Gammaplex
(Human normal immunoglobulin)
PL 08801/0053
UKPAR
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Gammaplex

(Human normal immunoglobulin)

PL 08801/0053

LAY SUMMARY

The MHRA granted Bio Products Laboratory (BPL) a Marketing Authorisation for the medicinal product Gammaplex (PL 08801/0053) on 05th October 2009. This medicine is subject to restricted medical prescription and is indicated for replacement therapy in primary immunodeficiency syndromes such as congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiency, and Wiskott Aldrich syndrome. Gammaplex is also indicated for the treatment of myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and for the treatment of children with congenital AIDS and recurrent infections.

Gammaplex contains the active ingredient human normal immunoglobulin (IgG), which has a broad spectrum of antibodies against various infectious agents. Gammaplex has a distribution of IgG subclasses that closely represents that found in native human plasma. Regular, adequate doses of Gammaplex via intravenous infusion may restore abnormally low IgG levels to the normal range. It is important to ensure that adequate concentrations of total IgG are achieved between infusions, combined with clinical evidence that there is control of the infections to which the patient is susceptible. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Gammaplex has been developed from BPL’s Vigam products, which were licensed in the UK in 1996 (Vigam-S, a lyophilised product, PL 08801/0036) and 1997 (Vigam Liquid, PL 08801/0040). Vigam has in excess of 50% of the UK IVIg market and is marketed in several other countries.

A critical review of the clinical, pharmaceutical and non-clinical data presented to the MHRA demonstrated that Gammaplex is effective as replacement therapy in primary immunodeficiency syndromes and treatment of myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and for the treatment of children with congenital AIDS and recurrent infections. No new safety risks were identified and the safety profile of Gammaplex was considered to be acceptable. It was therefore judged that the benefits of using this product outweigh the risks, hence a Marketing Authorisation has been granted.
Gammaplex
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PL 08801/0053

SCIENTIFIC DISCUSSION

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Based on the review of data on quality, safety and efficacy the UK granted a Marketing Authorisation to BPL for the medicinal product Gammaplex (PL 08801/0053) on 05th October 2009. This product is a restricted prescription only medicine.

This application was submitted as a standard abridged national application under Article 8(3) of Directive 2001/83/EC as amended.

Gammaplex contains human normal immunoglobulin G (IgG) and is indicated for replacement therapy in primary immunodeficiency syndromes such as congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiency, and Wiskott Aldrich syndrome. Gammaplex is also indicated for the treatment of myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and for the treatment of children with congenital AIDS and recurrent infections.

Gammaplex is a ready-prepared solution of a 5% concentration of human normal IgG at pH 4.9 for intravenous administration. The IgG is stabilised with sorbitol and is prepared from human plasma collected from donors in the USA. The collection centres are licensed by FDA.

The active ingredient in Gammaplex is the wide range of naturally occurring human antibodies present in a normal population of healthy donors. The mode of action in primary immunodeficiency disorders (PID) and secondary immunodeficiency is replacement of the antibodies responsible for protecting against infections. Thus the IVIg acts as replacement therapy. The dose and dosage regimen is dependent on the indication.

Gammaplex has been developed from BPL’s Vigam products, which are well-established products licensed in the UK in 1996. Gammaplex was granted a license on 05th October 2009.
QUALITY ASSESSMENT

I. INSPECTION STATUS
A product specific inspection has been performed and is satisfactory.

II. INTRODUCTION
Gammaplex is a human normal intravenous (IV) immunoglobulin (Ig). This product is prepared from plasma from screened donors. Donors are selected from the USA. Gammaplex contains 5g/100mL of human normal immunoglobulin (i.e. 50g/L, of which virtually 100% is IgG).

Bio Products Laboratories (BPL) originally set out to improve the formulation of its existing licensed IVIG product (Vigam Liquid) by removing sucrose and albumin.

Gammaplex is in pharmacotherapeutic group: Immune sera and immunoglobulin’s: immunoglobulin’s, normal human, for intravascular administration, ATC code: J06B A02.

III. DRUG SUBSTANCE

III.1 General Information
The applicant has submitted a satisfactory dossier containing information on the drug substance and drug product. A plasma master file (PMF) was submitted as part of the dossier and gives details on the quality and safety of the human plasma used in Gammaplex covering all aspects of the use of the plasma, from collection to plasma pool.

IV. DRUG PRODUCT

IV.1 Composition of the Drug Product
Gammaplex is supplied as a sterile liquid IgG in 2.5g, 5g and 10g doses. The excipients are sorbitol, glycine, sodium, chloride, acetate and polysorbate 80.

IV.2 Pharmaceutical Development
Gammaplex is a development of the applicant’s licensed product Vigam liquid. The development pharmaceutics and changes to the Vigam process are adequately described.

IV.3 Manufacture

IV.3.1 Batch Formula
All manufacturing takes place at the applicant’s site in Elstree, Hertfordshire, UK. Pyrogen testing is performed by Biological Laboratories Europe, Co. Mayo and sterility testing is performed by Tepnel Scientific Services, West Lothian. The applicant has provided a detailed batch manufacturing formula.

IV.3.2 Description of Manufacturing Process and Process Controls
A satisfactory account of the manufacturing process has been provided and is in accordance with current good manufacturing practice (GMP) requirements. The critical process parameters are generally appropriate and acceptable.

IV.3.3 Process Validation and/or Evaluation
Validation of analytical methods and the Gammaplex process has been presented and appropriately described. Validation of viral removal, virus filtration validation, and transmissible spongiform encephalopathies (TSE) risk assessment are adequate.

IV.4 Control of Excipients

IV.4.1 Specifications
All excipients are tested to pharmacopoeial standards or have in house testing to ensure they conform to the correct quality. Celite has an additional testing which is well described.

IV.5 Control of Drug Product

IV.5.1 Finished Product Specification
The finished product specification has been provided. Satisfactory control tests are applied at the time of release.

IV.5.2 Analytical Procedures
The analytical procedures are adequately described and summarised.

IV.5.3 Validation of Analytical Procedures
Summary validation data have been supplied and are considered adequate.

IV.5.4 Batch Analyses
In process batch analysis data has been provided and is acceptable. Final product data for several batches has also been provided and is acceptable.

IV.5.5 Characterisation of Impurities
The applicant has demonstrated that process related impurities are well controlled.

IV.5.6 Justification of Specification(s)
The applicant has provided the specifications for Gammaplex and has justified the differences to Vigam adequately.

IV.6 Reference Standards or Materials
The reference standards are listed and are satisfactory.

IV.7 Container Closure System
The container and stopper as an entity conform to Ph.Eur. and are acceptable. The facilities and equipment have also been adequately described.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion
The applicant has provided comprehensive data from full scale batches over appropriate time periods. On the basis of these data a shelf-life of 24 months is proposed when stored between 2-25°C. Gammaplex should be stored at temperatures between 2-25°C in its carton.

IV.8.2 Post-approval Stability Protocol and Stability Commitment
The applicant will continue stability studies that have been initiated to completion.

IV.8.3 Stability Data
The shelf-life claim for Gammaplex is 24 months at +2°C to +25°C for 2.5g, 5g and 10g doses of Gammaplex, within its original packaging, stored in the dark. All final batch stability is done after a terminal incubation for 2 weeks at 30-32°C. The applicant has provided a summary of the stability data which is satisfactory.

V. APPENDICES

V.1 Facilities and Equipment
Details of product manufacturing facilities and equipment are acceptable.

V.2 Adventitious Agents Safety Evaluation
TSE clearance studies have been provided and are considered adequate. A summary of virus clearance had also been provided and is satisfactory.

A risk assessment has also been submitted based on the prevalence of appropriate viruses in the donor population and is considered satisfactory.

V.3 Novel Excipients
None.

VI. REGIONAL INFORMATION
Not applicable.

VII ASSESSOR’S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

VII.1 Summary of Product Characteristics
The SPC is satisfactory.

VII.2 Patient Information Leaflet
The PIL is satisfactory.

VII.3 Labels
The labels are acceptable.

VII.4 MAA form
Acceptable.

VIII ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE
The application is approvable.
PRECLINICAL ASSESSMENT

INTRODUCTION

TYPE OF APPLICATION AND ASPECTS ON DEVELOPMENT
This is a national application for Gammaplex made under Directive 2001/83/EC, Article 8(3), known active substance. The active substance is a human normal immunoglobulin. Gammaplex is intended to provide a better formulation than the existing product, Vigam Liquid (UK PL 08801/0040).

Gammaplex is presented as a colourless sterile liquid for intravenous (IV) infusion in a concentration of 5% w/v and supplied in glass infusion bottles with halobytul rubber stoppers with a flip-off aluminium and polypropylene seal. The dose strengths are 2.5g, 5g and 10g. The ATC code is J06B A02, Immune sera and immunoglobulins.

The legal status is ‘subject to medical prescription’.

The drug product is composed of IgG, sorbitol, glycine, sodium chloride, sodium acetate and polysorbate 80.

Gammaplex is intended for replacement therapy in the following indications:
- Primary immunodeficiency syndromes (PID) such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency
  - severe combined immunodeficiency
  - Wiskott Aldrich syndrome
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections

For replacement therapy in primary immunodeficiency syndromes, the dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6g/L. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4-0.8g/kg followed by at least 0.2g/kg every three weeks. The dose required to achieve a trough level of 6g/L is of the order of 0.2-0.8g/kg/month. The dosage interval for steady-state to be reached varies from 2-4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval. Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, replacement therapy in children with AIDS and recurrent infections has a recommended dose of 0.2-0.4g/kg every 3 to 4 weeks.

The applicant notes that repeat-dosing in animals would not be feasible because of immune responses to the human antibodies contained in Gammaplex; testing in the human is considered more appropriate. However, some pharmacodynamic testing of Gammaplex was conducted in rats for cardiovascular effects using already established animal models.

The excipients/process contaminants are all used in other pharmaceuticals and some in the food or cosmetics industries; therefore bibliographical data have been presented for toxicology and pharmacological/pharmacokinetic considerations.
Where data are available on the various non-clinical investigations of either the active ingredient, excipients or residual substances, they are discussed under the relevant sections.

Scientific advice was given by the UK on three occasions. On the third occasion, a question was asked about the non-clinical testing of sorbitol. It was confirmed that literature data would be sufficient.

GLP ASPECTS
The two secondary pharmacodynamics studies were stated to be GLP-compliant and the reports both contain compliance statements. However, the second study was conducted in Canada, which does not have a GLP-monitoring authority; strictly speaking, the study is not fully GLP-compliant. Since the report appears to be of an acceptable standard, and the study appears to have been conducted within the spirit of the GLP regulations, it is not considered necessary to raise a point for clarification in this case.

Most of the remaining data are taken from published studies and the GLP status cannot be ascertained.

PHARMACOLOGY

BRIEF SUMMARY
Human normal immunoglobulin for intravenous administration (IVIg) is a well-defined drug that has monographs in all modern pharmacopoeiae. It contains mainly IgG with the four subclasses IgG1, IgG2, IgG3 and IgG4.

The general properties of IVIg are well-described in relevant textbooks.

PHYSICAL CHEMISTRY
Human immunoglobulin G is a protein with a molecular weight of about 150,000 Dalton, consisting of two heavy chains each having a molecular weight of about 50,000 Dalton and two light chains each having a molecular weight of about 25,000 Dalton. The chains are held together by disulphide bonds. The numbers and positions of the disulphide bonds vary between the four subclasses of IgG.

The amino acid sequences of the N-terminal part of both the heavy and the light chains (the Fab-part of immunoglobulin G) are variable providing the different specificities for different antigens. The constant portion of the heavy chains contains the Fc-fragment important for complement activation and Fc receptor interactions.

PRIMARY PHARMACODYNAMICS
The only studies conducted were antibody profiles carried out on the final product. The applicant reports that ratios of antibody concentrations are above the minima set by the European Pharmacopoeia for both viral and bacterial antibodies.

The presence or absence of an antibody with a particular specificity or activity in Gammaplex is dependent on several factors, in particular the presence or absence of that antibody in the source plasma from which the immunoglobulin was prepared, and the ability of the manufacturing process to concentrate the antibody. The antibody functions and testing methods have been provided and are acceptable.
The European Pharmacopoeial monograph on Human Immunoglobulin for IV use requires that the manufacturing process yield a product that, at an immunoglobulin concentration of 50g/L, contains a concentration of antibodies that is at least three times that in the initial plasma pool. The following results are for three viral and three bacterial antibodies from at least three clinical trial batches of Gammaplex prepared from different plasma start pools. The applicant has provided the antibody concentration and enrichment factors for 6 antibodies.

Some information on the concentrations of functional antibodies is also presented below.

The applicant notes that it would not be appropriate to conduct any studies in animals and that the pharmacodynamics are best investigated in humans.

The applicant's argument is accepted that there is no need for formal non-clinical pharmacodynamic studies. From a non-clinical point of view, the antibody content of Gammaplex appears satisfactory.

SECONDARY PHARMACODYNAMICS

**Gammaplex**

Two haemodynamic studies in the rat on the final product investigating cardiovascular effects are reported.

**Study A, GLP-compliant**

The first was a 3-way comparison of Gammaplex; Vigam Liquid, BPL’s currently licensed IGIV preparation; and Gammaplex vehicle, a control consisting of all ingredients of Gammaplex except the active substance, IgG.

The study was performed in conscious, male rats, 7 or 8 per group, (200 to 250 g body weight). Following surgical cannulation of the carotid artery for the recording of blood pressure, the animals were allowed to recover before infusion of the test product through the jugular vein. The test articles were infused at a rate of 1.5 mL/hour for 3 hours. This was equivalent to a maximum dose of 1,125 mg/kg, unadjusted for body weight. Systolic pressure, diastolic pressure, mean arterial blood pressure and heart rate were monitored during the infusion and for 2 hours after the end of the infusion.

Some statistically significant, hypertensive differences were seen in the Gammaplex group when compared with the vehicle control group after 140 minutes. These differences were thought by the applicant to be related to the rate of infusion in the cannulated jugular vein. Therefore, the study was repeated, but with a different cannulation site and a different infusion rate.

**Study B, GLP-compliant**

The second study was in twenty-four Wistar rats (300 to 370g body weight, 8 per treatment group). The femoral vein and the left carotid were isolated and cannulated. The 2 cannulae were exteriorised at an interscapular site. The animals were left to recover for a minimum of 3 days before infusion with test products (Vigam Liquid, Gammaplex or Gammaplex vehicle). Intravenous infusion of the test products through the femoral vein catheter was performed at a rate of 4.2mL/kg/hour (1.0mL/hour) equivalent to a nominal dose level of 630mg/kg. During the infusion, direct blood pressure and heart rate were monitored and recorded continuously by using the carotid artery catheter. Monitoring started 30 minutes before infusion and continued for 5 hours after the start of infusion.
There were no significant effects related to the test products, Gammaplex and Vigam Liquid, during the infusions or during the 2-hour monitoring period after infusion, compared with the Gammaplex vehicle.

In the first study, there was a mild to moderate rise in blood pressure of the order of 20% occurring during and after an infusion of Gammaplex. This occurred at the infusion rates in excess of 6mL/kg/h. The applicant’s conclusion is that the primary cause of the increase in blood pressure was the osmotic pressure exerted on the vasculature, a load governed by the rate of infusion. The margin between the rate of infusion used clinically and that causing hypertensive responses in rats is relatively small (2- to 7-fold).

In the second study, which used a lower infusion rate, there was no evidence of a hypertensive response.

In clinical use, Gammaplex will be infused at rates between 0.6 and 4.8mL/kg/h. In a clinical study of single doses of 400mg/kg, Gammaplex was infused at rates up to 6 mL/min (i.e. 4.5-5mL/kg/h), and although there were a few cases of hypertension, no adverse cardiovascular effects were seen.

**Polysorbate 80**

From published literature, in a behavioural screen, mice and rats were dosed at between 1g/kg to 10g/kg. Doses of 2g/kg and above produced potentiated pentobarbitone sleeping time, reduced locomotor activity, ptosis, ataxia and changes described as ‘depression’. A dose of 1g/kg was a no observable adverse effect level (NOAEL).

A dose of 1g/kg is approximately 800 times the maximal clinical dose (1.2mg/kg) on an applied dose basis and not scaling for body weight.

**Studies in isolated tissues**

In studies on smooth muscle in rats and guinea pigs, there were no direct effects of polysorbate 80 but there was an antagonistic effect on contractions induced by e.g. acetylcholine at doses as low as 7.5mg/L. One litre of Gammaplex contains 60mg polysorbate, which at a Gammaplex dose of 1g/kg is 1.2mg polysorbate 80/kg or 12mg/L Gammaplex. The dose level in these studies was therefore approximately 1.6 times lower than the maximal dose given to humans. Studies on rabbit smooth muscle tissue found a direct relaxant effect at doses of 250mg/L and above i.e. approximately 20 times the clinical maximal dose (250mg÷12mg).

At doses of 0.005g/kg (i.e. 41 times the clinical maximum dose, 50mg/kg+1.2mg/kg) paired rabbit and guinea pig atria exhibited some inotropic and chronotropic effects.

On partially ligated rabbit ear veins with induced thrombosis, doses of polysorbate 80 of 50mg given IV with urokinase every 30 minutes for 6.5 hours enhanced the lysis of thromboses compared with urokinase on its own with a four hour reduction. As polysorbate is used as a solvent to disrupt virus membranes, this is not unexpected. This equates to a total of 260mg polysorbate 80/kg body weight for a 2.5kg rabbit, far in excess of a 1.2mg/kg dose in humans so no such effect is expected in clinical use.

It is accepted that these findings do not suggest any risks at the likely clinical exposures.

**Cardiovascular studies**

Some studies report that a dose of 50mg polysorbate 80/kg IV in rats gives a rise in blood pressure but in cats and dogs, a fall in blood pressure (BP). Other studies in rats,
rabbits and monkeys, at the same dose, report a fall in blood pressure. In one study, cats given 5mg/kg had a slight rise in BP but at 10mg/kg a fall, whilst in dogs, 20mg/kg resulted in a fall in BP.

At 20mg/kg IV the cardiovascular effects were contradictory between humans and dogs; effects were only mild in patients. These dose levels are at least 4 times the normal clinical dose of polysorbate expected to be seen with Gammaplex infusion. These margins can be calculated by dividing the dose level/kg by the maximum polysorbate dose with Gammaplex of 1.2mg/kg.

It is accepted that these findings do not suggest any risks at the likely clinical exposures.

SAFETY PHARMACOLOGY
No safety pharmacology studies have been conducted (other than those previously described) and no relevant literature references are available. The applicant notes that safety pharmacology has been covered in the clinical studies.

The absence of safety pharmacology studies is acceptable. Human data will be more relevant for a product of this nature.

PHARMACODYNAMIC DRUG INTERACTIONS
No studies have been conducted and no relevant literature references are available. Gammaplex must not be mixed with any other drugs.

The absence of non-clinical drug interaction studies is acceptable.

ASSESSOR’S OVERALL CONCLUSIONS ON PHARMACOLOGY
The absence of formal non-clinical pharmacodynamic studies is acceptable and the antibody profiles described in the Quality module are acceptable from a non-clinical point of view.

The haemodynamic studies in rats with Gammaplex do not raise any safety concerns for the proposed dosing schedule; the literature data that were found for some of the constituents of the formulation also do not suggest that the product will have any harmful secondary effects at the proposed doses.

PHARMACOKINETICS
Pharmacokinetic studies
No studies have been conducted on Gammaplex.

The absence of non-clinical pharmacokinetic studies is acceptable, given that Gammaplex would be expected to induce an immune response in animals.

DISTRIBUTION
There are no data on distribution, although some aspects of distribution of some of the components are included under metabolism and excretion. This is acceptable for an intravenous product of this type and composition.
METABOLISM / EXCRETION

Excipients and contaminants

Sorbitol
Several papers showed similar metabolism of sorbitol in dogs when sorbitol was administered intravenously - an IV dose of 2.5mL/kg bw of a 50% solution showed a marked diuretic effect and approximately 50% of the sorbitol was excreted in the urine. This equates to 1.25g/kg body weight, approximately the same dose from Gammaplex usage. Another paper also confirmed similar metabolism in humans.

Around 50% of sorbitol given to anaesthetised dogs was recovered in the urine. Radiolabelled sorbitol-\textsuperscript{14}C was administered to rats by intraperitoneal injection. 57% sorbitol was excreted as CO\textsubscript{2}, 17% in the urine and 4.2% as liver glycogen.

Tri-n-butyl phosphate
In rats, 66% of an oral dose and 81% of an intraperitoneal dose was excreted in 24 hours. The metabolism of TnBP was extensive as judged from the pattern of metabolites found in the urine following intraperitoneal administration. The two major metabolites present in urine were the hydrolysis products dibutyl phosphate and monobutyl phosphate. Other metabolites present in urine resulted from oxidation of the butyl chains. Very little untransformed TnBP was observed in urine.

Polysorbate 80 (including data on Polysorbate 20)
The applicant has quoted data from the literature on polysorbate 20 administered to rats via the diet. The distribution of three labelled portions of the molecule was studied.

For the laurate portion of the molecule, the approximate distribution of radioactivity 24 hours after oral administration was: expired CO\textsubscript{2} 80%; carcass 12%, unabsorbed from the gastrointestinal tract 4%, urine 2.5% and liver 1.2%. The polyoxyethylene sorbitan moiety left after hydrolysis of the ester is poorly absorbed from the rat’s gastrointestinal tract. With a radioactive carbon label in the polyoxyethylene portion of polysorbate 20, 90% was excreted in the faeces and 8% in the urine. No radioactivity was found in the liver, carcass or expired CO\textsubscript{2}. When the sorbitol moiety of polysorbate 80 was labelled, 91% of the radioactivity was recovered in the faeces, 2.1% in the urine, 1.6% in the carcass and none in expired CO\textsubscript{2}, liver, kidney, spleen, adrenals, brain, gonads or fat.

It is reported that after intravenous injection into rats, the ester bond is hydrolysed by blood lipases. When polysorbate 20 was injected into rats, the labelled lauric acid moiety was metabolised and appeared mostly as expired CO\textsubscript{2}. The polyoxyethylene moiety was not catabolised, since no radioactivity was recovered as CO\textsubscript{2} when this portion of the molecule was labelled. Most of the labelled polyoxyethylene appeared in the urine, but some was present in the faeces, indicating biliary excretion. After intravenous injection of polysorbate 20 into rats in another study, the distribution of the labelled lauric acid moiety was: expired CO\textsubscript{2} 68%, carcass 22%, urine 5%, faeces and gastrointestinal contents 2.5%, and liver 0.7%. The distribution of the labelled polyoxyethylene moiety was: urine 83%, faeces 11%, carcass 2%, liver 0.15% and expired CO\textsubscript{2} nil.

The polysorbate 80 in Gammaplex would be expected to show a similar excretion profile. There were differences between oral and intravenous routes with the hydrolysed polyoxyethylene portion, with a reversal of the ratio in the urine to faeces.
ASSESSOR'S OVERALL CONCLUSIONS ON PHARMACOKINETICS

The absence of non-clinical data on pharmacokinetics is acceptable as these are unlikely to provide any useful information. For this type of product, data generated in humans are more relevant.

The applicant has provided a satisfactory review of the published data on the metabolic fate of the excipients and contaminants.

TOXICOLOGY

Excipients and contaminants

Viral inactivation is effected by the use of a solvent and detergent, tri-n-butyl phosphate (TnBP) and polysorbate 80 respectively. Following the virus inactivation step, the TnBP is removed by the addition of soybean oil, followed by the separation of the aqueous/organic phase. Any residual soybean oil still present in the product is removed in the following CM-Sepharose chromatographic step, which is used to remove polysorbate 80 and any residual TnBP.

The pharmacological and toxicological properties of soybean oil, polysorbate 80 and tri-n-butyl phosphate (TnBP), all of which are in contact with the product at various stages and which might be present in trace amounts in the final product, are reviewed.

Polysorbate 80, TnBP and soybean oil are well established viral inactivation and reagent removal agents for blood products and their residual contamination of final products has occurred in all blood products using this process step. Bibliographical data only are used to establish safety for these three reagents.

Soybean oil

The maximum total recommended dose of Gammaplex for a 70kg person per day would be 70 g (for a dose of 1,000 mg/kg body weight/day). Soybean oil is 98% triglyceride and 2% fatty acids. Therefore the dose of fatty acids is 0.14mg i.e. 70g Gammaplex x 0.5 mg Soybean oil/5g Gammaplex x 2%= 0.14 mg and triglycerides is 6.86mg i.e. 70g Gammaplex x 0.5mg Soybean oil/5g Gammaplex x 98%= 6.86mg per day respectively.

From published literature, there were no toxic effects in dogs dosed with soybean oil at 9g/kg; this is 90,000 times the dose in Gammaplex (0.1mg/kg). At 121g/kg in humans, there were some minor adverse effects. This dose is 120,000 times that in humans receiving Gammaplex.

In a 16-week study in rats, increased myocardial lesions were reported at a dose 120,000 times that in Gammaplex.

There has been a case reported in the literature of a child who initially thrived on an IV 10% soybean emulsion, then suddenly developed a life-threatening intolerance to the infusion called "fat overload syndrome". Effects included hyperlipidaemia, gastrointestinal disturbances, anaemia, thrombocytopenia, prolonged clotting time, elevated prothrombin time and spontaneous bleeding. The dose was 10,000 times that in Gammaplex.

Polysorbate 80

The trace residual levels of polysorbate 80 remaining after CM Sepharose chromatography are supplemented with a further 20mg/L. This is further increased to a
target level of 40mg/L during final formulation, which is designed to remain within the specification limit of 60mg/L. Thus polysorbate is an excipient in Gammaplex.

The recommended dose of Gammaplex for therapy of ITP is 400mg/kg body weight per day for three to five consecutive days, or a single dose of up to 1,000mg/kg body weight. For PID, a dose up to 800mg/kg is given once then at least 200mg/kg every two to four weeks. This would yield a maximal dose of 1200µg polysorbate 80/kg body weight at the high dose of 1,000mg Gammaplex/kg body weight based on analysis of polysorbate 80 content in the final product from several Gammaplex (5g) batches manufactured at BPL showing values below 60µg/mL.

Single-dose studies
In the published literature, acute toxicity was found with mice, rats, rabbits, cats and dog given Polysorbate 80 intraperitoneally and intravenously at dose levels approximately 8000 that of Gammaplex. Given orally, there were no deaths.

A vitamin E drug was found to inhibit the in vitro response of human lymphocytes to phytohaemagglutinin (PHA). This vitamin E drug contains polysorbate 80 at a dose 600 times the dose in Gammaplex. The drug was found to be responsible for fatalities in new-born babies and radio-labelling of polysorbate for intravenous injection into rats was investigated and established a causal effect of polysorbate. Further data in dogs and new born rabbits seem to confirm this assumption.

Repeat-dose studies
A three-month study at 5,000 times the Gammaplex dose levels reported congestive and degenerative changes in heart, liver and kidney concluding that they were related to capillary wall damage. Other studies dosing for 2 years at 2,500 times the dose in Gammaplex usage reported no effects but at doses above 5,000 times diarrhoea and other effects were seen.

Similarly, there were no significant gross or histopathological findings noted when monkeys were fed 1g/day polysorbate 80 in their diets for 17 months. This represents approximately 800 times the dose with Gammaplex use.

One reference reported that polysorbate 80 administered by intravenous injection to rabbits had no effects at 160 or 400 times the dose in Gammaplex, except for an apparent intravascular haemolysis at 400 times the Gammaplex dose level, which disappeared with repeated injections, and a transitory increase in blood cholesterol and phospholipid that returned to normal within 24 to 48 hours unless the injections were repeated. Doses of approximately 600 times that with Gammaplex use resulted in the death of the animals. Another study reported IV dosing at levels of 16,000 times that in Gammaplex use for 40-65 days resulting in 6/10 dying between 40 and 61 days of treatment. Histological examination showed greatly enlarged spleens with tremendous foam cell accumulation in the reticuloendothelial system and marked lipid infiltration of the renal tubular epithelium.

One reference describes polysorbate 80 prescriptions to more than 100 patients of both sexes of approximately equal distribution, and various ages ranging from 5 to 72 years. Oral doses of 4.5 to 6.0g were taken daily for various periods up to 4 years. Results indicated no adverse effects after long-term consumption, and polysorbate 80 was judged to be harmless for human consumption in amounts up to 6.0g per day (70 times that with Gammaplex use, based on 70kg man receiving 84mg polysorbate in Gammaplex). This same paper described dosing to patients with a variety of illnesses
with doses up to 160 times the Gammaplex levels. Apart from increased bowel activity, no other effects were observed.

The FAO/WHO Expert Committee on Food Additives has established a maximum acceptable daily oral intake of polysorbates of 25mg/kg body weight/day; this represents an intake of 20 times that with Gammaplex but orally.

**Tri-n-butyl phosphate**

The recommended doses would yield a dose of 20µg TnBP/kg body weight at the high dose of 1,000mg Gammaplex/kg body weight.

In rats, haematuria was reported at doses in the range of 50 mg/kg body weight to 750 mg/kg body weight. At 750mg/kg body weight, male rats exhibited excessive salivation (oral). This dose is 2,500 times that to be delivered in Gammaplex.

**Single-dose studies**

In mice and rats, intraperitoneal, oral and subcutaneous LD$_{50}$ values were reported to be between 45,000 and 765,000 times TnBP levels likely in humans receiving Gammaplex. In rats, some respiratory difficulty, loss of co-ordination and mild anaesthesia occurred at a dose 4,000 times that likely in clinical use.

In hens, the oral LD$_{50}$ was 1,500mg/kg (75,000 times the dose with Gammaplex). Also after a single dose, there was no inhibition (>70%) of brain neurotoxin esterase. TnBP was also studied for delayed neurotoxicity in 18-month-old leghorn hens. A single oral dose of 1.5g TnBP/kg body weight (the oral LD$_{50}$), in gelatine capsules, was given on day 0, and for those hens that survived, again on day 21 with atropine sulphate protection. 6 hens died following administration of TnBP, but of those that survived the 42-day experiment, none developed delayed neurotoxicity. Another group of hens were given 2 dermal doses of TnBP (1.5g/kg body weight) on days 0 and 21 with atropine sulphate. Those treated with dermal doses also survived and did not develop any signs of toxicity.

**Repeat-dose studies**

Very high doses (1,000,000 times the human dose from Gammaplex) in mice resulted in signs of neurotoxicity and death within 10 days.

Several oral studies are reported on mice for periods of 4 weeks or 3 months at varying doses from 500 to 1,000,000 times the dose with Gammaplex use. There were deaths at high doses. Weight loss was reported at all doses and those mice autopsied at higher doses had a black tarry substance throughout the alimentary tract. There was also liver enlargement and some papers reported increases in blood urea nitrogen (BUN) values and kidney tubular degeneration. One paper reported dose-dependent urinary bladder epithelial hyperplasia at the high dose levels.

In rats dosed orally, similar findings occurred. Nerve damage was also reported plus degenerative findings in the testes, increased spleen weights and other changes in serum concentrations of lipids and potassium.

In subchronic oral toxicity studies conducted in Sprague Dawley rats given TnBP in diets at concentrations of 500-250,000 times the Gammaplex level, no deaths occurred, and there were no treatment-related ocular effects. Signs of toxicity included abdomino-genital staining and reduced body weights, and increased activated partial thromboplastin times, all at high doses over 50,000 times the Gammaplex concentration.
Also, increased liver/body weights and liver/brain ratios were achieved at high doses. There was also generalised transitional-cell hyperplasia in urinary bladders at high doses of TnBP.

Neurotoxicity studies were carried out in rats orally at dose levels of 1,625-16,250 times that of Gammaplex for 13 weeks. Physical signs detected were: salivation, muzzle staining, urogenital/ventral surface staining, and alopecia, all at intermediate to high doses. Body weight gain and food consumption were reduced significantly in the high-dose animals. However, a variety of neurological tests did not reveal any neurotoxic effects caused by TnBP.

A skin sensitisation study was reported on guinea pigs. Doses of 1,500 times the Gammaplex levels did not produce any sensitising reactions.

**Sodium chloride**

Sodium chloride will be dosed clinically at 1mmol/kg (0.058g/kg)

Gammaplex contains sodium chloride at a concentration of ~40mmol/L, below the normal level in plasma which is typically 140mmol/L. There is therefore no risk of excessive levels of sodium chloride during infusion of Gammaplex and low levels are not considered to represent any risk to the patient providing tonicity (i.e. osmolality) is maintained. In general, both hypotonic and hypertonic solutions with osmolality ranging from 140 to 1710mOsmol/kg can be administered intravenously without causing haemolysis and a minimum level of 240 mOsmol/kg is specified by the pharmacopoeia. Sodium and chloride ions are freely permeable across the vascular endothelium and will be rapidly distributed between the interstitial and vascular spaces. Osmolality is maintained with contributions from the other Gammaplex excipients, and the reduced sodium chloride content is therefore not considered to be a risk to the patient during infusions of Gammaplex.

**Sodium acetate**

Sodium acetate will be dosed clinically at 0.52mmol/kg (0.04g/kg).

Sodium acetate is the sodium salt of acetic acid and is categorised as ‘generally regarded as safe’ by the US FDA (21CFR 184.1721 April 2007). Acetate is a normal constituent of the body and is derived from the diet and possibly from lipolysis. The normal circulating concentrations are <0.02 mM. The turnover of plasma acetate has been examined in subjects using [1-14C] acetate by infusion. The turnover rates ranged from 2.83 to 10.65µmol/min/kg and were negatively correlated with age (r=0.80, p<0.001). Moreover, the turnover rate was linearly related to the plasma concentrations, of which about 90% was “immediately oxidised”. Most of the acetate in the pool is excreted as CO₂.

The maximum rate of infusion of Gammaplex according to the Summary of Product Characteristics is 0.08mL/kg/minute. For a batch of Gammaplex that might contain, say, 26mmol/L, and infused at the maximum recommended infusion rate, 166µmol acetate per minute would be infused into an 80kg patient. From the published data presented, this amount of acetate would be fully metabolised during the infusion by a slightly built middle-aged or elderly subject weighing more than 35.3kg: i.e. 166µmol / 2.83µmol/min/kg [the slowest turnover rate] ~59 minutes. At a typical dose of Gammaplex of 400mg/kg, the time of this infusion would be ~100 minutes. The applicant concludes that the level of acetate in Gammaplex therefore is not a concern based on these published findings.
Sorbitol
Sorbitol is present in Gammaplex at a maximum limit of 55mg/mL; clinically, therefore, sorbitol will be dosed at 1,100mg/kg body weight at the maximal dose level for Gammaplex (i.e. 1g Gammaplex/kg body weight). Sorbitol is used as stabiliser for other IVIG products e.g. Flebogamma and Venoglobulin-S, both of which contain the same amount of sorbitol as Gammaplex.

Sorbitol has been evaluated by the FDA as ‘Generally Recognised as Safe’ and also by the Joint FAO/WHO Expert Committee for Food Additives as safe. Sorbitol is mainly metabolised to CO$_2$ through the glucose and fructose metabolic pathways. It is recognised in published papers that any remaining sorbitol will be excreted via the kidneys.

In rats, a minimal LD$_{50}$ of 7,100mg/kg body weight was reported, and this is 7 times the dose to humans with Gammaplex (7,100mg/kg divided by 1,100mg/kg). Infusions of 1.5g/kg in humans showed sorbitol to be mainly metabolised by the liver and there were transient rises in the serum concentration of uric acid and bilirubin. This is approximately 1.4 times the dose to man with Gammaplex but the metabolic pathway in humans is confirmed. The same paper detailed a study in rats: a dose of 20g/kg/day (approximately 18 times the Gammaplex dose) was administered, with high liver glycogen the only adverse finding.

Rats were given sorbitol at levels of 10 or 15% in the diet for 17 months. The top dose in this study represents a dose of approximately 18g/kg, 16 times the dose in Gammaplex use (1.2g sorbitol/kg). The rats showed no adverse effects from the supplemental sorbitol in their diet.

Glycine
Glycine would be dosed at 1.6mmol/kg (0.12g/kg).

Glycine is commonly used for stabilising IgG products at concentrations much higher than those in Gammaplex (0.08M in Gammaplex compared to ~0.3M in other IgG products). Glycine has also been reviewed by the Joint FAO/WHO Expert Committee on food advice; the conclusion was that dietary ingestion of glycine far outweighed the exposure from any other administration. On this basis, the relatively low levels of glycine present in Gammaplex are unlikely to represent a risk to the patient.

GENOTOXICITY

Soybean oil
Epoxidised soybean oil (ESO) was tested in histidine-dependent mutant Salmonella typhimurium strains. The soybean oil solutions containing 9, 18, 45, 90 and 455µg were tested for all strains. It was concluded that ESO was not mutagenic in any of the tester strains used at any of the levels incorporated into the assay.

Further mutagenicity studies using epoxidised soybean oil (ESO) and chlorinated epoxidised soybean oil (Cl-ESO) were done on Salmonella using test strains TA98 and TA100 in the presence and absence of a metabolic activation system (S9 mix). Up to an insoluble level of 3 mg/plate of ESO and Cl-ESO was used, but they did not exhibit toxicity. ESO was not mutagenic to TA98 or TA100 either in the presence or absence of S9 mix. Cl-ESO was not mutagenic to TA100 in the presence or absence of S9 mix, or to TA98 in the absence of S9 mix. Cl-ESO with TA98 in the presence of S9 mix gave a
statistically significant increase in revertants/plate. However these data do not meet the criteria for a clear positive response for mutagenesis.

Epoxidised soybean oil was tested for possible mutagenic potential in cultured Chinese hamster ovary (CHO) cells, for mutation at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) gene locus by standard test methods; the ESO concentrations ranged from 0.2 to 2mg/mL. No test chemical-related mutagenicity was observed. Hence ESO was not found to be a mutagen in CHO cells. The dose levels used in these CHO mutagenesis studies are at least 40 times that in Gammaplex.

**Tri-n-butyl phosphate (TnBP)**

In *Salmonella*, TnBP at 0.1, 1.0, 5.0, 10.0 and 100.0µL/plate, (approximately 0.1-100.0µg/plate, i.e. up to 5 times the concentration in Gammaplex use) did not cause a reproducible positive mutagenic effect in any of the strains, with or without added metabolic activation.

There was no evidence of recessive lethal mutation in Drosophila with TnBP.

TnBP was negative in a CHO cytogenetics assay at dose levels of 0.013-0.15µg/mL for the non-activated study and 0.01-0.15µg/mL for the S9 activated study.

TnBP was negative in a CHO HGRPT gene locus test at dose levels of 0.11-0.05µg/mL for the non-activated study and 0.15-0.06µg/mL for the S9 activated study.

Although the doses tested in the genotoxicity studies are generally lower than that from Gammaplex, the data provide some reassurance that TnBP does not present a genotoxic risk.

**Polysorbate 80**

One paper reported that Polysorbate 80 was tested for genotoxicity *in vitro* in the Ames test using several strains of Salmonella (with and without metabolic activation), in a *Bacillus subtilis* rec-assay for bacterial DNA repair and in a cytogenetic test using hamster lung fibroblasts. Another paper provided data on testing *in vivo* in the micronucleus test. No mutagenic activity was found in any of the tests.

**CARCINOGENICITY**

**Long-term studies**

**Soybean oil**

In a published study in rats, both sexes received margarine-emulsifier TOSM (thermally oxidised soybean oil interacted with mono- and diglycerides of food fatty acids) via the diet, at concentrations of 3% (approximately 2g/kg body weight/day), 6% (approximately 4g/kg body weight) or 12% (approximately 8g/kg body weight), for 2½ years. The study did not find any evidence of carcinogenicity or other adverse effects. 2g/kg is 20,000 times the dose with Gammaplex (based on 0.1mg soybean oil/kg with Gammaplex).

**Tri-n-butyl phosphate**

Groups of rats of both sexes were exposed to concentrations of 200ppm (200mg/kg body weight), 700ppm (700mg/kg body weight) and 3000 ppm (3g/kg body weight), TnBP in their diets for up to 2 years. Preliminary findings suggested that there was no evidence of malignant changes. Gross necropsy findings included 2x0.6cm calculi in the urinary bladder which was distended with yellow fluid, dilated renal pelvis with multiple
embedded white pinpoint foci, an ocular opacity and dark red lungs. There does not appear to be an updated full report of the final results.

**Polysorbate 80**

Long-term studies with polysorbate 80 were conducted in mice and rats to determine any signs of carcinogenesis. 28 mice were fed daily with 100mg Tween 80 in diets for 10 weeks, and no evidence of carcinogenicity was found. Upon topical application to the skin of mice; 100% polysorbate 80 once daily, 6 days per week; one benign dermal tumour was seen in one study but in another no tumours were found.

10 mice were subcutaneously dosed with 0.1mL of 0.5% polysorbate 80 in saline, (*i.e.* 0.5mg Tween 80) once weekly for 15 weeks. One case of pulmonary adenoma was found.

Repeated subcutaneous injections of 2mL of a 6% aqueous solution of polysorbate 80 (*i.e.* 120mg Tween 80) three times weekly for 40 weeks induced local sarcomas in 11 out of 17 rats.

**Short or medium-term studies**

**Soybean oil**

Published data are presented on dietary studies in rats with a mix of oils fed to show inhibition of a known carcinogen injected subcutaneously. Another study is presented using subcutaneous injection of soybean oil in rats with no carcinogenic effect. Dose levels were 200mg once a week; this equates to approximately 1g/kg body weight in these rats which is 10,000 times the dose level with Gammaplex.

**Polysorbate 80**

One paper details dietary dosing of rats and mice for various periods up to 2 years at doses of at least 25g/kg body weight, approximately 20,000 times the dose with Gammaplex. No short-term dosing effects were seen. There was a marginal but significant increase in the incidence of benign and malignant phaeochromocytomas in the adrenal medulla of high-dose (40,000 times Gammaplex dose levels) male rats (58% rats affected). However, in an evaluation of historical control incidences, there have been cases of phaeochromocytomas in untreated male rats as high as 65%. Hence the 58% rate in the present study was judged to be of questionable significance. However, there was also an increase in the incidence of adrenal medullary hyperplasia, a lesion usually formed as a precursor to phaeochromocytoma in the low-dose group, but not in the high-dose group. There was no evidence of carcinogenic activity for Polysorbate 80 in female rats or in mice. There were, however, inflammation and squamous hyperplasia of the fore-stomach in mice, and cases of ulcers of the fore-stomach in female mice, all at the high dose.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

**Fertility and early embryonic development**

**Soybean oil**

Two generations of male and female rats were fed on diets containing 15% (approximately 8g/kg body weight/day) of either fresh hydrogenated soybean oil, a similar oil used for frying foods for 56 hours, or an unhydrogenated mixture of fats and oils. During the third pregnancy of each generation, females were killed and inspected for early embryonic death. Neither deleterious effects on reproduction nor any teratogenic effects were found to be caused by; either hydrogenated soybean oil, the
similar oil used for frying, or the unhydrogenated mixture of fats and oils. This safety margin is 80,000 times the dose level in Gammaplex.

**Tri-n-butyl phosphate**
Reproductive toxicity tests were conducted in rats over 2 generations given TnBP from 200 to 3,000mg/kg body weight in diets for 10 weeks before mating; weanlings were exposed for 11 weeks to the diet, before mating. Adult toxicity was present at the top two dose levels in all generations but no reproductive toxicity or reproductive organ pathology at any dose tested was evident. Post-natal toxicity at 3g/kg body weight was evident with reduced weights. The NOAEL for reproductive toxicity was at least 3g/kg body weight and the NOAEL for post-natal toxicity was at or below 200mg/kg body weight in this study. For both these studies the low dose represents over a 9,000 fold increase on dose levels with Gammaplex.

**Sorbitol**
Rats were fed 0.25, 5 and 10% sorbitol (equivalent to a high dose of 12g/kg body weight, about 10 times the dose in Gammaplex use) over two generations. Apart from slight reductions in both food consumption and body weight gains, in test groups, there were no treatment-associated adverse effects.

**Embryo-fetal development**

**Soybean oil**
The applicant has cited the study quoted above under Section 4.3.1, Fertility and early embryonic development, in which the third litters of each generation were examined for malformations. There was no evidence of teratogenicity.

**Tri-n-butyl phosphate**
Dietary studies were conducted in rats at doses from 188 to 750mg/kg body weight. Rats were killed on day 20 and fetuses were examined. TnBP had little effect apart from reduced mean fetal weight at a dose of 750mg/kg body weight. The number of fetuses with ossification variations and/or delayed development was increased in all dose groups. Maternal toxicity was present at all doses. Food consumption was reduced and a high rate of deaths occurred at 750mg/kg. There was a general reduction in body weight gain, increased salivation, increased relative liver weight and yellow skin staining. The low dose represents over a 9,000-fold increase on dose levels with Gammaplex.

In rabbits dosed by gavage at doses of 50, 150 or 400mg/kg, there were no signs of toxicity below 400mg/kg, at which food consumption and body weight gain were reduced. The mean number of resorptions per pregnant female and the mean resorption/implant ratio for this high-dose level were increased. These results suggest there was embryonic toxicity at 20,000 times the TnBP dose in Gammaplex.

In rats dosed with TnBP in corn oil at doses of 188, 375 or 750mg/kg, significant fetotoxicity, delayed ossification and reduced foetal body weights were present in the 750mg/kg body weight dosage group only but there were no malformations.

**Prenatal and postnatal development, including maternal function**
No studies in addition to those presented above have been found.

**Studies in which the offspring (juvenile animals) are dosed and/or further evaluated**
No studies in this category have been published.
LOCAL TOLERANCE
No studies on local tolerance have been published.

OTHER TOXICITY STUDIES

Studies on impurities
No specific studies have been conducted on impurities. A summary of the impurities is presented below,

The impurities possibly present in Gammaplex are: impurities arising from the drug substance and which are co-purified during manufacture, such as IgA or IgM; chemicals that are introduced during processing and might not be completely removed in the drug product such as IgA, TnBP and PKA; phosphate; ethanol; turbidity; soybean oil.

It is accepted that there is no evidence of a toxic risk from the listed impurities.

Other studies
Soybean oil
A report is presented from a select FDA committee which considered extensive biological studies and consumer exposure data and concluded that “there is no evidence in the available information on hydrogenated soybean oil that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used as a direct or indirect food ingredient at levels that are now current or that might reasonably be expected in the future”.

ECOTOXICITY/ENVIRONMENTAL RISK ASSESSMENT
It is estimated that, from the current scale of production, patients world-wide are exposed to approximately 1,260kg protein/year. In general, entire bottles are used, but there might be a small volume of Gammaplex remaining in the bottle at disposal. The disposal procedures are agreed locally at specific hospitals or advice provided for patients on home-therapy. In general, biologically contaminated glassware would be incinerated.

As a result of metabolism of Gammaplex in the patient, minimal levels of any of the constituent chemicals are excreted largely in the urine and faeces, but some oxidation to CO₂ also occurs with some of the contaminants. The active ingredients are naturally occurring proteins present in all normal healthy individuals. In addition, the metabolites of Gammaplex are both common and of low toxicity and therefore pose little risk to the environment.

The manufacture of Gammaplex uses a combination of naturally occurring plasma proteins and chemicals used as either formulants; other compounds are essentially removed during the process, but remain at trace levels. Chemicals used in the process are not hazardous substances and the majority are widely used in many other pharmaceutical products and the food industry.

The applicant re-iterates that none of the chemicals used in the manufacture of Gammaplex are hazardous or extremely toxic. In addition metabolites of Gammaplex are not considered to pose an environmental hazard. Because of the low toxicity expected for Gammaplex, it is not considered necessary to present a detailed environmental risk assessment.
The applicant's argument is accepted that there is no need for a formal environmental risk assessment.

**ASSESSOR’S OVERALL CONCLUSIONS ON TOXICOLOGY**
The maximal unit dose of Gammaplex is 1g/kg and levels of excipients/contaminants, based on specification limits, in this dose are: 1200µg polysorbate 80/kg body weight, 0.1mg Soybean oil/kg body weight, 20µg TnBP/kg body weight and sorbitol at 1,100mg/kg body weight.

The applicant has presented a satisfactory review of the available data on the excipients and contaminants. The applicant’s view that there is no evidence that the use of Gammaplex will result in untoward toxicity is accepted.

**NON-CLINICAL EXPERT**
The non-clinical overview is adequate.

**ASSESSOR’S OVERALL CONCLUSIONS**
There are no non-clinical objections to the grant of a licence for Gammaplex.
CLINICAL ASSESSMENT REPORT

INTRODUCTION
Gammaplex has the ATC code: J06B A02 and is in the class of immune sera and immunoglobulins (Ig), normal human for intravascular administration. The product complies with the European Pharmacopoeia (Ph.Eur.) monograph 0918 for human immunoglobulin for intravenous administration.

Gammaplex has been developed from BPL’s Vigam products, which were licensed in the UK in 1996 (Vigam-S, a lyophilised product, PL 08801/0036) and 1997 (Vigam Liquid, PL 08801/0040). Vigam has in excess of 50% of the UK intravenous (IV) Ig market and is marketed in several other countries.

Gammaplex is a ready-prepared solution of a 5% concentration of human normal immunoglobulin G (IgG) at pH 4.8-5.1 for intravenous administration. The IgG is stabilised with D-sorbitol and polysorbate 80. It is prepared from human plasma collected from donors in the USA. The collection centres are licensed by FDA.

Gammaplex contains human Ig 50g/L (IgG virtually 100%) with an IgA content of less than 10 micrograms per mL and a sub-class distribution similar to normal plasma:
- IgG1~62%
- IgG2~31%
- IgG3~6%
- IgG4~1%

TYPE OF APPLICATION AND REGULATORY BACKGROUND
This is a new abridged application to seek a UK marketing authorisation for Gammaplex for replacement therapy in primary and secondary types of immunodeficiencies (including children with AIDS) in accordance with the Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for intravenous Administration (CPMP/BPWG/385/95 rev. 1).

CLINICAL BACKGROUND
The applicant has conducted a phase I pharmacokinetic (PK) study in normal healthy volunteers comparing PK parameters for Vigam and Gammaplex.

Two clinical studies have been submitted to support the indication for replacement therapy in patients with PID.

INDICATIONS
The clinical indications covered by this product licence application (PLA) are those that require replacement therapy with human normal IgG given intravenously according to the CHMP ‘Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg)’ of 29 July 2004 (CPMP/BPWG/859/95 rev.2).

The primary clinical role for IgG is as replacement therapy for patients with hereditary deficiencies of IgG. Examples cited in the Core SPC are congenital agammaglobulinaemia and hypogammaglobulinaemia, common variable immunodeficiency, severe combined immunodeficiency and Wiscott Aldrich syndrome. In addition, replacement therapy with IgG has been shown to be therapeutically useful for patients with chronic lymphocytic leukaemia (CLL) or myeloma with severe secondary hypogammaglobulinaemia and recurrent infections. Similarly, replacement therapy has been found useful in children with AIDS and recurrent infections.
Patients may develop antibody deficiency as a result of another condition. It has been shown that patients with chronic lymphocytic leukaemia or myeloma can develop low serum total IgG concentrations and become subject to recurrent infections. Similarly, children with AIDS can be subject to recurrent bacterial infections and management with IVIg can be beneficial. All these conditions are included in the Core SPC which states:

“4.1 Therapeutic indications

Replacement therapy in:

Primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. Children with congenital AIDS and recurrent infections.”

DOSE AND DOSE REGIMEN
The dose regimen and posology proposed in claimed indications are in line with Core SPC guidance.

GCP ASPECTS
The two studies provided in support of the current submission were carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) principles. Relevant audit certificates for both studies were provided.

ORPHAN MEDICINAL PRODUCTS
N/A

PAEDIATRIC DEVELOPMENT PROGRAMME (PDP)
The application was submitted before PDPs became a requirement.

SCIENTIFIC ADVICE
The company sought scientific advice from the MHRA regarding the clinical data on efficacy and safety of Gammaplex.

LEGAL STATUS
This is full new National abridged application.

CLINICAL PHARMACOLOGY
PHARMACOKINETICS (PK)

Introduction and overview
When a new method of manufacture of a blood-derived product is developed, inadvertent modification to the proteins may take place. One of the methods to evaluate the overall biological integrity of the immunoglobulin is to evaluate its pharmacokinetics. The normal half-life of IgG is around 19-27 days. Therefore in this study, the PK sampling was continued up to Day 85, which is three to four times the half life of IgG. There is an individual variation and, indeed, intercurrent infection can increase the
catabolism of immunoglobulin. Also, the rate of metabolism of normal immunoglobulin is, at least in part, governed by the absolute level in the circulation: the higher the level, the higher the metabolism. A control group included individuals receiving a marketed formulation, Vigam Liquid.

The licensed infusion rate for Vigam Liquid is up to 3mL/min. It was planned that this clinical trial would demonstrate that it is safe to infuse Gammaplex at a rate of up to 6mL/min.

It is usually recommended that a PK study in a new immunoglobulin product for intravenous use should be carried out for a period of 6 months (6.5 times the expected half-life) in patients with primary immunodeficiency disease (PID). At least 15 patients are required in the initial PK study and 15 should be followed up in the efficacy trial. However, in this case, study D was conducted in normal volunteers rather than in patients with PID, and only covered approximately 3 half-life periods. A total of 24 patients received Gammaplex (12 at 3 mL/min and 12 at 6 mL/min), and 12 received Vigam (3 mL/min).

The applicant states that a study in healthy volunteers allows for fuller exploration of PK variables over 3-4 half-lives and offers a stable IgG baseline (solely dependent on endogenous IgG synthesis) compared with patients with PID, in which the immediate baseline does not represent a stable value between two consecutive infusions (baseline values reflect a changing mix of endogenous synthesis and declining exogenous product). However, each study used a consistent method to calculate the PK variables and the same PK model was used for each study.

Therefore, the pharmacokinetic analysis in study D was based on the incremental serum IgG concentrations, calculated by subtraction of the pre-infusion serum IgG concentration from each of the post-infusion serum IgG concentrations in order to investigate the post-infusion changes in serum IgG concentrations after adjustment for endogenous synthesis of IgG.

Guidance also states that any modifications from the parental product (Vigam) would require PK data from patients with hypo- or agammaglobulinaemia.

As such, only data from study C in PID patients will be considered as a pivotal trial for this new abridged application. PK data obtained from normal volunteers in study D could be supportive of efficacy, safety and PK data derived from pivotal study C.

BIOEQUIVALENCE

Study D details
Study D was a Phase I, single centre, double-blind (Groups 1 and 2 only and open Group 3), randomised, controlled study conducted in the UK. This was because Group 3 had a higher maximum flow rate than Groups 1 and 2 (6mL/min versus 3mL/min) and it would not have been possible to disguise this. Vigam Liquid and Gammaplex are similar in appearance. Before dispensing, bottles were covered to maintain the blind so the two treatments looked identical.

The study consisted of a screening phase, a single dosing day and an 84-day follow-up period. Subjects were randomised into one of three treatment groups. Group 1 received Vigam Liquid infused at an initial rate of 0.01 to 0.02mL/kg/min increasing to a maximum of 3mL/min; Group 2 received Gammaplex infused at an initial rate of 0.01 to
0.02mL/kg/min increasing to a maximum of 3mL/min, and Group 3 received Gammaplex infused at an initial rate of 0.01 to 0.02mL/kg/min increasing to a maximum of 6mL/min. Groups 1 and 2 were double-blind, Group 3 was open. PK, safety and tolerability data were collected throughout the study.

**Figure 1. Study design**

![Study design diagram]

- **Pre-study screen**
  - (Within 28 days of dosing)

  ↓

  **Subjects randomised**

  - **Group 1**
    - 400 mg/kg Vigam® Liquid
    - Maximum infusion rate of 3 mL/min
    - N=12
  
  - **Group 2**
    - 400 mg/kg Gammaplex®
    - Maximum infusion rate of 3 mL/min
    - N=12
  
  ↓

  **Subjects discharged from Unit on Day 2**

  Follow up visits for assessments on Days 2 (30 hours post-end of dose), 3 (48 hours post-end of dose), 4, 8, 11, 15, 18, 22, 26, 38, 43, 50, 57 and 71

  ↓

  **Final study visit Day 85**

  Note. To avoid possible period effects, the plan was to treat the same number of subjects from each treatment group on each dosing day. (The ideal plan was to treat six subjects two from each of the three treatment groups). On any given treatment day, Groups 1 and 2 (double-blind treatment groups) started their infusions first. Group 3 (open treatment group) subjects started their infusions when Groups 1 and 2 were successfully established on their treatment regime. This was to ensure that any problems with giving the infusions were resolved before Group 3 received study medication given at a faster infusion rate.

**Test product, dose and mode of administration and batch number.**

Batch numbers of Vigam Liquid and Gammaplex have been provided.

**Objectives**

**Primary:**

To compare the AUC$_{0-84}$ of a single intravenous infusion of Vigam Liquid (infused at the licensed rate of up to 3mL/min) with Gammaplex (infused at up to 3mL/min and up to 6mL/min).

**Secondary:**

- To compare the AUC$_{0-21}$, C$_{max}$, t$_{max}$, MRT, t$_{1/2}$, CL and Vz of a single intravenous infusion of Vigam Liquid (infused at the licensed rate of up to 3mL/min) with Gammaplex (infused at up to 3mL/min and up to 6mL/min).
- To evaluate the safety and tolerability of Gammaplex (infused at up to 3mL/min and up to 6mL/min) compared to Vigam Liquid (infused at up to 3mL/min).
**Diagnosis and main criteria for inclusion**
Healthy, normotensive, non-smoking male and female volunteers aged 18 to 60 who gave written informed consent and fulfilled all of the inclusion criteria and none of the exclusion criteria. Female volunteers of childbearing potential had a negative pregnancy test before entering the study and had to use either a double barrier method of contraception or use the oral contraceptive pill. Postmenopausal or surgically sterile female volunteers could be enrolled.

**Duration of treatment**
Subjects received a single IV dose of either Vigam Liquid or Gammaplex. In Groups 1 and 2, the infusion lasted between 184-294 minutes. In Group 3, the infusion lasted between 96-203 minutes.

**Criteria for evaluation**

**Pharmacokinetics**
Area under concentration-time curve over Day 1 to Day 85 (AUC$_{0-84}$), area under concentration time curve over Day 1 to Day 22 (AUC$_{0-21}$), area under concentration-time curve extrapolated to infinity (AUC$_{0-\infty}$), peak concentration (C$_{max}$), time of peak concentration (t$_{max}$), mean residence time (MRT), elimination half-life (t$_{1/2}$), clearance adjusted for body weight (CL) and volume of distribution adjusted for body weight (Vz). The above PK parameters were calculated for serum immunoglobulin G (IgG) for all subjects. Pharmacokinetic calculations were based on increments over pre-dose (baseline) concentration.

**Safety**
Laboratory assessments (routine haematology, biochemistry, urinalysis and immunology), physical examination, 12 lead electrocardiogram (ECG), vital signs and adverse events (AEs). A venous blood sample was also tested for various viral markers (anti-HIV 1 and 2, anti-HCV and HBsAg) at screening, immediately before dosing and at the final visit.

**Statistical methods**

**Pharmacokinetic parameters**
PK assessments were based on serum IgG increments over pre-dose baseline. Data were summarised by treatment group and include arithmetic and geometric means with corresponding 95% confidence intervals, median, minimum, maximum, standard deviation and standard error of the mean. For AUC$_{0-21}$, AUC$_{0-84}$, AUC$_{0-\infty}$ and C$_{max}$, the values in the Gammaplex treatment groups were compared to the Vigam Liquid group as a reference using a one-way analysis of variance (ANOVA). According to the pre-defined in the protocol criteria, the bioequivalence was pre-defined if the 90% confidence interval for the parameter lay within the acceptable interval of 0.80-1.25.
Results of study D
Disposition of subjects
A total of 72 subjects underwent screening visits and of these, 36 subjects were enrolled in the study. In total, 36 subjects completed the study according to the protocol. Subject disposition is outlined below.

Figure 2. Subject disposition

Demographic and other baseline characteristics
A total of 36 subjects participated in the study. Seventeen subjects (47.2%) were male and 19 subjects (52.8%) were female. 28 subjects (77.8%) were Caucasian, 4 subjects (11.1%) were African and 4 subjects (11.1%) were Asian. Table 1 summarises the demographic characteristics of the subjects in each of the three treatment groups.
Table 1. Demographic data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 N=12</th>
<th>Group 2 N=12</th>
<th>Group 3 N=12</th>
<th>Overall N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>6 (50.0)</td>
<td>5 (41.7)</td>
<td>6 (50.0)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td>Age (years) Mean (range)</td>
<td>32.8 (19-59)</td>
<td>35.5 (22-51)</td>
<td>28.7 (20-44)</td>
<td>32.3 (19-59)</td>
</tr>
<tr>
<td>Height (cm) Mean (range)</td>
<td>171 (150-180)</td>
<td>188 (150-190)</td>
<td>168 (180-180)</td>
<td>159 (150-190)</td>
</tr>
<tr>
<td>Weight (kg) Mean (range)</td>
<td>70.68 (51.6-85.4)</td>
<td>68.07 (53.0-91.1)</td>
<td>65.71 (51.4-79.8)</td>
<td>68.15 (51.4-91.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 (20-28)</td>
<td>23.9 (20-28)</td>
<td>23.3 (19-27)</td>
<td>23.8 (19-28)</td>
</tr>
</tbody>
</table>

Group 1: Vigan® Liquid (3 mL/min); Group 2: Gammaplex® (3 mL/min); Group 3: Gammaplex® (6 mL/min)

PK results

IgG serum concentration-time data were provided by subject. All post-dose concentrations were adjusted for baseline endogenous IgG (actual concentration minus pre-dose value for the subject). 32 subjects demonstrated evidence of a distribution phase over approximately 48 hours post-end of infusion prior to the terminal elimination phase.

Figure 3. Mean incremental IgG serum concentrations by time and treatment group

All 36 subjects had measurable increments of IgG over baseline up to Day 22 and beyond and were therefore included in the PK analyses.
Table 2. Summary of IgG Pharmacokinetic Parameters (Geometric mean and Range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=12</td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-21&lt;/sub&gt;</td>
<td>h&lt;sup&gt;g&lt;/sup&gt;L</td>
<td>days&lt;sup&gt;g&lt;/sup&gt;L</td>
<td>h&lt;sup&gt;g&lt;/sup&gt;L</td>
</tr>
<tr>
<td></td>
<td>3490.7</td>
<td>145.4</td>
<td>3702.8</td>
</tr>
<tr>
<td></td>
<td>774-4972</td>
<td>32.3-207.2</td>
<td>1730-5844</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-21&lt;/sub&gt;</td>
<td>1866.6</td>
<td>77.8</td>
<td>2084.5</td>
</tr>
<tr>
<td></td>
<td>747-2505</td>
<td>31.1-104.4</td>
<td>1578-2929</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-21&lt;/sub&gt;</td>
<td>4193.4</td>
<td>174.3</td>
<td>4127.3</td>
</tr>
<tr>
<td></td>
<td>833-8886</td>
<td>34.7-286.9</td>
<td>1750-7015</td>
</tr>
<tr>
<td>CL</td>
<td>mL/h/kg</td>
<td>mL/day/kg</td>
<td>mL/h/kg</td>
</tr>
<tr>
<td></td>
<td>0.0656</td>
<td>2.29</td>
<td>0.0569</td>
</tr>
<tr>
<td></td>
<td>0.0681-0.4804</td>
<td>1.39-11.53</td>
<td>0.0570-0.2288</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>h</td>
<td>days</td>
<td>h</td>
</tr>
<tr>
<td></td>
<td>576.3</td>
<td>24.0</td>
<td>488.7</td>
</tr>
<tr>
<td></td>
<td>128-943</td>
<td>5.3-39.3</td>
<td>161-877</td>
</tr>
<tr>
<td>MRT</td>
<td>h</td>
<td>days</td>
<td>h</td>
</tr>
<tr>
<td></td>
<td>787.1</td>
<td>36.4</td>
<td>720.0</td>
</tr>
<tr>
<td></td>
<td>169-1562</td>
<td>7.9-55.8</td>
<td>218-1004</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>g/L</td>
<td>g/L</td>
<td>g/L</td>
</tr>
<tr>
<td></td>
<td>5.51-10.70</td>
<td>7.86-11.17</td>
<td>8.24-12.18</td>
</tr>
<tr>
<td>V&lt;sub&gt;r&lt;/sub&gt;</td>
<td>mL/kg</td>
<td>mL/kg</td>
<td>mL/kg</td>
</tr>
<tr>
<td></td>
<td>81-102</td>
<td>49-86</td>
<td>53-60</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>h</td>
<td>h</td>
<td>h</td>
</tr>
<tr>
<td></td>
<td>0.25-48.5</td>
<td>0.23-4.2</td>
<td>0.29-9.9</td>
</tr>
</tbody>
</table>

Group 1: Vifamab Liquid (3 mL/min); Group 2: Gammaflex (3 mL/min); Group 3: Gammaplex (5 mL/min)
1 N=12, except for the following parameters in Group 1 where N=11 (subject 19 omitted): t<sub>1/2</sub>, AUC<sub>0-21</sub>, MRT, CL, V<sub>r</sub>
2 Median data

Mean serum clearance (CL) was similar across all three treatment groups. Mean IgG half life (t<sub>1/2</sub>) and mean residence time (MRT) were longer in Group 1, while the volume of distribution (V<sub>r</sub>) was marginally higher in Group 1. Mean IgG half-lives for all three treatments were however within the literature quoted range of 19-27 days. The comparison of PK parameters using 90%CI was provided in Table 3.
Assessor's comment on Bioequivalence in study D

Full PK dataset in each treatment group was utilised in the comparison of PK parameters and statistical analysis. The bioequivalence between Vigam and Gammaplex was not demonstrated. The 90%CI for $C_{\text{max}}$, $\text{AUC}_{0-21}$, $\text{AUC}_{0-84}$, $\text{AUC}_{0-\infty}$ either exceed 1.25 or as in case of $\text{AUC}_{0-\infty}$ is completely outside of pre-specified margins 0.8-1.25. The bioequivalence between Gammaplex administered at different rates (3mL/min and 6mL/min, respectively) against the parental product Vigam has not been demonstrated in normal healthy volunteers. The only equivalence of PK parameters within the pre-specified range was shown for the comparison between treatment groups of patients administered with Gammaplex at different rate of administration. The results of study D indicate that Gammaplex has different PK characteristics compared to those seen with Vigam.

However, having failed the PK study in normal volunteers, the applicant has conducted a pivotal study in PID patients (study C), which included the PK assessment as well as allowed generation of efficacy and safety data for the current submission.

PHARMACODYNAMICS
The pharmacodynamic study is not formally required for this type of product and has not been carried out by the applicant. This is acceptable.
CLINICAL EFFICACY
INTRODUCTION

The primary immunodeficiency diseases are a heterogeneous group of disorders in which there is an intrinsic defect in the tissues, cells, and/or proteins of the immune system. Many of these disorders are characterised by hypogammaglobulinemia and/or defective antibody production and, as a consequence, increased susceptibility to infection.

Replacement therapy with IgG purified from pools of plasma from multiple donors has been used since the early 1950s. The initial products were administered intramuscularly, but were of limited efficacy because of the relatively small quantities that could be administered by that route. Beginning in the 1980s, intravenous immunoglobulin (IVIG) became available in the United States, and it is now the treatment of choice for patients with primary immunodeficiencies (PID) whose humoral immunity is impaired.

MAIN STUDY
Study design
Study C was a Phase III, Multicenter, Open-Label, non-randomised Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex in Primary Immunodeficiency Diseases conducted in 7 investigational sites in the USA between 6/02/2006-6/11/2007.

Assessor’s comment:
Study C was designed in accordance with FDA guidelines and required to monitor patients with PID for 1 year with primary endpoint of no more than 1 episode of serious bacterial infection per 1 patient/year treatment. CPMP/BPWG/388/95 rev. 1 (2000) requires at least 15 patients to be enrolled from the preceding 6 month PK study for a further 6 months replacement treatment with regular measurements of trough levels of IgG and documentation of infection episodes. There are no strict requirements to achieve the primary endpoint of less than 1 episode of serious acute bacterial infection. In addition, the lack of the initial PK study in PID patients could be justified by the conduct of the longer and larger (in 50 patients) efficacy trial.

Objectives
The primary objective of this study was to determine if Gammaplex is efficacious with respect to FDA minimal requirements (no more than 1 serious, acute, bacterial infection per subject per year) in subjects with PID.

The secondary objectives were to assess the safety and tolerability of Gammaplex and to determine if Gammaplex has PK profile comparable with that of intact IgG in subjects with PID.

Study population
Planned: 50 subjects were to be enrolled in order to obtain 40 evaluable subjects. A minimum of 20 subjects were to participate in a PK sub-study; at least 13 of these subjects were to be on a 28-day infusion schedule, and at least 7 were to be on the 21-day infusion schedule.

Diagnosis and main criteria for inclusion:
1. The subject was 3 years of age or older, of either sex, belonging to any ethnic group, and above a minimum weight of 27.5kg.
2. The subject had been receiving licensed or investigational (Phase III or IIIb) IVIG replacement therapy at a dose that had not changed by ±50% of the mean dose for at
least 3 months before study entry and was between 300 and 800mg/kg/infusion. The
infusion interval was between 21 and 28 days inclusive. The subject had maintained a
trough level at least 300mg/dL above baseline serum IgG levels (defined as before
initiation of any gamma globulin treatment for that subject). The trough level had to be
≥600mg/dL.
3. If a subject was a female of child-bearing potential, she must have had a negative
result on an HCG-based pregnancy test.
4. If a subject was a female who was or became sexually active, she had to practice
contraception by using a method of proven reliability for the duration of the study.

Study treatments
Gammaplex, 300 to 800mg/kg/infusion every 21 or 28 days, intravenously.

Two batches were used. There was no reference therapy in this study.

Duration of treatment:
The total planned duration of treatment was 12 months. The mean (SD) extent of
exposure to Gammaplex was 334.3 (67.35) days.

Primary efficacy endpoint:
The primary efficacy variable was the number of serious, acute, bacterial
infections/subject/year.

Secondary endpoints:
• Number and proportion of subjects with trough IgG levels that were ≤600mg/dL from
Week 15 onwards (estimated 5 half-lives);
• Number of days of work/school missed because of infection per subject years;
• Number and days of hospitalizations because of infection per subject year;
• Number of visits to physicians for acute problems and/or number of visits to hospital
emergency rooms per subject year;
• Other infections documented by fever, a positive result on a radiograph, and/or
culture;
• Number of infectious episodes per subject per year; and
• Number of days on therapeutic antibiotics.

Safety
Safety was assessed by using the following variables: adverse events (AEs), vital signs,
laboratory values (including Direct Coombs’ test), transmission of viruses, and physical
examinations.

Other
The pharmacokinetics of Gammaplex were determined for IgG overall and for antibodies
against Cytomegalovirus, Streptococcus pneumoniae, and Haemophilus influenzae B.

Statistical methods
Efficacy evaluations consisted of inferential analyses and summary statistics. For the
primary efficacy analysis, the estimated serious, acute, bacterial infection rate for
Gammaplex was calculated. The upper 1-sided 99% confidence bound was estimated
by using the generalised linear model procedure for Poisson regression with log link. The
exponential of the upper limit of the 98% 2-sided confidence interval gave the 99% 1-
sided upper confidence bound for the number of infections during the observed total
number of subject years. The equivalent upper bound per subject year was obtained by
dividing this figure by the number of subject years. If this figure was <1 infection per
subject year then the null hypotheses of a serious, acute, bacterial infection rate of ≥1 infections per subject year could be rejected at the 1% level of significance. No covariates were included in the Poisson regression model that was used to determine the primary efficacy results.

The secondary efficacy variables and the safety were analyzed by using descriptive statistics.

Safety data were analyzed by using descriptive statistics.

**Results**

**Patient disposition**

All subjects who received at least 1 infusion of Gammaplex were included in the intent-to-treat (ITT) population. The ITT population was used for all safety and efficacy analyses.

**Figure 4. Patient disposition**
Baseline characteristics and co-variates

Table 4. Demographic and baseline characteristics (ITT population)

<table>
<thead>
<tr>
<th>Category Statistic/Response</th>
<th>21-day Infusion Schedule N=22</th>
<th>28-Day Infusion Schedule N=28</th>
<th>Total N=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>39.6</td>
<td>47.4</td>
<td>44.0</td>
</tr>
<tr>
<td>SD</td>
<td>18.41</td>
<td>19.26</td>
<td>19.10</td>
</tr>
<tr>
<td>Median</td>
<td>39.0</td>
<td>45.5</td>
<td>44.3</td>
</tr>
<tr>
<td>Range</td>
<td>10 - 70</td>
<td>9 - 78</td>
<td>9 - 78</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (50.0%)</td>
<td>15 (53.6%)</td>
<td>26 (52.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (50.0%)</td>
<td>13 (46.4%)</td>
<td>24 (48.0%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>21 (95.5%)</td>
<td>25 (89.3%)</td>
<td>46 (92.0%)</td>
</tr>
<tr>
<td>African-American</td>
<td>0 (0.0%)</td>
<td>2 (7.1%)</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1 (4.5%)</td>
<td>1 (3.6%)</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common Variable Immunodeficiency</td>
<td>21 (95.5%)</td>
<td>25 (89.3%)</td>
<td>46 (92.0%)</td>
</tr>
<tr>
<td>X-Linked Agammaglobulinemia</td>
<td>1 (4.5%)</td>
<td>3 (10.7%)</td>
<td>4 (8.0%)</td>
</tr>
<tr>
<td>Baseline Chest X-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>20 (90.9%)</td>
<td>24 (85.7%)</td>
<td>44 (88.0%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>2 (9.1%)</td>
<td>4 (14.3%)</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>Any planned elective procedures scheduled?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0%)</td>
<td>6 (21.4%)</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>No</td>
<td>22 (100.0%)</td>
<td>22 (78.6%)</td>
<td>44 (88.0%)</td>
</tr>
</tbody>
</table>

a Elective procedures included angiogram, colonoscopy, face lift, breast reduction, disc replacement surgery, repair of herniated lumbar disc, and removal of wart-like growth. The face lift and breast reduction occurred in the same subject.

Past medical history
The majority of subjects entered the study with other pre-existing medical conditions other than PID. The most common three systems affected were ear, nose, and throat (44 subjects, 88.0%); surgical history (41 subjects, 82%), and respiratory (40 subjects, 80%).

Prior IVIG Therapy
All 50 subjects had prior IVIG therapy. The most common products used for the prior therapy were Gamunex (21 subjects, 42.0%), Gammagard (17 subjects, 34.0%), Carimune (16 subjects, 32.0%), Octagam (8 subjects, 16.0%), and investigational product (5 subjects, 10.0%). 42 subjects (84.0%) did not have a documented adverse event related to the prior IVIG therapy. For the remaining 8 subjects, adverse events included chills, nausea, headache, vomiting, malaise, and other (joint ache/pain, shaking, lack of energy, body aches, fluid retention, and leg cramps) in the previous 6 months.
Table 5. Number and percent of subjects with infections associated with prior IVIG therapy in the ITT population

<table>
<thead>
<tr>
<th>Category</th>
<th>Response</th>
<th>Subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection in past 6 months?</td>
<td>Yes</td>
<td>27 (54.0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>23 (46.0%)</td>
</tr>
<tr>
<td>Number of infections in past 6 months?</td>
<td>0</td>
<td>23 (46.0%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>23 (46.0%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>4 or more</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Any serious, acute, bacterial infections in past 6 months?</td>
<td>Yes</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>44 (88.0%)</td>
</tr>
<tr>
<td>Number of serious, acute, bacterial infections in past 6 months?</td>
<td>0</td>
<td>44 (88.0%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>5 (10.0%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1 (2.0%)</td>
</tr>
<tr>
<td></td>
<td>4 or more</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Any ongoing infections?</td>
<td>Yes</td>
<td>2 (4.0%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>48 (96.0%)</td>
</tr>
</tbody>
</table>

22 subjects (44.0%) had at least 1 course of prior antimicrobial medication. The following antimicrobial medications were previously taken by at least 5% of the population: amoxicillin clavulanate (6 subjects, 12.0%), azithromycin (6 subjects, 12.0%), and levofloxacin (4 subjects, 8.0%). 27 subjects had an infection in the previous 6 months; however, 5 of these subjects did not require antimicrobial medication.

Protocol amendments, deviations and violations
Several protocol deviations involved change rescheduling of visits outside of visit windows and isolated problems with shipment of lab samples. One interim analysis was planned but did not occur.

Efficacy Results

The primary efficacy variable was the number of serious, acute, bacterial infections per subject per year; these infections were bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis. The mean event rate of serious, acute, bacterial infections per subject per year was zero. This included infections with an onset date between the first infusion of Gammaplex and the first follow-up visit, inclusive.

One subject was completing treatment for bacterial pneumonia at the time of the first infusion with Gammaplex. The start date for this infection was before the date of the first infusion with Gammaplex; therefore, it was not included in the primary efficacy calculation.

The secondary efficacy variables were analyzed, and the results were as follows:

- Trough IgG levels consistently remained above 600mg/dL after 15 weeks (estimated 5 half-lives) with exceptions in 2 subjects (levels >500 but <600mg/dL).

A total of 29 subjects provided data on trough levels of IgG1 antibodies on prior IVIG and median trough levels of IgG1 antibodies on prior IVIG were 659mg/dL. During the course of treatment with Gammaplex, median trough levels of IgG1 antibodies remained close.
to 600 mg/dL, with a range of 566-662 mg/dL. Median trough levels of IgG2 antibodies generally remained in the region of 280-300 mg/dL. Median trough levels of IgG3 antibodies generally remained in the region of 21 to 25 mg/dL. Median trough levels of IgG4 antibodies showed a gradual decline, reaching a value of 6.6 mg/dL at Visit 10.

**Assessor's comment**
Trough levels for previous IVIG treatments were not available for 21 patients in study C. The applicant notes that missing data relates to IgG subclass levels not to total IgG and that this omission is minor since prior trough IgG subclass values provide little insight into the disease severity of individual patients and, as such, have little or no impact on the study conclusions. This is acceptable.

- 40 subjects (80.0%) had at least one infection during the study. The median number of infectious episodes per subject per year was 3.07 with a range of 0 - 14.9.
- 18 subjects (36.0%) had at least 1 episode of fever (>38°C); however, the mean (SD) number of days with fever was 1.09 (1.970) days per subject per year.
- The majority of subjects (38 subjects, 76.0%) had at least 1 course of systemic antibiotic medication for therapeutic purposes. 16 subjects (32.0%) took at least 1 course of prophylactic systemic antibiotic medication during the study. The most common oral medications given therapeutically during the study were fluoroquinolones (18 subjects, 36.0%), macrolides (14 subjects, 28.0%), combinations of penicillins (13 subjects, 26.0%), penicillins with extended spectrum (5 subjects, 10.0%), and tetracyclines (5 subjects, 10.0%).

**Assessor's comment:**
A higher incidence of use of antibiotics was reported during the study C compared to during the 6 months previous to the study, however the applicant states that this may be due to retrospective data being obtained from patients’ hospital notes only and therefore omitting any antibiotics prescribed by primary care clinicians. This is acceptable.

- The majority of subjects (46 subjects, 92.0%) did not require hospitalization because of an infection or other medical problem during the study.

Of the 4 subjects hospitalised:
Two subjects were hospitalised for a planned lumbar surgery and uterine haemorrhage, respectively. Another subject was hospitalised for an SAE of viral gastroenteritis. One of the subjects hospitalised for an SAE of viral gastroenteritis was hospitalised for the equivalent of 30.2 days per year. The first hospitalisation was for a planned disk replacement surgery. The next two admissions to the hospital were for SAEs of thrombosis and chest pain (treated as suspected acute coronary syndrome).

- 41 subjects (82.0%) did visit a physician and/or hospital ER because of an infection or other medical problem [39 subjects (78.0%) for physician's office; 12 subjects (24.0%) for ER]. The mean (SD) number of visits to a physician and/or hospital ER was 5.95 (8.478) visits per subject per year. Subjects who had a maximum number of visits were planned for various elective surgeries or in 1 patient required a number of visits due to squamous carcinoma.
- The majority of subjects (27 subjects, 54.0%) did not miss a day of school/work because of an infection or other medical problem. The mean (SD) number of days off work/school was 8.73 (34.41). The majority of the subjects who missed days of work/school (17 of 23, 74%) missed less than 14 days per year.
Pharmacokinetic Results:
The pharmacokinetic profile of Gammaplex was evaluated in a subset of 24 subjects. Levels of total IgG and antibodies against certain antigens were determined. The two infusion schedules (21-day and 28-day) had similar values for both parameters (Figures 5 and 6):

**Figure 5.** Total IgG levels measured for pharmacokinetic assessment (Mean ± 1 Std Error) 21-day infusion schedule (N=9)

![](image1)

**Figure 6.** Total IgG levels measured for pharmacokinetic assessment (Mean ± 1 Std Error) 28-day infusion schedule (N=15)

![](image2)

**Total IgG**
The median $C_{\text{max}}$ and median $T_{\text{max}}$ values for total IgG were 2.02g/dL and 3.30hr, respectively. Total exposure was measured by AUC(0-28), and the mean (SD) AUC(0-28) value was 35.1 (5.023) days x g/dL. The mean (SD) half-life was 41.1 (19.19) days.
for all 24 subjects analyzed. Overall mean (SD) clearance and volume of distribution were 0.585 (0.2508) mL/day/kg and 0.297 (0.0539) dL/kg, respectively and mean (SD) MRT was 56.1 (23.06) days.

**Specific antibodies**
The results of PK analyses of antibody against *S. pneumoniae* serotypes 4, 14, 19, 6B and 9V are summarised in Table 6.

**Table 6. Pharmacokinetic parameters for antibodies specific for *S. pneumoniae* serotypes (PK Population)**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>4</th>
<th>14</th>
<th>19</th>
<th>6B</th>
<th>9V</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C</em>(_{\text{max}}) (AU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Mean</td>
<td>2.93</td>
<td>19.4</td>
<td>16.2</td>
<td>11.1</td>
<td>9.38</td>
</tr>
<tr>
<td>SD</td>
<td>1.741</td>
<td>8.876</td>
<td>16.43</td>
<td>4.109</td>
<td>2.660</td>
</tr>
<tr>
<td>(T_{\text{max}}) (hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Median</td>
<td>3.38</td>
<td>3.33</td>
<td>3.65</td>
<td>3.38</td>
<td>3.42</td>
</tr>
<tr>
<td>Min - Max</td>
<td>2.15 - 340</td>
<td>2.15 - 49.1</td>
<td>2.08 - 504</td>
<td>2.08 - 49.6</td>
<td>2.15 - 96.0</td>
</tr>
<tr>
<td>AUC(_{\text{0-3B}}) (days*AU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>23</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>41.6</td>
<td>315</td>
<td>163</td>
<td>160</td>
<td>134</td>
</tr>
<tr>
<td>SD</td>
<td>17.27</td>
<td>185.9</td>
<td>78.72</td>
<td>87.18</td>
<td>39.68</td>
</tr>
<tr>
<td>AUC(_{\text{TAD}}) (days*AU/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22</td>
<td>23</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>38.3</td>
<td>281</td>
<td>150</td>
<td>148</td>
<td>124</td>
</tr>
<tr>
<td>SD</td>
<td>17.27</td>
<td>136.1</td>
<td>79.03</td>
<td>87.56</td>
<td>33.81</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>22</td>
<td>19</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>25.0</td>
<td>27.2</td>
<td>27.0</td>
<td>24.4</td>
<td>24.4</td>
</tr>
<tr>
<td>SD</td>
<td>7.689</td>
<td>12.03</td>
<td>8.720</td>
<td>5.804</td>
<td>9.216</td>
</tr>
<tr>
<td>MRT (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>22</td>
<td>19</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>36.4</td>
<td>39.5</td>
<td>39.6</td>
<td>35.4</td>
<td>34.9</td>
</tr>
<tr>
<td>SD</td>
<td>11.13</td>
<td>16.45</td>
<td>12.64</td>
<td>8.38</td>
<td>12.54</td>
</tr>
</tbody>
</table>

The overall mean half-lives for specific antibodies ranged from 15.6 days for anti-*Haemophilus influenzae* B antibody to 31.6 days for anti-*Cytomegalovirus* antibody. The short dosing intervals relative to the long half-lives in this clinical trial did not permit an accurate assessment of half-life. Thus, any assessment of the clinical relevance of half-life measurements of antibodies against *Haemophilus influenzae B* and *CMV* in this study should be viewed with caution.
Table 7. Pharmacokinetic parameters for antibodies specific for *H. influenzae B* and CMV (PK population)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>H. influenzae B</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (AU/mL)</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>$n$</td>
<td>6.36</td>
<td>62.4</td>
</tr>
<tr>
<td>Mean</td>
<td>1.550</td>
<td>22.70</td>
</tr>
<tr>
<td>SD</td>
<td>3.48</td>
<td>3.09</td>
</tr>
<tr>
<td>Min - Max</td>
<td>2.17 - 50.4</td>
<td>2.08 - 96.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>$T_{\text{max}}$ (hr)</th>
<th>22</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Median</td>
<td>24.92</td>
<td>482.8</td>
</tr>
<tr>
<td>SD</td>
<td>73.7</td>
<td>1210</td>
</tr>
<tr>
<td>$AUC_{0-3.15}$ (days*AU/mL)</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>$n$</td>
<td>66.5</td>
<td>1150</td>
</tr>
<tr>
<td>Mean</td>
<td>19.05</td>
<td>520.1</td>
</tr>
<tr>
<td>SD</td>
<td>15.6</td>
<td>31.6</td>
</tr>
<tr>
<td>$AUC_{\text{TARV}}$ (days*AU/mL)</td>
<td>9.693</td>
<td>12.55</td>
</tr>
<tr>
<td>$n$</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>Mean</td>
<td>12.13</td>
<td>19.43</td>
</tr>
</tbody>
</table>

**ASSESSORS' OVERALL CONCLUSIONS ON CLINICAL EFFICACY**

The efficacy data for a new IVIG product should include data on PK parameters established in at least 15 patients with PID during 6 month followed by the efficacy study with monitoring of trough levels of IgG in the same cohort of PID patients remaining on continuous treatment with intravenous infusions of the immunoglobulin. The efficacy data should be supported with data on the incidence of severe infections and use of antibiotics. Supportive clinical data on the distribution of IgG classes of antibodies and PK of therapeutically relevant classes of antibodies are beneficial. The applicant has effectively conducted a larger pivotal study C (in 50 patients with PID) than a study required by CHMP. The design of the pivotal study was tailored towards FDA requirements for licensure of IVIG product. The duration of the study was 1 year (compared to 6 months according to CHMP requirements). All patients in this study had a prior history of IVIG use and history of various infections and use of antibiotics. The PK parameters for IgG overall and individual classes of antibodies against certain serotypes of *S. pneumoniae, H. influenzae B* and CMV were derived from PK subset of patients. In vast majority of patients trough levels of IgG were around the required maintenance level of 6 g/L (as per Core SPC CPMP/BPWG/859/95 rev. 2 requirements). Therefore the clinical data for efficacy were in excess of those required by CHMP.

There were no cases of severe acute bacterial infections in study C, except 1 case of pneumonia, which was diagnosed before the initiation of treatment with Gammaplex.

The secondary efficacy parameters indicated that the treatment was accompanied with a relatively low incidence of hospitalizations, emergency visits to the doctor, sickness leaves and absences.
The half-life for Gammaplex derived from PK subset of 24 patients with PID was 41.1 (SD+/−19.19) days for all 24 subjects analyzed. This value is comparable with half-lives of most other IVIG preparations determined in immunodeficient patients (Morrell et al. 1997). The pattern of half-lives of specific antibodies seen in patients with PID treated with Gammaplex is comparable to half-lives seen with other licensed IVIG products (see Benefit-Risk section). Study D in healthy normal volunteers failed to demonstrate bioequivalence between Vigam and Gammaplex but should be treated with caution due to methodological challenges of PK parameters adjustment towards the baseline IgG levels in healthy subjects. The results of study D indicate that Gammaplex should be treated as different from Vigam product with different PK profile and therefore potentially requiring different approaches in long-term dosing and maintenance and replacement therapy. However, overall efficacy results from pivotal study C in PID patients are adequate and sufficient.

CLINICAL SAFETY

INTRODUCTION

Safety of Gammaplex was evaluated in two studies: D (normal healthy volunteers) and C (in patients with primary immunodeficiency disease).

PATIENT EXPOSURE

In C, there were 703 infusions received by the 50 patients. The protocol allowed for the patients on the 21-day schedule to have 17 infusions of Gammaplex each and those on the 28-day regimen a total of 13 infusions each. 5 patients (10%) were withdrawn during the study (including 3 due to AEs) but 45 (90%) completed all infusions.

Table 8. Exposure to Gammaplex (study C)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Schedule</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21-day (N=22)</td>
<td>28-day (N=28)</td>
</tr>
<tr>
<td>Duration of exposure (days):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>338.8</td>
<td>330.8</td>
</tr>
<tr>
<td>SD</td>
<td>64.83</td>
<td>70.24</td>
</tr>
<tr>
<td>Median</td>
<td>351.0</td>
<td>350.0</td>
</tr>
<tr>
<td>Minimum</td>
<td>49</td>
<td>29</td>
</tr>
<tr>
<td>Maximum</td>
<td>364</td>
<td>374</td>
</tr>
<tr>
<td>Time of withdrawal:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 month</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 to ≤2 months</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5 to ≤6 months</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10 to ≤11 months</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Completed study:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;11 to ≤12 months</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

In study D, there were 24 infusions of Gammaplex given to 24 subjects (an additional 12 subjects received a single dose of Vigam Liquid). They were all monitored for 84 days after infusion.

Therefore, in total, there were 727 infusions of Gammaplex on which safety data were collected.
Doses of Gammaplex
The doses in study C had been clinically determined. The total amount of Gammaplex administered is summarised in Table 9.

Table 9: Total Gammaplex administered during the study (study C)

<table>
<thead>
<tr>
<th>Statistic</th>
<th>21-day (N=22)</th>
<th>28-day (N=28)</th>
<th>Combined (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of exposure (mg/kg):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7589</td>
<td>5623</td>
<td>6488</td>
</tr>
<tr>
<td>SD</td>
<td>2321</td>
<td>1875</td>
<td>2284</td>
</tr>
<tr>
<td>Median</td>
<td>7613</td>
<td>5428</td>
<td>6411</td>
</tr>
<tr>
<td>Minimum</td>
<td>965</td>
<td>898</td>
<td>898</td>
</tr>
<tr>
<td>Maximum</td>
<td>11670</td>
<td>10278</td>
<td>11670</td>
</tr>
</tbody>
</table>

In study D, 24 subjects received precisely 400 mg/kg of Gammaplex as a single intravenous infusion.

Rates of Infusions
There were 24 healthy subjects in study D who received Gammaplex. Each received a single dose of 400mg/kg (24 infusions in this study) given according to the rates in Table 10. A faster schedule of rate increases was also used in study C (shown in bold in the table 11).

Table 10: Infusion rates of Gammaplex during the study (D and C studies)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time after start of infusion (min)</th>
<th>Infusion rate mL/Kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study D group 2 (and group 1 given Vigam Liquid)</td>
<td>0-30</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>46-60</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>60 onwards</td>
<td>0.07</td>
</tr>
<tr>
<td>Study D group 3</td>
<td>0-15</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>16-30</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>46 onwards</td>
<td>0.13</td>
</tr>
<tr>
<td>Study C</td>
<td>0-15</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>16-30</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>31-45</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>46-60</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>61 to end of infusion</td>
<td>0.08</td>
</tr>
</tbody>
</table>
There was a slight trend observed of an increased incidence of AEs with increased infusion rate (especially headaches) and with infusions carried out without use of in-line filters.

DEATHS
There were no deaths in either of the studies.

SERIOUS ADVERSE EVENTS (SAEs)
There were no SAEs reported in study C.
SAEs seen in the pivotal study C are summarised in Table 11.

**Table 11: Number and percent of subjects with SAEs in study C (ITT population: N=50)**

<table>
<thead>
<tr>
<th>System, Organ, Class</th>
<th>Preferred Term</th>
<th>Subjects n (%)</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Serious Adverse Event</td>
<td>5 (10.0)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>1 (2.0)</td>
<td>(Related)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis viral</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>2 (4.0)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Syncope vasovagal</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 (2.0)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1 (2.0)</td>
<td>(Related)</td>
<td></td>
</tr>
</tbody>
</table>

**Assessor’s comment**
Narratives of SAEs were reviewed and it is unlikely that any of SAEs could have a plausible relationship to the administration of Gammaplex. This refers to the case of thrombosis of the subclavian vein. The patient developed the thrombosis on the contralateral site from the administration infusion site and subsequently was diagnosed with antiphospholipid syndrome.

COMMON ADVERSE EVENTS
In study D a total of 28 subjects (77.8%) reported 100 treatment-emergent AEs. 90 of the AEs were mild and 10 were moderate. There were no severe AEs. 41 AEs were reported in 9 subjects in Group 1, 30 AEs in 10 subjects in Group 2 and 29 AEs in 9 subjects in Group 3. There were no SAEs during the study and no AEs leading to withdrawal.

There was a trend towards a higher percentage (50%) of subjects with drug-related headaches in Group 3 (i.e. using the faster infusion rate). All treatment emergent headaches in this group occurred between 24 and 48 h post-dose and may mean that
the higher infusion rate is more likely to cause headache. It is difficult to draw firm conclusions from such small sample size (11 of 36 subjects).

A summary of AEs in the pivotal study C was provided in Table 12.

Table 12. AEs occurring in at least 10% of individuals in either study alone or in the studies combined.

<table>
<thead>
<tr>
<th>MedDRA Term (version 8.0)</th>
<th>Study C N=50</th>
<th>Study D N=24</th>
<th>Total N=74</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (%)</td>
<td>Subjects (%)</td>
<td>Number of events</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (20.0)</td>
<td>13 (8.3)</td>
<td>2 (16.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (18.0)</td>
<td>12 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (6.0)</td>
<td>3 (12.5)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>5 (10.0)</td>
<td>5 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (10.0)</td>
<td>10 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (10.0)</td>
<td>6 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (10.0)</td>
<td>7 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (30.0)</td>
<td>26 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (14.0)</td>
<td>22 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (36.0)</td>
<td>97 (50.0)</td>
<td>21 (40.5)</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>7 (14.0)</td>
<td>11 (3.125)</td>
<td>3 (13.5)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>6 (12.0)</td>
<td>7 (1.42)</td>
<td>1 (9.5)</td>
</tr>
<tr>
<td>Rash</td>
<td>5 (10.0)</td>
<td>6 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

The most common AE, both when expressed as a proportion of individuals in each study and the number of reports, is headache. This symptom was reported by a slightly larger proportion of the healthy subjects (12, 50%) than the PID patients (18, 36%). However, 12 of 26 headaches in study D occurred remotely from the infusion, i.e. more than three weeks after infusion.

Pyrexia was the next most common but was only reported by the patients in study C and only one patient reported pyrexia within the first 24 hours after one infusion. This event is expected because the PID patients are predisposed to recurrent infections. Likewise, fatigue was reported only by the PID patients, which is also explicable by their chronic disease. Diarrhoea was more common in the patients and may be related to the relapsing enteroviral infections some of them suffer or even the antibiotics they need. Nausea was confined to the PID patients. Pharyngolaryngeal pain and nasal congestion were slightly more common in the patient group which is again not unexpected because of their propensity for infections. These apparent differences also have to be interpreted in the knowledge that the patients were under observation for a much longer period than the healthy subjects. Non-specific rashes were reported by 5 patients in study C but the investigators did not categorise any of them as severe. Rash only occurred in the patient group, which may suggest that co-morbidities and/or concomitant medications may play a significant role.
Of the 50 patients in study C, 16 (32%) had at least one AE which was categorised as severe. The severe AEs included three patients with headache, two with hypertension and one each with hypotension, chest pain, a vasovagal attack, asthma and the thrombosis mentioned above. The others described as severe were single reports of a pruritic rash, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, haemangioma, insomnia, intervertebral disc degeneration, a decrease in WBC, sunburn, acute bronchitis and viral gastroenteritis; one patient became pregnant soon after starting in the study and was withdrawn.

There were no reports of renal failure.

DISCONTINUATION DUE TO ADVERSE EVENTS
There were no withdrawals in study D.
3 patients withdrew because of an adverse event:
• One patient withdrew because of paraesthesia;
• One patient became pregnant after the second infusion of Gammaplex and withdrew seven weeks after her first infusion;
• One patient withdrew after recurrent syncope about 10-11 months after the first infusion of Gammaplex (this patient had previously had two SAEs: a thrombotic episode, and chest pains; she was then diagnosed with anti-phospholipid syndrome

LABORATORY FINDINGS

Biochemistry & Haematology
In general, haematological and clinical chemistry parameters were within normal limits within both studies although minor deviations from the normal reference ranges for some parameters were seen.

ECG
ECG results were normal for all subjects at all time points in both studies.

Vital signs
There were no clinically significant abnormalities or changes in vital signs parameters during both studies. Vital signs were, in general, within normal limits. In study C, there were 3 patients with hypertension as an infusion-associated AE; 2 had a medical history of hypertension. These 3 patients had 10 recorded AEs of hypertension (3 mild, 4 moderate and 3 severe) during or immediately after 4 infusions.

Others: Viral screens, IgA, Direct Coombs’ and Haptoglobin tests
Two subjects in study D had serum IgA levels above the normal range of 4.0g/L. All other subjects had serum IgA levels within normal limits. Results from the Direct Coombs’ and haptoglobin tests in study D were within normal limits in both studies except 1 positive direct Coombs test in normal subject in study D. The result had IgG specificity and was considered as clinically irrelevant.

All subjects and patients from both studies were negative for HIV 1 and 2 antibody and HbsAg at screening and at the end of studies. One subject in study D had a weakly positive result to the hepatitis C antibody enzyme linked immunosorbent assay (ELISA). The ELISA was repeated several times with the same weakly positive result. PCR was
set up to detect HCV RNA with negative result. It was concluded that the subject was negative for HCV.

Therefore, there were no viral transmissions recorded in either study.

SAFETY IN SPECIAL POPULATIONS

None of the patients or subjects in the studies had renal failure or was elderly or grossly obese. It is known that IVIg can present an increased risk of thrombo-embolic episodes for patients with previous thrombo-embolic or ischaemic pathology or who are obese. IVIg has also been associated with renal failure, especially in at-risk patients and is particularly associated with products stabilised with sucrose (Gammaplex is stabilised with sorbitol).

One patient in study C developed a subclavian clot on the contralateral side to an intravenous port and later developed chest pain, but the origin of this was not identified despite extensive investigation. As a result of the extensive investigations which followed the venous thrombosis, she was diagnosed with anti-phospholipid syndrome, giving her a thrombotic diathesis.

One patient became pregnant during the study. She withdrew and later had a therapeutic abortion.

SAFETY RELATED TO INTERACTIONS

No drug interactions have been associated with IVIg. However, the IgG can affect immunization from live virus vaccines due to the presence of specific antibodies in the product. IVIg is unlikely to contain antibodies to yellow fever virus so interference with immunization by this vaccine is inconceivable. It was noted that specifications for Gammaplex indicate levels of anti-HBsAg higher than required by Ph.Eur., that may interfere in serological testing for Hepatitis B.

POST MARKETING EXPERIENCE

Gammaplex has not been marketed in any country.

ONGOING STUDIES

BPL is sponsoring a study with Gammaplex in autoimmune idiopathic thrombocytopenic purpura (ITP), which is being conducted in USA under an IND. The product being used in this study is manufactured in an almost identical way to Gammaplex used in study C.

To date (03 July 2008), 5 patients have been recruited. The scheduled dosage is an intravenous dose of 1g/kg on two consecutive days (total dose 2g/kg). The rate of infusion is the same as used in study C. Twelve infusions have been given so far. One of these subjects did not receive the first course of infusions on Day 1 and Day 2 at the recommended rate. There has been one SAE reported, headache with vomiting and dehydration in a 6 year old boy.

ASSESSOR’S OVERALL CONCLUSIONS ON CLINICAL SAFETY

There were no new safety signals or concerns identified during study C and study D studies. The pattern and the range of adverse events seen with Gammaplex are comparable to the safety data seen with the other licensed IVIG products and with the list of undesirable events proposed by the Core SPC CHMP guidance. There were no
cases of renal failure, anaphylactic reactions, severe hypotension, aseptic meningitis or haemolytic anaemia within both studies. One case of thrombosis, which is unlikely to be related to Gammaplex, was described in study D.

On the basis of data provided it was concluded that the safety profile of Gammaplex is acceptable.

**Pharmacovigilance system and risk management plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The applicant has provided a Risk Management Plan that is considered to adequately monitor identified and potential risks in relation to suspected adverse reactions.

**PRODUCT LITERATURE**

**SPC**
As proposed by the applicant.

**PATIENT INFORMATION LEAFLET**
PIL was accompanied with readability test to fulfil the requirements of article 59(3). The layout and design of PIL are acceptable. Key safety messages are clearly displayed. The bridging report to User test conducted for Vigam PIL was provided. The user test was satisfactory. Based on this, the PIL for Gammaplex is considered to be approvable.

**LABEL**
Enclosed and no comments suggested.

**OVERALL CONCLUSION**
RISK BENEFIT ASSESSMENT

BENEFIT

Patients with congenital agamma- or hypogammaglobulinemia represent a prime indication for replacement therapy with IVIG preparations. There are other groups of patients who benefit from the replacement therapy with IVIG products: such as pre-term born neonates, infants with congenital AIDS and recurrent infections; allogeneic bone marrow transplant (BMT) recipients. IVIG replacement therapy was furthermore shown to be beneficial to patients with low-grade B-cell tumours such as chronic lymphocytic leukaemia (CLL) or low-grade non-Hodgkin's lymphoma (NHL). These patients often have severely decreased levels of serum immunoglobulin and of specific antibodies. The level of replacement therapy required in different patients with primary or secondary immunodeficiencies is guided normally by the product label and regular monitoring of immunological and clinical parameters to maintain an optimal level of total IgG and specific antibody classes.

CHMP requires that the efficacy data for a new IVIG product should include data on PK characterisation established in at least 15 patients with PID during 6 month followed by the efficacy study with monitoring of trough levels of IgG in the same cohort of PID patients remaining on continuous treatment with intravenous infusions of the immunoglobulin. Currently, a number of replacement indications are considered as “well established”. According to CPMP/BPWG/388/95 rev. 1 (2000) the availability of sufficient efficacy data in PID patients will allow to grant a replacement indication in patients with myeloma, CLL, severe secondary hypogammaglobulinaemia and recurrent infections, congenital AIDS and recurrent infections.

The applicant has effectively conducted a pivotal study C in 50 patients with PID. The design of the pivotal study was tailored towards FDA requirements for the licensure of IVIG product. The duration of the study was 1 year (compared to 6 months according to CHMP requirements). All patients in this study had a prior history of IVIG use and history of various infections and use of antibiotics. The PK parameters for IgG overall and individual classes of antibodies against certain serotypes of S. pneumoniae, H. influenzae B and CMV were derived from the PK subset of patients. In vast majority of patients trough levels of IgG were around the required maintenance level of 6g/L (as per recommendations from the Core SPC CPMP/BPWG/859/95 rev. 2).

There were no cases of severe acute bacterial infections in study C except the case of pneumonia which was diagnosed before the initiation of treatment with Gammaplex.

The secondary efficacy parameters indicated that the treatment was accompanied with a relatively low incidence of hospitalizations, emergency visits to the doctor, sickness leaves and absences.

The half-life for Gammaplex derived from PK subset of 24 patients with PID was 41.1 (SD +/-19.19) days for all 24 subjects analyzed. This value is comparable with half-lives of most other IVIG preparations determined in immunodeficient patients (Table 13).
Table 13. In vivo behaviour of IVIG preparations after infusion of 0.4g/kg body weight in patients with congenital humoral immunodeficiency (from Morrell, et al. 1997).

<table>
<thead>
<tr>
<th></th>
<th>Gammagard</th>
<th>Sandoglobulin</th>
<th>Gamimune-N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG plasma concentrations (g/L):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preinfusion</td>
<td>3.90</td>
<td>5.41</td>
<td>6.37</td>
</tr>
<tr>
<td>15 min after infusion (peak)</td>
<td>13.72</td>
<td>12.32</td>
<td>14.89</td>
</tr>
<tr>
<td>day 7</td>
<td>6.93</td>
<td>8.62</td>
<td>10.80*</td>
</tr>
<tr>
<td>day 28</td>
<td>3.79</td>
<td>5.78</td>
<td>6.60*</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>26</td>
<td>32</td>
<td>35</td>
</tr>
</tbody>
</table>

Pharmacokinetics of antibodies directed against bacterial and viral antigens in immunodeficient patients showed a variable pattern. Half-lives of antibodies against serotypes 4, 14, 19, 6B and 9V of *Streptococcus pneumoniae* capsular polysaccharides showed half-lives varying between 24.4-27.2 days (literature data 26-32 days) (see Table 15). Antibodies against *Haemophilus influenzae* type b polysaccharide had a somewhat shorter survival of 15.6 days (compared to an average of 23 days with the previous products: see Table 12). Interestingly, a shorter half-life for this type of antibody was pointed out previously in the literature. This could mean that consumption of the antibody isotype was selectively increased in these chronically infected patients. The half-life of anti-CMV antibodies with Gammaplex infusions was comparable to the half-lives seen with other IVIG products: 31.6 days and 32 days, respectively (Table 14).

There are certain limitations in the interpretation of PK data from study C since only a certain subset of patients was amenable for therapeutic class of antibodies measurements. Results may be influenced by a carryover effect of extrinsic IgG from previous IVIG infusions and level of chronic persistent infections.

The reassurance was provided with the evidence from study C that sufficient trough levels can be maintained using proposed 21 and 28 day regimens of Gammaplex infusions in the majority of PID patients. After a series of infusions, an equilibrium was reached and maintained around the required threshold of 6g/L level.
Table 14. Half-life of IgG antibodies in patients with congenital humoral immunodeficiencies after IVIG infusions (mean values or ranges) (from Morrell et al., 1997).

<table>
<thead>
<tr>
<th>Antibody specificity</th>
<th>$T_{1/2}$ (days)</th>
<th>IVIG preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial polysaccharides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. pneumoniae</em>, types 1, 6A, 7, 3</td>
<td>26–32</td>
<td>Gammagard, Gamimune-N, Sandoglobulin</td>
</tr>
<tr>
<td>Core lipopolysaccharide, <em>S. minnesota</em>, Re 595 mutant</td>
<td>30</td>
<td>Gammagard</td>
</tr>
<tr>
<td><em>S. pyogenes</em>, group A</td>
<td>36</td>
<td>Sandoglobulin</td>
</tr>
<tr>
<td><em>H. influenzae</em>, type B</td>
<td>23</td>
<td>Sandoglobulin</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>21–27</td>
<td>Gammagard, Gamimune-N, Ivecgam, Intraglobin</td>
</tr>
<tr>
<td><strong>Viral antigens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>32</td>
<td>Sandoglobulin</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>32</td>
<td>Sandoglobulin</td>
</tr>
</tbody>
</table>

The efficacy data derived from the pivotal study C in PID patients is sufficient alone to support the licensure of Gammaplex.

Study D in normal healthy volunteers failed to demonstrate the bioequivalence between Vigam and Gammaplex. The PK parameters established in study D for Vigam and Gammaplex (around 20-24 days) is shorter than the half-life seen in PID patients (study C). This phenomenon was previously described. In immunologically normal persons, the $T_{1/2}$ values of IVIG preparations were between 14 and 24 days, and those of various IgG antibodies between 12 and 35 days. Some of these variations were probably due to individual differences in the IgG catabolism. However, the wide range of $T_{1/2}$ values may at least in part also reflect molecular disparities of IVIG preparations and methodological differences between the studies.

On the other hand, the interpretation of PK data derived from the study in normal volunteers with an adjustment of PK parameters to the baseline levels of IgG in normal subjects can be challenging and problematic and hence should be treated with caution (Morrell et al., 1997). Therefore PID patients represent an ideal prime population for robust pharmacokinetic studies with IVIG products. Conclusively, the pharmacokinetic and the efficacy results of the pivotal study C are sufficient for claim made by the applicant in the replacement therapy.

The efficacy data derived from the pivotal study C in PID patients is sufficient alone to support the licensure of Gammaplex.

**RISKS**

No new safety risks were identified in both studies. The safety profile of Gammaplex is considered to be acceptable.
**BALANCE**
On the basis of the efficacy and safety evidence provided, the B/R ratio for Gammaplex is considered to be positive.

**CONCLUSION**
On the basis of positive benefit/risk ratio, Gammaplex is considered to be approvable.
Gammaplex

(Human normal immunoglobulin)

PL 08801/0053

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application 28th of July 2008
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 28th of July 2008
3. Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 12th December 2008
4. The applicant submitted its response to the supplementary information request in a letter dated 7th April 2009
5. The application was finalised on 27th October 2009
Gammaplex  
(Human normal immunoglobulin)  
PL 08801/0053

### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/12/09</td>
<td>Bio Variation Type II (Standard) – National</td>
<td>To extend AE data from 48 hours to 72 hours in line with the revised data submitted to FDA for Gammaplex BLA</td>
<td>Pending</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Gammaplex® is a sterile liquid of 5 % w/v normal immunoglobulin.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Human normal immunoglobulin for intravenous administration. This product is prepared from plasma from carefully screened and healthy donors. Donors are selected from the USA.

Gammaplex® contains 5 g/100 mL of human normal immunoglobulin (i.e. 50 g/L, of which virtually 100% is IgG).

Gammaplex® has an IgA content of less than 10 micrograms per mL (typically ~4 micrograms per mL) and a sub-class distribution of IgG1:IgG2:IgG3:IgG4 of approximately 62:31:6:1; this is similar to plasma.

For excipients see 6.1.

3 PHARMACEUTICAL FORM
Gammaplex® is a colourless sterile liquid for intravenous administration.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
Replacement therapy in:
- Primary immunodeficiency syndromes such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency
  - severe combined immunodeficiency
  - Wiskott Aldrich syndrome

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

Children with congenital AIDS and recurrent infections.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Posology
The dose and dosage regimen is dependent on the indication.
In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.
Replacement therapy in primary immunodeficiency syndromes
The dosage regimen should achieve a trough level of IgG (measured before the
next infusion) of at least 4 - 6 g/L. Three to six months are required after the
initiation of therapy for equilibration to occur. The recommended starting dose is
0.4 - 0.8 g/kg followed by at least 0.2 g/kg every three weeks.
The dose required to achieve a trough level of 6 g/L is of the order of 0.2 - 0.8
g/kg/month. The dosage interval when steady state has been reached varies
from 2 - 4 weeks. Trough levels should be measured in order to adjust the dose
and dosage interval.

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe
secondary hypogammaglobulinaemia and recurrent infections; replacement
therapy in children with AIDS and recurrent infections
The recommended dose is 0.2 - 0.4 g/kg every 3 to 4 weeks.

The dosage recommendations are summarised in the following table:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency of injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement therapy in primary immunodeficiency</td>
<td>- starting dose: 0.4 - 0.8 g/kg</td>
<td>every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/L</td>
</tr>
<tr>
<td></td>
<td>- thereafter: 0.2 - 0.8 g/kg</td>
<td></td>
</tr>
<tr>
<td>Replacement therapy in secondary immunodeficiency</td>
<td>0.2 - 0.4 g/kg</td>
<td>every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/L</td>
</tr>
<tr>
<td>Children with AIDS</td>
<td>0.2 - 0.4 g/kg</td>
<td>every 3 - 4 weeks</td>
</tr>
</tbody>
</table>

**Method of administration**
Gammaplex® should be infused intravenously, preferably using an intravenous
infusion set fitted with an in-line 15 micron filter, at an initial rate of 0.01 - 0.02
mL/kg/minute for 15 minutes. If well tolerated, the rate of administration may be
gradually increased to 0.04 mL/kg/minute up to a maximum of 0.08
mL/kg/minute, for the remainder of the infusion. Due to the absence of any anti-
microbial preservatives, it is recommended that administration should begin
immediately after piercing the cap.

4.3 **CONTRAINDICATIONS**
Hypersensitivity to any of the components.
Hypersensitivity to homologous immunoglobulins, especially in very rare cases of
IgA deficiency when the patient has antibodies against IgA.
Fructose intolerance (see section 4.4).

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**
Certain severe adverse drug reactions may be related to the rate of infusion. The
recommended infusion rate given under “4.2 Method of administration” must be
closely followed. Patients must be closely monitored and carefully observed for
any symptoms throughout the infusion period. Certain adverse reactions may occur more frequently
- in case of high infusion rate;
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency;
- in patients who receive human normal immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

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

Potential complications can often be avoided by ensuring:
- that patients are not sensitive to human normal immunoglobulin by initially injecting Gammaplex® slowly (0.01 mL/kg/min);
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration;

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

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

In case of renal impairment, IVIg discontinuation should be considered. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.
In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the infusion of IVIg;
- monitoring of urine output;
- monitoring of serum creatinine levels;
- avoidance of concomitant use of loop diuretics.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the side effect. In case of shock, standard medical treatment for shock should be implemented.

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

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped viruses HAV and parvovirus B19.

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

It is strongly recommended that every time that Gammaplex® is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

This medicinal product contains 50 mg of sorbitol per mL as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Special precautions should be taken with babies and young children because this fructose intolerance may not yet be diagnosed and may be fatal.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Interference with serological testing
After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient’s blood may result in misleading positive results in serological testing.
Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs’ test), reticulocyte count and haptoglobin.

4.6 PREGNANCY AND LACTATION
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the fetus and the neonate are to be expected. Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No effects on the ability to drive and use machines have been observed.

4.8 UNDESIRABLE EFFECTS
In clinical trials adverse reactions were experienced by almost 50% of the patients. The most frequent adverse reaction was headache.

Events reported for this product are (proportions of patients experiencing):
Incidence (&gt;1/100 to &lt;1/10) is defined as common, (&gt;1/10) is defined as very common

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Undesirable effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition</td>
<td>Decreased appetite, fluid retention, iron deficiency</td>
<td>Common</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Common</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Dizziness, hypoesthesia, paraesthesia, lethargy, migraine</td>
<td>Common</td>
</tr>
<tr>
<td>Ear and labyrinth</td>
<td>Vertigo, tinnitus</td>
<td>Common</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia, palpitations</td>
<td>Common</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension, hot flush, thrombosis</td>
<td>Common</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Nasal congestion, epistaxis, pharyngolaryngeal pain, bronchospasm</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, vomiting, diarrhoea, abdominal distension, abdominal pain, constipation, stomatitis</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue</td>
<td>Myalgia, arthralgia, back pain, muscle spasms, musculoskeletal</td>
<td>Common</td>
</tr>
</tbody>
</table>
**disorders and bone disorders**

| General disorders and administration site conditions | Pyrexia, fatigue, pain, asthenia, chills, chest discomfort, infusion site reaction | Common |
| Investigations | Coombs’ direct test positive | Common |

Other adverse reactions associated with intravenous immunoglobulins which may occur occasionally include allergic reactions, low blood pressure. Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

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

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

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

For safety with respect to transmissible agents, see 4.4.

### 4.9 OVERDOSE
Overdosage may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

### 5 PHARMACOLOGICAL PROPERTIES

**5.1 PHARMACODYNAMIC PROPERTIES**
Gammaplex® is in pharmacotherapeutic group: Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06B A02.
Gammaplex® contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against various infectious agents.
Gammaplex® contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors.
Gammaplex® has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma.
Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

**5.2 PHARMACOKINETIC PROPERTIES**
Human normal immunoglobulin is immediately and completely bioavailable in the recipient’s circulation after intravenous administration. It is distributed relatively
rapidly between the plasma and extravascular fluid, after approximately 3 - 5
days equilibrium is reached between the intra- and extravascular compartments.
The half-life of Gammaplex® has been found to be 21.7 days (mean after single
dose) and 35.5 days (median at steady state). This half-life may vary from patient
to patient, in particular in primary immunodeficiency.
IgG and IgG-complexes are broken down in cells of the reticuloendothelial
system.

5.3 PRECLINICAL SAFETY DATA
Immunoglobulins are normal constituents of human plasma and therefore toxicity
testing in heterologous species is of no relevance. Gammaplex® contains highly
purified immunoglobulins and has been tested in non-clinical haemodynamic
monitoring studies. There was no evidence of effects on blood pressure or heart
rate at infusion rates similar to those used clinically. At higher infusion rates of
approximately 2- to 7-fold those used clinically, a hypertensive effect was found.
No other preclinical studies have been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
D-sorbitol
Glycine
Sodium
Chloride
Acetate
Polysorbate 80

The product pH is 4.8 - 5.1.

6.2 INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE
24 months if stored unopened at temperatures between 2°C and 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Gammaplex® should be stored at temperatures between 2°C and 25°C in its
carton.
DO NOT FREEZE.
Do not use after the expiry date printed on the label. The conditions of expired or
incorrectly stored product cannot be guaranteed. Such product may be unsafe
and should not be used.
6.5 **NATURE AND CONTENTS OF CONTAINER**
Gammaplex® is a sterile colourless liquid immunoglobulin G supplied as 2.5 g, 5 g and 10 g doses. The product is contained in a clear glass bottle, closed with a stopper and oversealed with a tamper-evident cap.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**
The product should be brought to room or body temperature before use. Gammaplex® should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Any unused product or waste material should be disposed of in accordance with local requirements.

7 **MARKETING AUTHORISATION HOLDER**
Bio Products Laboratory
Dagger Lane
Elstree
Hertfordshire
WD6 3BX
United Kingdom.
E-mail: info@bpl.co.uk

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 08801/0053

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
05/10/2009

10 **DATE OF REVISION OF THE TEXT**
05/10/2009
Patient Information Leaflet

Gammaplex

(Human normal immunoglobulin)

PL 08801/0053
Labelling
Gammaplex
(Human normal immunoglobulin)
PL 08801/0053
PACKAGE LEAFLET: INFORMATION FOR THE USER

GAMMAPLEX® 2.5 G, 5 G AND 10 G.
5% W/V SOLUTION FOR INFUSION
HUMAN NORMAL IMMUNOGLOBULIN

PLEASE READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS MEDICINE.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In This Leaflet:
1. WHAT GAMMAPLEX® IS AND WHAT IT IS USED FOR
2. BEFORE YOU ARE GIVEN GAMMAPLEX®
3. HOW YOU WILL BE GIVEN GAMMAPLEX®
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE GAMMAPLEX®
6. FURTHER INFORMATION

1. WHAT GAMMAPLEX® IS AND WHAT IT IS USED FOR

Gammaplex® is a solution containing the active substance called human normal immunoglobulin (a protein in the body used to fight infections) which is obtained from blood plasma from screened donors. These donors are selected from carefully screened and healthy donors from the USA. The product is given by injection into a vein (intravenous infusion). It can be given in a hospital or for use at home and is only available on a doctor's prescription.

Gammaplex® is used to treat several illnesses. Your doctor will advise you what you are receiving Gammaplex® for.

This medicine is used to replace antibodies which are missing from your body in primary antibody deficiencies (lack of certain proteins protective against infection that you may either have been born with or may develop during life such as: agammaglobulinemia (deficiency of gamma globulins in the blood), hypogammaglobulinaemia (low levels of immunoglobulin G, IgG), with or without low IgA and/or IgM), common variable immunodeficiency (failure of the immune system to produce antibodies against infections), severe combined immunodeficiency (a severe genetic disorder of the immune system making you susceptible to infections), Wiskott-Aldrich syndrome (hereditary disorder with signs of eczema, recurring infections, and a decrease in the number of white blood cells).

Gammaplex® is also used to replace antibodies in secondary antibody deficiencies caused by: lymphocytic leukaemia (cancer of the blood where too many white blood cells are produced), some other bone marrow cancers, AIDS in children born with the disease, when repeated infections occur.

2. BEFORE YOU ARE GIVEN GAMMAPLEX®

Do not allow Gammaplex® to be given to you if you:
- are allergic to human normal immunoglobulin or any of the other ingredients of Gammaplex® (see end of Section 6). If you do experience an allergic reaction, seek medical attention immediately.
- lack IgA or have developed antibodies to IgA. Your doctor will advise you if this affects you.

Take special care with Gammaplex®

You must tell your doctor before receiving Gammaplex® if any of the following conditions applies to you. You may need to be monitored closely during treatment and the dose may have to be altered.
- diabetes
- obesity
- kidney disorder
- stroke (now or in the past)
- heart complaint (now or in the past)
- are elderly
- taking other medicines
- pregnant or breast-feeding.

Immunoglobulin infusions may also interfere with immunisation with certain viral vaccines such as measles, rubella, mumps and varicella for a period of at least 6 weeks and up to 3 months. In the case of measles, this impairment may persist for up to a year.

If you need a blood test during this period, tell your doctor when you last had an injection of Gammaplex®, as false positive results may occur with certain tests. This medicine will raise the level of various antibodies in your blood for several weeks or longer.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any that you have bought yourself from a chemist without a prescription. No other medicines or fluids should be added to this product, as their effects on the product have not been established.

Pregnancy and breast-feeding

If you are pregnant, likely to become pregnant or are breast-feeding, you must tell your doctor before receiving Gammaplex®.

Driving and using machines

There are no restrictions driving or using machines after being treated with Gammaplex®.

Important information about some of the ingredients of Gammaplex®

D-sorbitol and sodium are ingredients in this product.

Important information about some of the ingredients of Gammaplex®

D-sorbitol and sodium are ingredients in this product. If you were born with intolerance to fructose, do not use this product.

If you are on a sodium-controlled diet, tell the doctor before he/she gives you the infusion.

3. HOW YOU WILL BE GIVEN GAMMAPLEX®

Always use Gammaplex® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

DO NOT EXCEED THE RECOMMENDED DOSE. See below for full dosage recommendations. Your doctor will decide the appropriate dose. DO NOT ADD any other medicines or fluids to Gammaplex®.

The medicine is given by intravenous injection (infusion) using a giving set which your doctor or nurse will provide. The maximum safe rate of infusion is determined by your body weight. An infusion rate of 0.03 - 0.02 mL/kg/minute is recommended for the first 15 minutes, gradually increasing it to 0.08 mL/kg/minute.

To reduce the risk of side-effects, the infusion rate in the first 15 minutes must be low (0.03 - 0.02 mL/kg/minute). Some severe side effects may be caused by injecting the product too quickly.

The recommended infusion rate must be checked closely and you must be carefully observed for any symptoms throughout this period. If you feel unwell, tell your doctor and the infusion will either be slowed or stopped until you feel better.

You should remain with another person for at least 20 minutes after the infusion is complete for as long as it is the first time you have had this product.

Dosage recommendations:

- antibody deficiency disease: the dosage is initially 0.4 - 0.8 g/kg body weight every 2 - 4 weeks, then 0.2 - 0.4 g/kg body weight, depending on your clinical response and measurements of immunoglobulins in the bloodstream.
- bone marrow cancers (including leukaemia) and children born with AIDS resulting in antibody deficiencies: 0.2 - 0.4 g/kg body weight every 3 to 4 weeks.

Keep the medicine at room temperature for at least 2 hours before infusion. Do not use if there are any particles in the medicine or it is discoloured. Contact your doctor if you are not sure if your medicine is fit for use.

The product does not contain any additives to prevent the growth of germs once it has been opened. Therefore the infusion should begin immediately after piercing the cap.
This product is for single injection only. Safely throw away any used materials or unused solution. To help you, your doctor will provide instructions and a box.

If you use more Gammagrip® than you should
If you use more Gammagrip® than you should there is no cause for alarm. However, if you feel unwell afterwards or have any discomfort, tell your doctor.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Gammagrip® can cause side effects, although not everybody gets them. If you feel unwell, you must tell your doctor immediately. The risk of side effects can be minimised by making sure that the infusion rate is no more than 1.5 mL/min (see Section 3 “How you will be given Gammagrip®”).

The following side effects have also been reported to occur:

Very common side effects (affecting more than 1 in 10 people)
- headache
- Common side effects (affecting less than 1 in 10 people)
  - tiredness or weakness
  - throat pain
  - high temperature
  - chills
  - feeling or being sick
  - diarrhoea or constipation
  - increased appetite
  - fluid retention
  - low blood pressure
  - muscle pain or spasm
  - joint pain
  - body pains or stiffness
  - infection at the injection site
  - nervousness
  - nasal or eye congestion
  - pins-and-needles or numbness
  - migraine
  - ringing in the ears
  - palpitations
  - raised blood pressure
  - hot flashes
  - cold
  - chest discomfort or wheeze
  - bleeding or stomach pain
  - sore mouth
  - blood (Coombs) test positive

Rare side effects (occurring in less than 1 in 1,000 and more than 1 in 10,000 people)
- sudden fall in blood pressure, which could lead to shock
- allergic reaction

If you are using this medicine at home and you feel unwell during the infusion, stop the infusion and contact your doctor immediately. If you feel unwell during an infusion in hospital, tell the doctor or nurse. The rate of infusion will be reduced if you feel better. The rate of infusion may then be increased to that achieved when you started to feel unwell. If you still feel unwell, the infusion should be stopped, but may be resumed after about 1 hour when you are feeling better.

Please note
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure that those at risk of carrying infections are excluded, and the testing of each donation and pool of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on an infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections. The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parovirus B19 viruses. Immune globulins have not been associated with hepatitis A or parovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective. It is strongly recommended that every time you receive a dose of Gammagrip® the name and batch number of the product are recorded in order to maintain a record of the batches used.

Please remember:
If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE Gammagrip®
Keep Gammagrip® out of the reach and sight of children.

The medicine should be stored in its carton, between 2°C and 30°C. DO NOT FREEZE.

Do not use Gammagrip® if the vial or the vial is cloudy or has deposits.

Do not use Gammagrip® after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

The condition of date-expired or incorrectly stored product cannot be guaranteed.

Disposal
Safely throw away any unused materials or unused solution. To help you, your doctor will provide instructions and a box. Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION
What Gammagrip® contains
The active substance in human normal immunoglobulin, mainly immunoglobulin G (IgG) and is obtained from blood plasma from screened donors. These donors are selected from the USA.

The other ingredients are D-sorbitol, glycine, sodium, chloride, saccharose and polysorbate 80.

(see also last of Section 2 “Important information about some of the ingredients of Gammagrip®”)

Gammagrip® is slightly acidic, but this will not have any unpleasant effects as your blood will neutralise it rapidly. The maximum amount of sodium is 50 mmol/L.

The high content of Gammagrip® is less than 10 micروgrams/mL (typically about 5 micrógrams/mL).

Gammagrip® has a composition of the different types of immunoglobulins similar to that in blood.

What Gammagrip® looks like and contents of the pack
Gammagrip® is a sterile, colourless liquid. This product comes in 2.5 g, 5 g and 10 g dose sizes, with a string to hold the bottle during infusion.

Marketing Authorisation Holder, and manufacturer
BPL, Bio Products Laboratory
Dagger Lane
Elstree
Hertfordshire
WD6 1BQ
United Kingdom.
Tel: +44 (0) 20 8258 2200

Marketing Authorisation Number
PL08001/0053

Date of Revision of Text
July 2009
V5L2

For further information or if you have any questions about the use of this product, please contact BPL via the Marketing Department at the address above or by e-mail: info@bpl.co.uk.
Human Normal Immunoglobulin (Intravenous)

- Store between 2°C and 25°C. Retain vial in carton to protect from light.
- DO NOT FREEZE.

This bottle of Gammaplex® contains approximately:
5 g Human Normal Immunoglobulin Intravenous, 5 g Borohol, 0.33% g Bicarbonate, 0.28 g Sodium Chloride, 0.2 g Sodium Chloride, <0.006 g Polyethylene 4000.
Total protein concentration 9.9 g/L in a volume of 100 mL.
Acidification is achieved by adjustment with small quantities of sodium hydroxide and hydrochloric acid as required.

For intravenous use only.
- Dosage and administration: Read enclosed package insert.
- Use immediately after opening cap.
- Store out of reach and sight of children.
- Maximum infusion rate 0.25 mL/kg per minute.
- DO NOT USE UNLESS CLEAR AND FREE FROM DEPOSIT.