches of migraine (2) and aseptic meningitis (2), which makes a total of 17 of 19 (90%) patients in all[27], compared to the frequency of 59% of all types of headaches for Intragam P in the treatment of ITP (PI for Intragam P). As well, the incidence of aseptic meningitis (2 cases from 19 patients) was unexpectedly high compared to other IVIg products (including Intragam P), and as reported in recent studies of larger numbers of patients with ITP (no cases in 24 patients with ITP treated with high dose IVIg [Colovic *et al*, 2003[28]]).

The clinical evaluator speculated that if patients were given a choice of possible benefits with Intragam 10NF of an unspecified shorter infusion time and a mostly unnecessary smaller volume of infusion associated with a 37% chance of suffering a potentially moderate or severe headache, and about a 1 in 10 chance of developing very disabling and painful aseptic meningitis, with the need for lumbar puncture and associated investigations, compared to treatment with the registered product, Intragam P, with a lower risk of ASM (none were reported in the currently approved PI for Intragam P in treating ITP), their choice would be for Intragam P. As well, the treating physicians would make the same choice in their patients' interests and this would also avoid concerns about the procedures needed for diagnosis of possible meningitis, especially in patients at risk of bleeding from low platelet concentrations.

Conclusions

It was concluded that the overall balance of benefit and risk is not positive for Intragam 10NF in the treatment of PID and ITP. It is therefore premature to register the new formulation.

The main reason for not recommending Intragam 10NF for registration is the high incidence of two adverse reactions, moderate or severe headache and aseptic meningitis, when compared to the presently available product Intragam P, administered in the same doses at similar rates, and the uncertainty of the cause of a high frequency of respiratory infections in treated PID patients.

Considering the (published references on) efficacy and safety issues, the clinical evaluator recommended that Intragam P be approved for the treatment of

- chronic inflammatory demyelinating polyneuropathy (CIDP);
- myasthenia gravis (MG) in acute exacerbation (myasthenia crisis) and prior to surgery;
- treatment of significant functional impairment in patients with have a verified diagnosis of stiff person syndrome (SPS).

[27] The sponsor added the comment that the total number of patients reporting headache, migraine or AMS, considered to be related to Intragam 10 NF was 14 (73.7%). The evaluators total of 17 patients double counts the two patients who reported headache with AMS and the one patient who reported headache with migraine.

[28] Colovic M, Dimitrijevic M, Sonnenburg C, Suvajdzic N, Donfrid M, Bogdanovic A.Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematol J. 2003;4(5):358-62.

V. Pharmacovigilance Findings

Risk Management Plan (RMP)

A summary of the Important Safety Concerns identified by the sponsor in the submitted RMP are shown in Table 21 below.

Table 21. Summary of Ongoing Safety Concerns

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Headache and migraine	Routine Pharmacovigilance Additional activities: · Active post-marketing surveillance · Review of available safety data at 6, 12 & 24 month milestones following product launch	Routine risk minimisation Additional risk minimisation: Education program. Included in the adverse effects section of the PI.
Aseptic meningitis syndrome	Routine Pharmacovigilance Additional activities: · Active post-marketing surveillance · Review of available safety data at 6, 12 & 24 month milestones following product launch	Routine risk minimisation. Additional risk minimisation: Education program. Included in the precautions and adverse effects sections of the PI.
Thromboembolic events	Routine pharmacovigilance. Additional activities: Evaluation of available safety data at 6, 12 and 24 month milestones.	Routine risk minimisation. Included in the precautions and adverse effects sections of the PI.
Haemolysis	Routine pharmacovigilance. Additional activities: Evaluation of available safety data at 6, 12 and 24 month milestones.	Routine risk minimisation. Included in the precautions and adverse effects sections of the PI.
Hypersensitivity and anaphylactic reactions	Routine pharmacovigilance. Additional activities: Evaluation of available safety data at 6, 12 and 24 month milestones.	Routine risk minimisation. Included in the contraindications, precautions and adverse effects sections of the PI.
Important potential risks		
No potential risks identified		
Important missing information		
No exposure in children and adolescents <18 years of age	Routine pharmacovigilance. Evaluation of available safety data at 6, 12 and 24 month milestones.	Statement in the PI that the use of Intragam® 10 NF in the paediatric population has not been established in clinical studies

The sponsor proposed to apply routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* to all of the above important safety concerns. The sponsor submitted a revised RMP consistent with the guideline in response to the Advisory Committee on Prescription Medicines (ACPM) recommendation (see Risk/Benefit analysis below). The sponsor has also proposed additional pharmacovigilance activities related to aseptic meningitis syndrome (AMS) and this was accepted by the TGA.

Recommendations

Approval for the extension of indications are sought to bring the PI document in closer alignment with Australian guidelines for clinical use of IVIgs. In addition, the corresponding recommended dosages do not exceed the currently approved maximum cumulative dose of 2 g IgG/kg over 2 to 5 days. The sponsor also states that the proposed excipient glycine is not a novel excipient for parenteral use and glycine stabilised 10% IVIg solutions have been well tolerated in human studies. Consequently it would appear that these changes do not adversely affect the risk-benefit or safety profile of these products and the proposed application of routine pharmacovigilance activities for all the important safety concerns and the application of additional pharmacovigilance activities as specified for AMS are acceptable. The proposed application of routine risk minimisation activities to the safety concerns, as specified by the sponsor, is also acceptable.

Nevertheless the sponsor has not provided any information concerning how it will appropriately manage the phase out of the old product (Intragam P – 6% w/v) and introduction of the new product (Intragam 10 NF – 10% w/v). It may be expected that the potential for medication errors will be greatest during the transition phase, given the availability of two Intragam branded product ranges at different strengths in the market. Consequently the sponsor should provide adequate information to the TGA regarding their strategy for minimising such a risk. This information should then be included in the revised RMP (see below).

The sponsor's responses to these issues are discussed below in the *Delegate's Overview*.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

Intragam 10 NF is a sterile preservative free solution for IV infusion containing 10 g per 100 mL of total human plasma protein with purity of at least 98% IgG. The product contains glycine 2.25 g per 100 mL. The company states the product complies with the British Pharmacopeia (BP) and the European Pharmacopeia (Ph Eur) monograph for 'Normal Immunoglobulin (Human) for Intravenous Use'. All validation studies provided with the dossier were performed on the two batches of product used for clinical trials. Manufacture and quality aspects have been satisfactorily resolved. PSC reviewed the application at the February 2010 meeting.

Nonclinical

Nonclinical data consist of an acute toxicity study with a similar 10% IgG formulation (0.25 M glycine), and IV safety, repeat dose and developmental toxicity studies with glycine. The nonclinical studies raise no objections to registration. Animal studies are

limited by immune reactions against human IgG and volume constraints, and demonstration of safety and efficacy will depend mainly on clinical data.

Clinical

The clinical evaluator considers that from the patients' perspective, the benefits of the proposed product are a shorter infusion time and a smaller volume of infusion (of benefit for some patients).

In the treatment of PID, the risks are a high observed frequency of respiratory infections. In the treatment of ITP the risks are the frequency of moderately and severe headache as well as the unexpectedly high incidence of aseptic meningitis syndrome (two cases from 19 patients). Aseptic meningitis syndrome is very distressing for the affected patients and associated with invasive diagnostic procedures in patients at risk of bleeding. The clinical evaluator concludes the overall balance of benefit and risk is not positive for Intragam 10 NF and it would be premature to register the new formulation.

Extension of Indications

The application for extension of indications to provide closer alignment with "established use" of IVIg, in Australia and international clinical guidelines, was supported by a literature-based submission.

Proposed indications for Intragam 10 NF, which are additional to the indications currently approved for Intragam P, are:

Intragam 10 NF is indicated for immunomodulatory therapy in:

- chronic inflammatory demyelinating polyneuropathy (CIDP);
- multifocal motor neuropathy (MMN);
- myasthenia gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and, or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects;
- short term treatment for severely affected non-paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients;
- the treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome (SPS).

The literature based submission complies with TGA Guidelines for Literature Based Submissions that require a product to be marketed for 10 or more years. The literature search strategy and results are acceptable for evaluation. Guidelines, Meta-analyses and Cochrane Collaboration systematic reviews were identified in addition to published studies. For CIDP, there were 7 RCTs submitted. For MMN, four RCT were submitted. For MG, five RCT were submitted. In LEMS and SPS, one RCT for each condition was submitted.

Efficacy in chronic inflammatory demyelinating polyneuropathy

The seven RCTs are summarised in the clinical evaluation report (CER). The first five RCTs compared IVIg with placebo and the last two with plasma exchange and with treatment with oral prednisolone.

Reference 1 (Hughes, 2008) provided convincing evidence of efficacy in improvement of disability score. Two systematic reviews were submitted. The more recent Cochrane Review (Eftimov, 2009) considered 14 studies and accepted the seven RCT listed in the CER. A total of 287 patients were included in the seven studies. The review concluded:

"The evidence from randomised controlled trials shows that IV immunoglobulin improves disability for at least two to six weeks compared with placebo, with a number needed to treat of 3.00. During this period it has similar efficacy to plasma exchange and oral prednisolone. In one large trial, benefit of IVIg persisted for 24 and possibly 48 weeks". The clinical evaluator agreed but commenting that a minimum effective dose was not established.

An earlier systematic review (Fergusson, 2005) evaluated six of the RCTs included in the Cochrane Review. It did not include Hughes, 2008. The earlier systematic review reached similar conclusions to the Cochrane Review. Guidelines and consensus documents relating to treatment of CIDP with IVIg were discussed in the CER.

The CER presents overall conclusions on efficacy of IVIg in CIDP.

The LBS convincingly and consistently supported the efficacy of IVIg in treating CIDP. Little data are available on minimum effective dose.

Efficacy in multifocal motor neuropathy

The four RCTs are summarised in the CER. Frederico 2000 was of acceptable quality and showed an improvement in muscle strength and disability but reported disability was a summed score of strength in 26 muscle groups. The other RCTs had serious methodological problems. The total number of patients studied was small. Disability was assessed by three differing scores. RCT assessed efficacy for short periods in a chronic disease, although long term open studies were also presented. A 2005 Cochrane Review (van Schaik, 2005) identified 16 studies but included only the four identified in the CER where the pooling of studies was considered problematic.

The CER considers that in RCTs initial treatment of MMN with IVIg produced increase in muscle strength in some patients. Those patients in who muscle strength improved required ongoing treatment. Accompanying improvement in disability was not demonstrated to be significantly improved. The clinical evaluator did not support registration of this indication as efficacy has not been convincingly demonstrated.

Efficacy in myasthenia gravis

The five RCT are summarised the CER. Zinman, 2007 was considered a well designed and conducted study which supported efficacy in patients with MG and worsening weakness. A Cochrane Review (Gajdos, 2008) reviewed the five RCT identified above but studies could not be pooled for review. The conclusions were "In severe myasthenia gravis exacerbation, one randomised controlled trial of IVIg versus placebo demonstrated the efficacy of IVIg. Another did not show a significant difference between IVIg and plasma exchange in severe myasthenia gravis exacerbation. Another showed no significant difference in efficacy between 1 g/kg and 2 g/kg of IVIg. A further, yet underpowered, trial showed no significant difference between IVIg and oral methylprednisolone. In chronic myasthenia gravis, there is insufficient evidence from randomised trials to determine whether IVIg is efficacious".

Guidelines and consensus documents relating to treatment of MG with IVIg are discussed in the CER. There is convincing evidence that treatment with IVIg is effective in acute exacerbations of MG, but significant benefit of IVIg treatment in chronic MG has not been convincingly demonstrated. There is some uncertainty about the efficacy of IVIg in myasthenia crisis (as patients in myasthenia crisis were excluded from Zinman, 2007) but these indications can be accepted.

Efficacy in Lambert-Eaton myasthenic syndrome

One RCT is described in the CER. The clinical evaluator and a Cochrane review both concluded that the degree of improvement with IVIg could not be estimated from the Bain, 1996 study. The clinical evaluator concluded that efficacy of IVIg in patients with LEMS has not been convincingly demonstrated.

Efficacy in stiff person syndrome

One RCT is described in the CER followed by description of open studies and case reports. Dalakas, 2001 convincingly demonstrated reduction of stiffness scores in 16 patients with stiff person syndrome and GAD65 antibodies.

Safety in studies for use of IVIg in neurological conditions

The rigor of reporting of AE in published papers varied widely. The best safety data was that from CIDP studies in which the type and incidence of AEs were headache 32-67%; fever 13-33%; nausea 0-33%; chills 8-30%; hypotension 3-10%; hypertension 0-9%; indigestion 0-20%; asthenia 0-8%; back pain 0-8%; rash 0-7% and dizziness 0-6%. To these should be added flushing 0-10%, fatigue 14% and aseptic meningitis 0-11%. The range of neurological condition AE associated with use of IVIg have all previously been associated with this kind of treatment. The extension of indications was not considered to raise significant concerns with the use of IVIg in the manner proposed.

Clinical Evaluator's Conclusion

Considering the efficacy and safety issues described in Section V Clinical Findings, it was recommended that Intragam P be approved for the treatment of

- chronic inflammatory demyelinating polyneuropathy (CIDP);
- myasthenia gravis (MG) in acute exacerbation (myasthenia crisis) and prior to surgery;
- treatment of significant functional impairment in patients with have a verified diagnosis of stiff person syndrome (SPS).

Risk Management Plan

The sponsor has proposed routine pharmacovigilance activities and in addition activities related to aseptic meningitis syndrome (AMS); The sponsor responded to an evaluation of RMP stating they commit to provide further information on the risk of medication errors in the phase-in of the new product. The RMP Evaluator has commented that in light of the clinical review conclusion on the new formulation product the RMP would require further revision before approval for registration which has been completed by the sponsor.

For the extension of indications routine pharmacovigilance is accepted in the initial RMP evaluation.

Risk-Benefit Analysis

Delegate considerations

Taking account of the sponsor response to the clinical evaluation report, it was considered that the four patients (21%) with severe headache (or migraine or AMS) in the Intragam 10 NF ITP study compared to one patient (5.9%) with severe headache (or migraine or AMS) in the Intragam P study provides a signal of risk of severe headache with the new formulation. The numbers of patients with mild and moderate headaches are comparable in the two studies.

The clinical evaluator considered the sponsor's response on AMS supports a classification of one patient as not meeting criteria for a SAE. In other respects, the response does not change the conclusions on AMS presented in clinical evaluation.

The Delegate considered the sponsor response on respiratory infections in the PID studies supports an overall frequency that is not unexpected in the PID population and the patients with SAE of infections having underlying medical history including bronchiectasis, pneumonia or recurrent chest infections. The exploratory analysis of two serious bacterial infections in 8.47 patient years of observation is also considered relevant. Although the guideline (CPMP/BPWG/388/95 rev 1) upon which clinical development of the new formulation product was based on does not require analysis of efficacy in PID, the EMA has now adopted a replacement guideline (EMA/CHMP/BPWP/94033/2007 rev 2) in which assessment of efficacy with a primary endpoint of serious bacterial infections is included for new IVIg products. The new EMA guideline is not yet effective in EU and has not yet been adopted by TGA. The Delegate considered the overall benefits and risk listed in the clinical report which included the risks of a high frequency of respiratory tract infection in the PID study.

In relation to the new formulation, the development of the product has been based on guidance in CPMP/BPWG/388/95 rev1 which states that for "Modified Products" if significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics, safety and efficacy in ITP should be provided. Animal studies for this product are limited and demonstration of safety and efficacy relies on clinical data.

The unexpectedly high incidence of aseptic meningitis syndrome (2 cases from 19 patients) observed in the ITP represents a very major uncertainty concerning the safety of the new formulation. It was not considered that post-approval strategy to monitor safety including monthly signal detection for AMS and AMS questionnaire can address the incidence of aseptic meningitis syndrome associated with the new formulation. Controlled patient exposure and active surveillance for AMS are required in a further clinical study if further product development is undertaken.

In relation the balance of benefit and risk for Intragam 10 NF, the Delegate considered that the benefits of the product are a shorter infusion time and a smaller volume of infusion (of benefit for some patients). In the treatment of ITP the risks are the frequency of severe headache (21%) as well as the unexpectedly high incidence of aseptic meningitis syndrome (2 cases from 19 patients). Aseptic meningitis syndrome is very distressing for the affected patients and associated with invasive diagnostic procedures in patients at risk of bleeding. The Delegate concluded that the overall balance of benefit and risk is not positive for Intragam 10 NF and do not support the registration of Intragam 10 NF.

In relation to the application for extension of indications, the Delegate concurred with the clinical evaluator's conclusions. The relevant guideline (EMA/CHMP/BPWP/94033/2007 rev 2) has recommended that to support other disorders, in particular MMN, CIDP and MG, the applicant should provide confirmatory data with their own, proposed IVIg product.

The recent EMA guideline was not available when the application was developed, and this guideline is not yet effective in EU or adopted by TGA, whereas the TGA literature based submission guideline was adequately addressed in the application. It is also problematic that confirmatory clinical data for this Australian sourced human plasma product would have been generated solely in the Australian population.

Delegate's proposed action

The Delegate proposed to reject the application for Intragam 10 NF, Immunoglobulin – normal (Human), in 10% w/v protein strength, with excipient glycine and additional nanofiltration viral filtration step in the manufacture. The grounds for rejection are the risks of aseptic meningitis syndrome and severe headache, and an unfavourable risk benefit balance of the new formulation compared to the currently registered product Intragam P.

The Delegate proposed to register an extension of indications for Intragam P, for immunomodulatory therapy in:

- chronic inflammatory demyelinating polyneuropathy (CIDP);
- myasthenia gravis (MG) in acute exacerbation (myasthenia crisis) and prior to surgery;
- the treatment of significant functional impairment in patients with a verified diagnosis of stiff person syndrome (SPS).

The Delegate proposed to reject the extension of indications, for immunomodulatory therapy in:

- multifocal motor neuropathy,
- maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects;
- short term treatment for severely affected non-paraneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients

on the grounds that efficacy has not been convincingly demonstrated.

The advice of ACPM is requested.

Response from sponsor

The sponsor submitted a response to the clinical evaluation. Responses to the key issues are summarised below.

Issue 1). Moderate or severe headaches when compared to Intragam P.

The sponsor commented that in the PID study that a comparison of Cycle 0 with the total for Cycles 1-7 is not appropriate. The sponsor considered that comparison of Cycle 0 (steady state with Intragam P) and Cycle 7 (steady state with Intragam 10 NF) or an average per cycle comparison is reasonable. The sponsor provided data from the Intragam P ITP study which showed that the total of all patients with headaches was comparable between the two studies.

Issue 2). Aseptic meningitis syndrome compared to Intragam P.

The sponsor responded by providing additional descriptions of the two AMS patients and proposed a post-approval strategy to monitor safety, which was accepted by the TGA.

Issue 3). Respiratory infections in patients treated for PID .

The sponsor argued that the observed frequency of respiratory tract infections in the PID study was not unexpected for the patient population.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents recommended approval of the submission from CSL Pty Ltd to register normal immunoglobulin (human) (Intragam 10 NF) solution for injection 2.5g / 25 mL, 5 g / 50 mL, 10 g / 100 mL and 20 g/ 200 mL to include the extension of indication:

For immunomodulatory therapy in:

Chronic inflammatory demyelinating polyneuropathy (CIDP);

Multifocal motor neuropathy (MM)

Myasthenia Gravis (MG);

Lambert-Eaton myasthenic syndrome (LEMS) patients; and

Stiff person syndrome (SPS).

In making these recommendations the ACPM noted the concerns by the Delegate over the lack of comprehensive data to support a clear positive risk-benefit profile across all indications and also noted the low incidence of these conditions. However, the ACPM advised that appropriate post market surveillance and education would be appropriate to address the safety concerns in this instance.

The ACPM noted the need for a period of increased scrutiny to ensure reliance on the previous quality and safety studies.

The specific conditions of registration should include:

Development and implementation of a risk management plan to include robust physician education, to the satisfaction of the delegate.

Amendments to the Product Information (PI) and Consumer Medicines Information (CMI) which should be made prior to approval include:

Disclosure of the limitations of the studies particularly for the indications of MNN, LEMS and MG in the Clinical Trials section of the PI;

Information about the speed of administration and the risk of headache in the Dosage and Administration and Precautions sections of the PI;

In the Precaution section, prescribers should be informed and advised on the safety risks associated with the continuum between the more common adverse event of headache compared with aseptic meningitis.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Intragam 10 NF for 2.5g/25mL, 5g/50mL, 10g/10mL and 20g/200mL solution for injection vial, indicated for:

Replacement IgG therapy in:

- *primary immunodeficiency disease (PID)*
- *myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections*
- *congenital or acquired immune deficiency syndrome with recurrent infections.*

Intragam 10 NF is indicated for immunomodulatory therapy in:

- i*mmune thrombocytopenic purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count*
- *allogeneic bone marrow transplantation*
- *Kawasaki disease*
- *Guillain-Barre syndrome (GBS)*
- *chronic inflammatory demyelinating polyneuropathy (CIDP)*
- *multifocal motor neuropathy (MMN)*
- *myasthenia gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects*
- *short-term therapy for severely affected nonparaneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients*
- *treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.*

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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.

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
Reference/Publication #

Product Information

Intragam® 10 NF

Australia

NAME OF THE MEDICINE

Human Normal Immunoglobulin 10% (10 g per 100 mL) solution for intravenous infusion.

DESCRIPTION

Intragam® 10 NF is a sterile solution containing 10 g per 100 mL of total human plasma protein with a purity of at least 98% immunoglobulin G (IgG). At least 90% of the IgG consists of monomers and dimers (typically > 96%). Aggregates are < 3%. The distribution of the IgG subclasses closely resembles that found in normal human plasma (approximate mean ranges: 47.6 - 56.2% IgG_1, 41.5 - 49.5% IgG_2, 1.3 - 1.6 % IgG_3, 0.9 - 1.3% IgG_4).

Intragam 10 NF has a nominal osmolality of 350 mOsmol/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.25. The product contains 2.25 g of glycine in each 100 mL as a stabiliser which is a physiological non-essential amino acid. Intragam 10 NF does not contain a carbohydrate stabiliser (eg. sucrose, maltose) and contains no preservative. Intragam 10 NF contains only trace amounts of IgA, typically < 0.001 mg/mL (10 µg/g). The maximum prekallikrein activator (PKA) levels are less than 28.6 IU/mL (typically ≤ 1.2 IU/mL).

Intragam 10 NF is manufactured from large pools of human plasma (obtained from Australia's voluntary, non remunerated blood donors) by chromatographic fractionation. It is distributed by the Australian Red Cross Blood Service.

The manufacturing process contains three dedicated steps to reduce the possibility of pathogen transmission:

- pasteurisation (heating at 60°C for 10 hours)
- nanofiltration
- incubation at low pH.

PHARMACOLOGY

Pharmacodynamic properties

Intragam 10 NF contains the IgG antibodies present in the donor population. It is prepared from pooled plasma collected from not fewer than 1000 donors. It has an IgG subclass distribution closely proportional to native human plasma.

Intragam 10 NF contains functionally intact IgG with a broad spectrum of antibodies against infectious agents. The IgG molecules have not been chemically or enzymatically modified and the Fc and Fab functions are retained.

Adequate doses of human normal immunoglobulin 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

Intragam 10 NF is immediately and completely bioavailable in the recipient's circulation after intravenous infusion. It is distributed relatively rapidly between plasma and extravascular fluid. After approximately 3 to 5 days, equilibrium is reached between the intra- and extravascular compartments.

The pharmacokinetic parameters for Intragam 10 NF were established in a clinical study (see **CLINICAL TRIALS**) in patients with primary immunodeficiency disease (PID). Nineteen patients (aged 18 to 69 years) participated in the pharmacokinetic assessment (see table below). The median half-life of Intragam 10 NF in patients with PID was 34 days. This half-life may vary from patient to patient. IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

Pharmacokinetic Parameters of Intragam 10 NF in 19 PID patients

Parameter	**Median (Range)**
C_{max} (peak, g/L)	17.4 (11.9 - 21.4)
C_{min} (trough, g/L)	7.8 (4.9 - 11.3)
t½ (days)	34.0 (25.0 - 50.6)

C_{max}, maximum serum IgG concentration.
C_{min}, trough (minimum) serum IgG concentration.
$t_{½}$, elimination half-life of IgG.

CLINICAL TRIALS

Treatment of primary immunodeficiency disease (PID)

Intragam P is CSL's 6% w/v intravenous immunoglobulin (IVIg) and parent product for Intragam 10 NF which differs from Intragam P only in formulation, concentration and additional pathogen removal step as part of the manufacturing process. The efficacy of Intragam 10 NF in PID is confirmed by previous clinical trials conducted with Intragam P, as the biological, pharmacokinetic and safety data showed no significant differences between the two products. Therefore, the following clinical trial information for Intragam P supports the efficacy of Intragam 10 NF in PID patients.

The efficacy of Intragam P was assessed in 35 subjects (age 6-76 years; 21 male) with PID, following the administration of monthly intravenous infusions of Intragam P for six months. The dose of Intragam P was individualised in the range 0.2 to 0.67 g/kg. The mean number of days of hospitalisation over the 6 month period was 2.8 ± 9.0 and the mean number of days absent from work or school due to illness was 5.3 ± 6.4. These figures were similar to historical data relating to other IVIgs.

Treatment of immune thrombocytopenic purpura (ITP)

The efficacy of Intragam 10 NF was established in a multi-centre open-label clinical trial in patients with ITP, which was consistent with the results from the previous Intragam P clinical

trials. A total of 17 subjects aged 20 to 76 years with ITP and a platelet count of < 50 x 10^9/L were treated with 1 g/kg body weight of Intragam 10 NF on each of two consecutive days (a total cumulative dose of 2 g/kg). A rise in platelet count to at least 50 x 10^9/L within 7 days after the first infusion was observed in 15 of the 17 subjects studied. The median time to achieve this platelet response was 4 days after the first infusion, and 71% of the subjects reached this response within four days (i.e. two days after the second infusion). For those subjects who responded, the median duration of platelet count ≥ 50 x 10^9/L was 17 days (range: 7 to > 85 days).

Adverse events encountered during the Intragam 10 NF clinical trials are outlined in **ADVERSE EFFECTS.**

Treatment of neurological disorders
There are several randomised controlled clinical trials demonstrating the efficacy and safety of the use of IVIg in the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and myasthenia gravis (MG). Whilst the evidence for the efficacy of IVIg in the management of CIDP and acute exacerbations of MG is clear, data for the treatment of chronic MG and MMN is not as definitive. Clinical trials for the use of IVIg for MMN showed an increase in muscle strength but no impact on the disability scale.

The efficacy and safety of IVIg in the treatment of patients with stiff person syndrome and Lambert-Eaton myasthenic syndrome (LEMS) has only been demonstrated in a single randomised controlled clinical trial for each condition.

The adverse reactions reported in the literature for IVIg when used in CIDP, MMN, MG, LEMS and stiff person syndrome were consistent with those reported for other indications (see **ADVERSE EFFECTS**).

Intragam 10 NF has similar characteristics to other IVIg products that have been used in the management of CIDP, MMN, MG, LEMS and stiff person syndrome.

INDICATIONS

Intragam 10 NF is indicated for replacement IgG therapy in:

- primary immunodeficiency disease (PID)
- myeloma and chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections
- congenital or acquired immune deficiency syndrome with recurrent infections.

Intragam 10 NF is indicated for immunomodulatory therapy in:

- immune thrombocytopenic purpura (ITP), in adults or children at high risk of bleeding or prior to surgery to correct the platelet count
- allogeneic bone marrow transplantation
- Kawasaki disease
- Ÿ Guillain-Barré syndrome (GBS)
- Ÿ chronic inflammatory demyelinating polyneuropathy (CIDP)
- Ÿ multifocal motor neuropathy (MMN)

- Ÿ myasthenia gravis (MG) in acute exacerbation (myasthenic crisis) or prior to surgery and/or thymectomy; as maintenance therapy for moderate to severe MG when other treatments have been ineffective or caused intolerable side effects
- Ÿ short-term therapy for severely affected nonparaneoplastic Lambert-Eaton myasthenic syndrome (LEMS) patients
- Ÿ treatment of significant functional impairment in patients who have a verified diagnosis of stiff person syndrome.

CONTRAINDICATIONS

Intragam 10 NF is contraindicated in patients who have had a true anaphylactic reaction to human immunoglobulins (especially in patients with antibodies against IgA) or to the excipient glycine.

PRECAUTIONS

The recommended infusion rate of Intragam 10 NF must be closely followed (see **DOSAGE AND ADMINISTRATION**). Certain severe adverse reactions may be related to the rate of infusion. Reactions to IVIg tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. In case of adverse reaction, the rate of administration should be reduced or the infusion stopped to alleviate symptoms. Once a reaction has resolved, based on clinical judgement, the infusion may cautiously be recommenced at a slower rate.

Certain adverse reactions may occur more frequently:

- with a higher infusion rate
- in patients with hypo- or agammaglobulinemia 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.

Potential complications can often be avoided by ensuring that:

- patients are not sensitive to human normal immunoglobulin by first infusing the product slowly (1 mL/min)
- patients are carefully monitored for any symptoms throughout the infusion period
- reducing the infusion rate in patients who are naive to Intragam 10 NF or who are at increased risk of adverse events.

True hypersensitivity reactions to immunoglobulins are rare. They can occur in patients with anti-IgA antibodies, such as those with IgA deficiency. Intragam 10 NF should be used with caution in patients with a known allergy to constituents of the preparation. Intragam 10 NF contains traces of IgA which seldomly may provoke anaphylaxis in IgA deficient patients 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. In case of anaphylactic reaction, the infusion should be stopped immediately.

Cases of renal dysfunction and acute renal failure have been reported in patients receiving IVIg therapy. Risk factors may include: pre-existing renal insufficiency, diabetes mellitus, hypovolemia, concomitant nephrotoxic medicinal products, sepsis, paraproteinaemia, being overweight or aged over 65 years. The majority of cases of renal dysfunction and acute renal failure have been associated with the use of those IVIg products containing sucrose as a stabiliser. There is no sucrose in Intragam 10 NF. The formulation enables the same dose to be delivered within a reduced infusion volume compared to Intragam P. In case of renal impairment, IVIg discontinuation should be considered. The following precautions should be followed for all patients:

- ensuring adequate hydration prior to the initiation of Intragam 10 NF
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant loop diuretics.

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

There is clinical evidence of an association between IVIg administration and thromboembolic events 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 when prescribing and infusing IVIg for patients with pre-existing risk factors for thrombotic events (for example advanced age, a history of hypertension, diabetes, vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, severe hypovolaemia or diseases which increase blood viscosity, or being overweight). Reports have included cases of thrombophlebitis. In case of thromboembolic adverse reaction, the benefit and risk of treatment should be assessed before IVIg therapy is continued.

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

Aseptic meningitis syndrome (AMS) has been reported in association with IVIg treatment. It has been hypothesised that IVIg-associated AMS is the severe presentation of a continuum that begins with the more common adverse event of headache. The AMS syndrome usually begins within several hours to two days following IVIg treatment. It is characterised 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, predominantly from the granulocytic series, and elevated protein levels. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high dose (2 g/kg) IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Patients with a history of AMS, migraine or frequent headaches may be more susceptible to the syndrome. For these patients the following precautions should be taken:

- assessment of hydration status and ensuring adequate hydration prior to commencment of infusion of Intragam 10 NF
- administration of a pre-medication (e.g. paracetamol/paracetamol & codeine) if needed prior to each infusion of Intragam 10 NF (e.g. if headache present)
- administration of the minimum dose at the minimum rate practicable.

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.
In patients with limited or compromised acid-base compensatory mechanisms including neonates, consideration should be given to the effect of the additional acid load that the preparation might present.

It is recommended that the name and batch number of the product are recorded every time the product is administered to a patient.

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

Pathogen safety
This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain pathogen markers. In addition, three dedicated pathogen reduction steps are included in the manufacturing process of Intragam 10 NF to reduce the possibility of pathogen transmission including pasteurisation (heating at 60°C for 10 hours), nanofiltration and incubation at low pH. The current procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses, and the non-enveloped viruses hepatitis A (HAV) and parvovirus B19. In addition, Intragam 10 NF contains specific antibodies directed against parvovirus B19.

Despite these measures, there remains the potential that such products may transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products. Vaccination of patients in receipt of plasma-derived therapeutics should be considered where appropriate.

Carcinogenicity and genotoxicity
No carcinogenicity or genotoxicity studies have been conducted with Intragam 10 NF.

Effects on fertility
No fertility studies have been conducted with Intragam 10 NF.

Use in pregnancy
No animal reproduction studies have been conducted with Intragam 10 NF. Intragam 10 NF should be given to pregnant women only if clearly indicated.

An embryofetal development study in which rats were infused IV with the excipient glycine 945 mg/kg/day on gestation days 6-17 showed no adverse effects.

Use in lactation
No lactation studies have been conducted with Intragam 10 NF. Immunoglobulins are excreted in breast milk and may contribute to the transfer of protective antibodies to the neonate.

Paediatric use
The use of Intragam 10 NF in the paediatric population has not been established in clinical studies.

Use in the elderly
Clinical studies of Intragam 10 NF did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to younger subjects.

Effects on laboratory tests
After immunoglobulin infusion 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 for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

Interactions with other medicines
Immunoglobulin infusion may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella for a period of at least six weeks and up to three months. After infusion of Intragam 10 NF, an interval of three months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to one year. Therefore patients receiving measles vaccine should have their antibody status checked. Additionally, immunoglobulins should not be administered for at least two weeks after these vaccines are given.

The interaction of Intragam 10 NF with other drugs has not been established.

ADVERSE EFFECTS
Two clinical studies with Intragam 10 NF were performed, one study of 19 patients with PID and one study of 19 patients with ITP.

Based on their pharmacological plausibility and as known class effects of IVIg products, adverse reactions reported in the studies are summarised and categorised according to the MedDRA System organ class and frequency in the following table (very common (≥ 10% patients), or common (≥ 1% and < 10% patients)).

Causally related adverse drug reactions (ADRs) observed in clinical studies with Intragam 10 NF.

System organ class	Very common (≥ 10%)	Common (≥ 1% and < 10%)
Nervous system disorders	Headache Lethargy Migraine* Dizziness*	
Gastrointestinal disorders	Nausea Vomiting*	Abdominal pain*
General disorders and administration site reactions	Infusion site pain* Pyrexia Pain	
Musculoskeletal and connective tissue disorders	Arthralgia Myalgia Musculoskeletal stiffness*	
Infections and infestations	Meningitis aseptic*	
Skin and subcutaneous tissue disorders	Pruritus	Rash*
Vascular disorders	Hot flush	
Immune system disorders		Hypersensitivity*
Respiratory, thoracic and mediastinal disorders		Dyspnoea*

* These adverse events were only observed in the clinical study for the treatment of ITP.

Adverse events (AEs) reported by two or more patients (>10%) in the studies, ***irrespective of causal relationship to the product***, are presented in the following table.

Adverse events occurring in two or more patients (>10%) in at least one of the clinical studies with Intragam 10 NF*, irrespective of causality*

MedDRA System organ class **Preferred term**	**PID Patients** **N=19** **n (%)**	**ITP Patients** **N=19** **n (%)**
Infections and infestations		
Upper respiratory tract infection	8 (42.1%)	0
Lower respiratory tract infection	7 (36.8%)	0
Gastroenteritis	5 (26.3%)	0
Sinusitis	5 (26.3%)	0
Viral infection	2 (10.5%)	0
Meningitis aseptic	0	2 (10.5%)
Nervous system disorder		
Headache	7 (36.8%)	14 (73.7%)
Lethargy	4 (21.1%)	2 (10.5%)
Dizziness	0	2 (10.5%)
Migraine	0	2 (10.5%)
Gastrointestinal disorders		
Nausea	3 (15.8%)	9 (47.4%)
Vomiting	0	6 (31.6%)
Diarrhoea	3 (15.8%)	1 (5.3%)
Musculoskeletal and connective tissue disorders		
Osteopenia	4 (21.1%)	0
Arthralgia	2 (10.5%)	3 (15.8%)
Myalgia	2 (10.5%)	0
Osteoporosis	2 (10.5%)	0
Musculoskeletal stiffness	0	2 (10.5%)
Pain in extremity	0	2 (10.5%)
General disorders and administration site conditions	0	3 (15.8%)
Fatigue	2 (10.5%)	1 (5.3%)
Pyrexia	0	2 (10.5%)
Infusion site pain	2 (10.5%)	0
Pain		
Respiratory, thoracic and mediastinal disorders		
Cough	4 (21.1%)	0
Injury, poisoning and procedural complications		
Animal bite	0	2 (10.5%)
Contusion	0	2 (10.5%)
Procedural pain	0	2 (10.5%)
Vascular disorders		
Hot flush	3 (15.8%)	0
Eye disorders		
Conjunctivitis	2 (10.5%)	0
Skin and subcutaneous tissue disorders		
Pruritus	2 (10.5%)	0

General effects associated with intravenous immunoglobulins

True hypersensitivity reactions to IVIg products, such as urticaria, angioedema, bronchospasm, or a sudden drop in blood pressure, have been observed in patients. In isolated cases immunoglobulins may cause anaphylactic shock, even when the patient has shown no known hypersensitivity to previous administration (see **PRECAUTIONS**). Should an anaphylactic reaction to Intragam 10 NF develop, the infusion should be stopped immediately and appropriate treatment initiated.

Adverse reactions (such as chills, headache, fever, vomiting, nausea, arthralgia, changes in blood pressure or moderate lower back pain) or allergic-type reactions (such as flushing, pruritis, lethargy, restlessness, tachycardia, tingling, tissue swelling, wheezing or shortness of breath) may occur occasaionally with the use of IVIg products.

Other general types of reactions that may occur include: malaise, abdominal pain, chest-tightness, facial flushing or pallor, erythema, hot sensations, respiratory difficulty, non-urticarial skin rash, cutaneous vasculitis, or infusion/injection site reactions (such as pain, swelling, erythema, pruritis or rash at the site).

Some patients may develop delayed adverse reactions to IVIg products such as: nausea, vomiting, chest pain, rigors, dizziness, aching legs or arthralgia. These adverse reactions occur after the infusion has stopped but usually within 24 hours.

Cases of reversible AMS (see **PRECAUTIONS**), isolated cases of reversible haemolytic anaemia/haemolysis (see **PRECAUTIONS**), and cases of transient cutaneous reactions, have been reported with IVIg treatment. Neutropenia has been reported in rare instances. Increase in serum creatinine level and/or acute renal failure (see **PRECAUTIONS**) have been observed.

Mild and moderate elevations of serum transaminases (AST, ALT, gamma GT) have been observed in a small number of patients given IVIg. Such changes were transient and not associated with the transmission of hepatitis.

Very rarely, thrombotic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses have been associated with IVIg treatment (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Dosage

The dosage recommendations are summarised in the following table*:

Indication	Dose	Frequency of infusion
Replacement therapy†:		
Primary or secondary immunodeficiency	0.2 to 0.8 g IgG/kg	Every 3 to 4 weeks to achieve IgG serum level of at least 5 g/L
Immunomodulatory therapy‡:		
Immune thrombocytopenic purpura	Maximum cumulative dose of 2 g IgG/kg	Over 2 to 5 days
Allogeneic bone marrow transplantation	May be used as part of the conditioning regime and after transplant Starting dose: 0.5 g/kg (dosage individualised)	Every week (frequency individualised)
Guillain-Barré syndrome (GBS)	0.4 g IgG/kg	Daily for 5 days
Kawasaki disease	1.6 to 2 g IgG/kg or 2 g IgG/kg	In divided doses over 2 to 5 days in association with acetylsalicylic acid As a single dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Induction: 2 g IgG/kg	In divided doses over 2 to 5 days
	Maintenance: 0.4 - 1 g/kg	Every 2 to 6 weeks
Multifocal motor neuropathy (MMN)	Induction: 2 g IgG/kg	In divided doses over 2 to 5 days
	Maintenance: 0.4 - 2 g/kg	Every 2 to 6 weeks
Myasthenia gravis (MG)	Prior to surgery or during myasthenic crisis Induction: 1 - 2 g IgG/kg	In divided doses over 2 to 5 days
	Maintenance: 0.4 - 1 g/kg	Every 4 to 6 weeks
Lambert-Eaton myasthenic syndrome (LEMS)	Induction: 2 g IgG/kg	In divided doses over 2 to 5 days
	Maintenance: 0.4 - 1 g/kg	Every 2 to 6 weeks
Stiff person syndrome	Induction: 2 g IgG/kg	In divided doses over 2 to 5 days
	Maintenance: 1 - 2 g/kg	Every 4 to 6 weeks

* The optimal dose and frequency of administration of Intragam 10 NF must be determined for each patient.

† Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state and the pre-infusion IgG level.

‡ Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

Administration
Intragam 10 NF should be administered through a standard intravenous infusion giving set. Allow the preparation to reach room temperature before use. Intragam 10 NF should be administered separately from intravenous fluids (other than normal saline) or medications the patient might be receiving.

Intragam 10 NF may be infused undiluted or diluted with up to 2 parts of 0.9% saline. The infusion should be commenced at the rate of 1 mL per minute. After 15 minutes the rate may be gradually increased to a maximum of 3 to 4 mL per minute over a further 15 minutes. Infusion rates higher than recommended may increase the incidence of headache. Consideration should be given to reducing the rate of infusion in patients naive to Intragam 10 NF, patients switching from an alternative IVIg, patients who have not received IVIg for a long time, elderly patients and in patients with pre-existing renal disease (see **PRECAUTIONS**).

If Intragam 10 NF appears to be turbid or to contain any sediment, it must not be used. The unopened bottle should be returned to the Australian Red Cross Blood Service. Intragam 10 NF contains no antimicrobial preservative. Therefore it must be used immediately after opening the bottle. Any unused portion should be discarded. Use in one patient on one occasion only. Do not use if the solution has been frozen.

OVERDOSE
Overdose with immunoglobulin products may lead to fluid overload and hyperviscosity, particularly in the elderly and in patients with renal impairment.

PRESENTATION AND STORAGE CONDITIONS
The presentations available for Intragam 10 NF are summarised in the table below:

Amount of IgG (g)	Volume of solution (mL)	Vial size (mL)	AUSTR
2.5	25	50	162486
5	50	50	162487
10	100	100	162488
20	200	250	162489

Intragam 10 NF is packaged in latex free materials. Store at 2°C to 8°C (Refrigerate. Do not freeze). Once removed from refrigeration, store below 25°C and use within 3 months. Protect from light.
Do not use after the expiry date.

NAME AND ADDRESS OF THE SPONSOR
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POISON SCHEDULE OF THE MEDICINE
S4

Distributed by
Australian Red Cross Blood Service

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