European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/228233/2008

ASSESSMENT REPORT FOR PRIVIGEN

International Nonproprietary Name:
human normal immunoglobulin

Procedure No. EMEA/H/C/000831

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant CSL Behring GmbH submitted on 31 January 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Privigen, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 April 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The legal basis for this application refers to: Centralised / Article 8(3) / New active substance.
Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier:
composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).
The applicant applied for the following indication:
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 (CLL) with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections

Immunomodulation
Idiopathic thrombocytopenic purpura (ITP), in children and adults at high risk of bleeding or prior to surgery to correct the platelet count

- Guillain-Barré syndrome
- Kawasaki disease

Allogeneic bone marrow transplantation
Licensing status:
Privigen has been given a Marketing Authorisation in US on 26 July 2007, and in Canada 9 January 2008.

A new application was filed in the following countries: Switzerland (26.02.07) and Australia (29.06.07).
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Christian K. Schneider** Co-Rapporteur: **Pasqualino Rossi**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 31 January 2007.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2007 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2007.

- During the meeting on 18-21 June 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 June 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 5 October 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 November 2007.
- During the CHMP meeting on 10-13 December 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- On 21, 30 January 2008 and 7 February 2008, outstanding issues were addressed in writing by the applicant.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 4 February 2008, and an updated version on 12 February 2008.
- During the meeting on 18-21 February 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Privigen on 21 February 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 20 February.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 25 April 2008.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Problem statement

Clinical indications of intravenous immunoglobulins (IVIg)
Privigen is applied for in the indications listed in the core SPC for IVIg. These include the indications based on the principle of the replacement of lacking immunoglobulins in patients with primary immunodeficiency syndromes, in patients with certain severe secondary hypogammaglobulinaemia and recurrent infections such as myeloma or chronic lymphocytic leukaemia (CLL) and in children with HIV infection and recurrent serious bacterial infections.
Another part of the mode of action of IVIg is related to the so-called immunomodulative action which refers to the indications Idiopathic thrombocytopenic purpura (ITP), Guillain-Barré syndrome, Kawasaki disease and allogeneic bone marrow transplantation.

Since the early 1980s, highly purified preparations of IgG for intravenous administration (IVIg) were developed by a number of manufacturers whereas the first products consisted of so-called modified products (modification of the Fc-part of the IgG to allow intravenous administration). Nowadays non-modified, native IVIgs are the standard of care for the replacement therapy of patients with primary immunodeficiency and they are part of the therapy regimen of the other indications mentioned before.

About the product

Privigen is a newly developed plasma-derived IVIg preparation manufactured by CSL Behring, Switzerland. CSL Behring AG.
The intermediates were manufactured in the US (intermediate fraction II+III precipitate (II+III PPT), obtained by fractionation of human plasma according to Cohn) and in Switzerland (intermediate Precipitate A (NA PPT), obtained by fractionation of human plasma according to Kistler-Nitschmann)

Privigen is a concentrated (100 g/L) liquid immunoglobulin product for intravenous use (IVIg). The product is formulated with 250 mmol/L L-proline at pH 4.8. The IgA content is typically below 25 mg/L. Other serum proteins are present in trace amounts.
Privigen is prepared from large donor pools and represents the antibody spectrum present in the donor population. IgG functionality is fully retained (Fc function and Fab mediated activity) and the IgG subclass distribution is similar to that found in normal human plasma. More than 90% of the IgG consists of monomers and dimers.

The sodium concentration of Privigen is low and the osmolality is about 320 mOsmol/kg. Privigen does not contain any preservatives. Privigen complies with the Ph. Eur. monograph for human normal immunoglobulin for intravenous administration.

Pharmacological classification
Human Normal Immunoglobulin G
ATC code: J06B A02

The following indications are applied for:

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 (CLL) with severe secondary hypogammaglobulinemia and recurrent infections
Children with congenital AIDS and recurrent infections

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

Allogeneic bone marrow transplantation

The posology is applied for as described in the core SPC for IVIg (CPMP/BWG/859/95 rev.1) and is individualised according to the clinical condition to be treated.

No separate paediatric development has been described by the applicant as it is not specifically required according to the relevant Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (CPMP/BPWG/388/95 rev.2). However, children are included in the PID study.

No formal scientific advice was obtained from CHMP.

2.2 Quality aspects

Introduction

Active Substance

- **General Information**

Human normal immunoglobulin is a highly concentrated liquid formulation of polyvalent human immunoglobulin G (IgG) for intravenous administration (IVIg). The ATC Code is J06BA02. The concentration is 100 g/L (10% w/v) and the product is formulated with 250 mmol/L L-proline as the only stabilizer at pH 4.8. The IgA content is normally below 25 mg/L. Other serum proteins are present in trace amounts.
Polyvalent human immunoglobulin G is manufactured from human plasma and is therefore a biological product. Privigen is prepared from large donor pools and represents the antibody spectrum present in the donor population. IgG functionality is fully retained (Fc function and Fab mediated activity) and the IgG subclass distribution is similar to that found in normal human plasma. More than 90% of the IgG consists of monomers and dimers. The sodium concentration of Privigen is low and the osmolality is about 320 mOsmol/kg. Privigen does not contain any preservatives.
Privigen complies with the Ph. Eur. Monograph for human normal immunoglobulin for intravenous administration. The manufacturing and control procedures for Privigen complies with the current version of the CPMP/BWP/269/95 Note for Guidance on Plasma Derived Medicinal Products. The company has selected when possible specifications and analytical methods in compliance with both the USP and the Ph. Eur.

- **Manufacture**

Manufacturers
The production Site of the Drug Substance (IgPro10-SOL) is CSL Behring AG, Bern (Wankdorfstrasse) and the production Site of the intermediates is either CSL Behring AG, Bern (Wankdorfstrasse) (manufacturer of the intermediate Precipitate A (NA PPT), obtained by fractionation of human plasma according to Kistler-Nitschmann) or CSL Behring L.L.C, Kankakee (USA) (manufacturer of the intermediate fraction II+III precipitate (II+III PPT), obtained by fractionation of human plasma according to Cohn). The manufacturers responsible for in-process controls and testing of drug substance are CSL Behring AG, Bern (Wankdorfstrasse) (in-process

controls, testing of drug substance IgPro10-SOL) and CSL Behring L.L.C, Kankakee (USA) (in-process controls. For the manufacturing site CSL Behring LLC, Kankakee, a National Competent Authority of Germany (Regierungspräsidium Darmstadt) issued a GMP certificate. For the Bern site a valid authorization to manufacture medicinal products, to import medicinal products, for the wholesale trade in medicinal products, to export medicinal products, to trade in medicinal products abroad issued by the Swiss Agency for Therapeutic Products, SwissMedic, is provided.

Description of Manufacturing Process and Process Controls
Pooled human plasma undergoes cold ethanol fractionation into either Precipitate A (NA PPT) according to the Kistler-Nitschmann procedure or Fraction II+III Precipitate (II/III PPT) according to the Cohn-Oncley procedure in facilities in Bern, Switzerland and in Kankakee, Illinois, respectively. These precipitates are the only intermediates between plasma pooling and drug substance solution (IgPro10-SOL) isolation. Therefore the drug substance is neither isolated, characterised nor stored but continuously processed to the bulk product.

The intermediates (Precipitate A or Fraction II+III Precipitate) are re-suspended in a buffer and fractionated with octanoic acid (= caprylic acid) to selectively remove certain proteins and plasma derived lipids. A following pH shift step removes IgM and aggregates, whereas the subsequent anion exchange chromatography removes almost all IgA and remaining IgM molecules leading to an IgG purity of greater than 98 %. The manufacturing process also includes four virus reduction steps: (i) octanoic acid fractionation followed by liquid/solid separation, (ii) low pH inactivation, (iii) depth filtration, and (iv) virus filtration.
The drug substance, IgPro10-SOL, is immediately further processed and formulated to the drug product (IgPro10-Bulk), which can be stored up to 8 days prior to aseptic filling into infusion bottles (final finished drug product, Privigen). Filling sizes include 50 ml, 100 ml and 200 ml. The primary packaging material is Type I and Type II glass infusion vials.

The following is a list of manufacturing process steps leading to the drug substance IgPro10-SOL.

- *cold ethanol fractionation*
- *octanoic acid (OA) fractionation,*
- *ultra- diafiltration 1*
- *low pH treatment*
- *pH shift and filtration*
- *anion exchange (AIEX) chromatography*
- *virus filtration*
- *ultra- diafiltration 2*

Description of manufacturing process and controls
The single manufacturing steps have been described in detail and precisely.
Conditions of use and reuse of materials/ Reprocessing / Reworking
No materials are reused during the fractionation process to yield Fraction II+III Precipitate. Materials reused in the method of isolation for Precipitate A have been summarised. For the manufacture of the Privigen drug substance reprocessing and reworking are not foreseen.

- **Control of Materials**

Starting Material
The starting material containing the active ingredient is human plasma which complies with the requirements of the Ph. Eur. Monograph Plasma Humanum ad Separationem and with the Note for Guidance on Plasma-Derived Medicinal products CPMP/BWP/269/95 rev.3. The starting material is registered in a Plasma Master File via the Centralised Procedure and is updated annually in accordance with Commission Directive 2003/63/EC. Human plasma collected in the USA is used for the production of the alternative starting paste (fraction II+III precipitate at the CSL Behring site, Kankakee, USA.

Ingredients used for processing meet the requirements of Ph. Eur. Caprylic acid and polysorbate 80 are both of plant origin. Filter aid meets compendial requirements, whereas other auxiliary materials and filter materials meets in-house requirements.

Controls of Critical Steps and Intermediates

Critical process steps have been identified and suitable in-process controls as well as critical quality attributes suitable for controlling the manufacturing steps were established.
The critical process modules are (i) the OA fractionation step , (ii) the low pH-treatment step, (iii) the pH shift step, (iv) the chromatography step (only pH adjustment), and (v) the virus filtration step. The only identified critical process modules for the following production of the drug product is the filling step.

Process Validation and Evaluation

Validation of intermediate Precipitate A manufacturing

The manufacturing process from plasma to Precipitate A according to the method of Kistler and Nitschmann has been comprehensively validated. This retrospective process validation included the evaluation of data from 30 consecutive manufacturing batches.

Validation of intermediate Fraction II+III Precipitate manufacturing

The Performance Qualification for the Process Validation of Fraction I and Fraction II+III Precipitation Process was executed and has successfully demonstrated conformance to the acceptance criteria specified in the protocol provided in the dossier.

Validation of Fraction II+III Precipitate Manufacturing: Transport validation

The Fraction II+III Precipitate is manufactured in Kankakee, USA and its transport to Bern, Switzerland via air freight and land/sea freight has been validated by two transport validation studies.

Validation of drug substance (IgPro10-SOL) manufacturing from intermediates

As the manufacturing process of the drug substance IgPro10-SOL is a continuous process from Precipitate A or Fraction II+III Precipitate to the bulk drug product IgPro10-Bulk, the process validation has been documented in the part of the dossier. regarding the drug product.

Manufacturing Process Development

In the development of Privigen, the goal was to establish a purification process of the drug substance for Privigen, IgPro10 – SOL, which is designed to be robust, reliable, gentle and high yielding. This process was designed to start with two different intermediates from Precipitate A manufactured according to Kistler & Nitschmann at CSL Behring AG, Berne, Switzerland, and Fraction II + III Precipitate manufactured according to Cohn at CSL Behring Kankakee.

Transfers and scale up were accompanied by an extensive program to ensure constant quality of the isolated drug substance and to understand the behaviour of the drug substance and the process requirements.
For manufacturing process development, the following procedural steps were pre-defined and tested:

- *Development of the octanoic acid (OA) fractionation,*
- *Ultra- diafiltration 1 - low pH treatment*
- *pH shift and filtration*
- *anion exchange (AIEX) chromatography*
- *virus filtration and ultra- diafiltration 2*
- *anion Exchange (AIEX) Chromatography: introduction of gradients for buffer changes*
- *anion Exchange (AIEX) Chromatography: change of chromatography column diameter*

- **Characterisation**

The drug substance is an aqueous solution of human immunoglobulins (90 – 110 g/L) isolated from human plasma. Protein composition determined by cellulose acetate membrane electrophoresis reveals a principle band with an electrophoretic mobility of gamma globulins. Human IgG is the major compound (≥ 98.0%). IgM and IgA are present in minor amounts (≤ 25mg/L each), IgE and other human plasma proteins in trace amounts. All IgG-subclasses were determined by nephelometry

against a reference preparation ultimately based on the WHO 67/97 reference material. The resulting IgG sub class distribution shows that all IgG-subclasses are not present with a typical subclass distribution because during manufacture of Privigen, the subclasses IgG3 and IgG4 are partially depleted leading to a final product with a different IgG subclass distribution as compared to the starting materials.
The drug substance is prepared from the pooled plasma of not less than 1000 but not more than 60000 donors and contains the IgG antibodies of normal subjects. The functional integrity of the IgG molecule is demonstrated by the Fc-function test.

- **Control of Drug Substance**

The drug substance, human normal immunoglobulin, is neither isolated, characterised nor stored but continuously processed to the bulk product. The manufacturing process from Precipitate A (NA PPT) or Fraction II+III Precipitate (II+III PPT) to the formulated bulk is considered as one continuous process and is not divided into sub-processes. As a consequence no specifications could be fixed or justified and no batches of drug substance could be analysed.

- **Reference Materials**

The different in house-materials used for drug product testing were described.

- **Container Closure System**

The drug substance, IgPro10-SOL, is not stored but continuously processed to the bulk product.

- **Stability**

The drug substance, immunoglobulin G solution (IgPro10-SOL), is not isolated and analyzed because the manufacturing process from Precipitate A or Fraction II+III Precipitate to the formulated bulk is a continuous process and is not divided into sub-processes with stored intermediates.-

Drug Product

- **Formulation development:**

Liquid IVIg products have limited stability mainly due to the potential of IgG to form excessive idiotype/anti-idiotype dimers and to become degraded and aggregated. Oxidative reactions induced by the oxygen dissolved in the solution are thought to be the primary cause of discoloration in protein solutions. It is known that liquid IVIg solutions have the tendency to acquire a yellowish to brownish tint during storage.
During evaluation and development of the formulation of Privigen these issues have been addressed resulting in a 10% IgG formulation, stabilized with 250 mmol/L L-proline at pH 4.8.
Low pH and the choice of the excipient L-proline , significantly reduce IgG-dimer formation. A comparison of IVIg preparations formulated with either L-proline or glycine shows that, under the conditions analyzed, the presence of L-proline resulted in a 30% reduction in dimer content as compared to the corresponding glycine formulation.

Overages:
Overages in Privigen are used only to compensate for volume that is unable to be withdrawn. The overages are within pharmacopoeia recommendations.

Physicochemical and biological properties:
The distribution of IgG subclasses is similar to that found in normal human plasma (approximate values are IgG_1, 67.8%; IgG_2, 28.7%; IgG_3, 2.3%; and IgG_4, 1.2%). The reactivity to a variety of investigated antigens relevant for the efficacy of Privigen has been retained in the final product.
Fc-function of Privigen was evaluated in stability studies under real temperature, accelerated and stress conditions.

Test parameters for the final product include a large number of physicochemical, biological and immunological assays.These batch data are clearly inside the specification-range and demonstrate uniformity of the product and show consistency of the manufacturing process.

Manufacturing Process Development
The manufacturing steps 0.2µm Filtration, Sterile Filtration, Aseptic Filling, Visual Inspection and Labelling & Packaging were not part of the development activities for the Privigen drug product as the production methodology of other immunoglobulin preparations could be applied directly. The formulation development for Privigen was based on small scale experimental work and was completed before the process transfer from a small production facility to the commercial production plant.

In the early development phase Privigen was filled manually (e.g. for formulation development including preliminary stability studies). Privigen produced in the commercial plant for clinical and stability studies was filled on an aseptic filling line which is used for commercial filling. Twelve bulk lots manufactured so far as well as their associated 29 filling lots have been manufactured from both, Precipitate A and Fraction II+III Precipitate for the purposes of clinical testing, process validation and stability testing. IPCs of all batches manufactured demonstrate acceptable lot-to-lot consistency for microbiological attributes and for protein content.

Container Closure System
The Container Closure System is described in the dossier. In general, the selected containers and closures meet the requirements and quality standards.

Microbiological Attributes
Privigen does not contain any antimicrobial preservatives and is tested for sterility and for exogenous pyrogens on a lot-by-lot basis prior to batch release. To ensure the product stability throughout the shelf-life of the drug product, container closure integrity has been validated through a program of microbial container closure integrity tests (microbial CCIT) during the development phase of Privigen. Container closure integrity has further been confirmed by the sterility tests performed within the ongoing stability programs after 12 months storage time.

- **Manufacture**

Manufacturer
The manufacturing process of the final product is performed at CSL Behring AG, Bern Switzerland.

Batch Formula
The average batch size of IgPro10-SOL is 200 kg resulting from variable amounts of either Precipitate A or Fraction II+III Precipitate..

Description of the Manufacturing Process and Controls
It is well demonstrated that the process is carried out under aseptic conditions and under pharmaceutical control in accordance with the rules of Good Manufacturing Practice. The manufacturing and control procedures for Privigen complies with the current version of the CPMP/BWP/269/95: Note for Guidance on Plasma Derived Medicinal Products.
The drug substance IgPro10–SOL is neither isolated nor stored at any time. IgPro10–SOL is directly formulated to IgPro10-Bulk.

The manufacturing process from the drug substance, IgPro10-SOL through formulation (IgPro10-Bulk), including subsequent aseptic filling and packaging is listed below:

- formulation
- sterile filtration
- aseptic filling
- visual inspection
- packaging

Controls of Critical Steps and Intermediates

The identification of critical parameters (PCPs) and quality attributes (QATs) has been performed by the review of the manufacturing procedure, process validation data, adventitious agents safety evaluation reports, sterile filter validation, and other developmental data with regard to safety, quality, identity, purity, potency, and robustness of the product.

Process Validation and/or Evaluation

Scope of the studies for Privigen are bulk manufacturing (IgPro10-Bulk) and filling of the final product. Bulk manufacturing comprised production of the drug substance (IgPro10-SOL) including final formulation (IgPro10-Bulk). Filling comprised the process of sterile filtration, aseptic filling and visual inspection of the drug product. The critical process parameters and critical quality attributes for process validation were evaluated and defined in risk analyses. All validation studies revealed that the entire production process of Privigen has been acceptably validated. It can be concluded that the production conditions and filling equipment are proficient to achieve a final product that meets the specifications.

- **Control of Excipients**

The control of excipients was found to be adequate with reliable analytical procedures and well justified specifications. The excipients used are L-Proline, which is of plant origin and Water for Injection (WFI), which is generated on siteSpecifications comply with Ph. Eur. and USP. No excipients of animal or human origin are used.

- **Control of Drug Product**

Proposed specifications for the drug product are in compliance with the requirements laid down in the Ph. Eur. Monograph “Human normal immunoglobulin for intravenous administration”. For additional tests separate specifications have been fixed. The specifications for some of the parameters are even tighter than those required.
Results of the analysis for 29 filling lots, manufactured from 12 different bulk lots demonstrate uniformity of the product and show consistency of the manufacturing process.

- **Reference Standards or Materials**

Reference standards used for drug product testing were described.

- **Container Closure System**

Protection of the dosage form, prevention of microbial contamination, compatibility of drug product with container and closure, and product safety were key considerations during the selection of primary and secondary packaging materials. The selected glass containers and rubber stoppers fulfill Ph. Eur. requirements. A cardboard outer box designed for the final market presentation will protect Privigen from light. The bottle sizes offered are 50 ml, 100 ml and 200 ml.

- **Stability**

The stability data of Privigen has been derived from lots that were manufactured from the intermediates Precipitate A (NA PPT) or Fraction II+III Precipitate (II+III PPT) from different sites and different glass types (I & II) in the intended future commercial facilities. Two types of stability studies have been performed: long-term and accelerated stability studies. The stability studies, including the selection of test parameters and test intervals, were performed according to ICH guidelines Q1A (R2) and Q5C.

The study bracketing design complies with the comparability approaches for intermediates and bottle sizes make use of a bracketing design according to ICH Guideline Q1D.

The submitted stability data for the drug product filled in 50 or 100 ml **glass type I vials** justify the acceptance of a shelf life of 36 months (at ≤ 25°C). However, the submitted stability data (bracketing study design) for the drug product filled in 50 or 200 ml **glass type II vials** currently justify only a shelf life of 24 months (at ≤ 25°C)in accordance with ICH Guideline Q1E (Evaluation for Stability Data).

Therefore, a shelf life of **24 months** (at ≤ 25°C) for the drug product, independently from the type of glass vial, has been accepted.
Based on the results of the ongoing stability studies, this shelf life might be extended to the applied shelf life of 36 months.

APPENDIX

1. Facilities and Equipment

The Privigen production process begins with the fractionation of human plasma at CSL Behring AG Berne, Switzerland and CSL Behring LLC, Kankakee (Illinois) USA to yield intermediate Privigen starting materials, Precipitate A and Fraction II+III Precipitate, respectively. These intermediates are further processed at CSL Behring AG Berne to yield Privigen final product.
The CSL Behring LLC Kankakee site is regularly inspected by a European health authority. The Fraction II+III Precipitate production areas, amongst others, were GMP certified by the German Health Authority RP Darmstadt/PEI upon successful inspection.
All Privigen production operations at CSL Behring are performed in already licensed and inspected facilities with the exception of intermediate subfractionation and IgPro10-bulk purification. These two manufacturing steps take place in an entirely new production plant, at the CSL Behring AG Berne facility. The CSL Behring AG Berne production site is regularly inspected by the Swiss health authorities Swissmedic.
All methods, procedures, and operations used for the manufacture and distribution of CSL Behring human plasma derived medicinal products comply with current Good Manufacturing Practices (cGMP). Furthermore, all activities conducted at CSL Behring Bern and Kankakee sites are in compliance with local laws and regulations.
A description of all the facilities for the commercial manufacture, the product flow, material flow and personnel flow are provided. The preparation, cleaning and sterilisation of the equipment are described. The prevention of cross contamination is illustrated. Floor plans for all facilities are provided.
Overall the information is very detailed and fully complies with current requirements.

2. Adventitious agents safety

Risk on contamination with animal TSE
No material used in the manufacturing of Human normal immunoglobulin Privigen is of risk that could be affected by the "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products".
In the manufacturing process of Human normal immunoglobulin Privigen, no material of human origin, other that human plasma is used.

Adventitious viruses
Normal human immunoglobulin Privigen is manufactured from human plasma. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Plasma is collected in Austria, Denmark, Switzerland, Germany and the USA and single donations are screened by an adequate testing program for viral infections (anti-HIV-1 and 2 antibodies, HBs antigen and anti-HCV antibodies).
Manufacturing pools are tested for HIV-1 and 2 antibodies, HBs antigen and HCV RNA. Furthermore, testing of the manufacturing pools is performed by NAT for HIV-1 RNA, HBV DNA and parvovirus B19 DNA. Donors with an increased risk for sporadic or variant Creutzfeldt-Jakob-Disease are excluded. The donor selection and plasma donation testing strategy for viral markers is considered adequate. The immunoglobulins are purified from two alternative starting pastes (precipitate A from

Kistler-Nitschmann or fraction II+III precipitate from Cold-Ethanol Fractionation). No animal-derived TSE risk material is used during production.
Effective reduction of prion protein during octanoic acid fractionation, CH9/Z^+-filtration and filtration using Pall DV20 has been demonstrated. In addition, several steps for virus inactivation/removal have been introduced into the manufacturing process: (1) octanoic acid fractionation followed by liquid/solid separation, (2) low pH treatment, (3) CH9/Z^+ clarifying depth filtration, and (4) Pall DV20 filtration. Effective inactivation/removal of enveloped viruses has been demonstrated for three out of four validated production steps (octanoic acid fractionation followed by liquid/solid separation, low pH treatment, Pall DV20 filtration). The 20 nm-filter has been demonstrated to remove effectively the small non enveloped model virus MMV. Therefore, it is reasonable to postulate a similar or higher reduction capacity for the larger enveloped viruses such as HIV, HBV, HCV and most enveloped viruses including also the non enveloped Hepatitis A virus. The combination of four production steps with different mechanisms for virus inactivation or virus removal (octanoic acid treatment, low pH, precipitation and depth filtration, Pall DV20 filtration), results in a high overall reduction capacity for enveloped viruses and an acceptable reduction capacity for the non enveloped Hepatitis A virus and parvovirus B19. In summary, virus safety has been convincingly demonstrated.

General comments on compliance with GMP

The manufacturing of the Active Ingredient takes place at two different sites. Manufacturing site 1 is CSL Behring AG, Wankdorfstrasse 10, 3000 Bern 22, Switzerland and manufacturing site 2 is: CSL Behring LLC, PO Box 511, Kankakee, IL, 60901, USA.
Manufacturing site 1 (CSL Behring AG, Bern) has been last inspected by Swiss Medic on 21 – 23 June 2005 and was found to be in GMP compliance. Therefore an inspection of this site was not requested during the procedure.
For the manufacturing site 2 (CSL Behring LLC, Kankakee) a National Competent Authority of Germany (Regierungspräsidium Darmstadt) issued a GMP certificate for this site valid till 30/09/2008. Therefore an inspection of this site is not requested.
The manufacturing of the finished drug product is performed also at CSL Behring AG, Wankdorfstrasse 10, 3000 Bern 22, Switzerland (see above).

Since Privigen is a plasma-derived product, it is subject to OMCL batch release. During the assessment phase a pre-licensing experimental testing of the drug product was performed. For that reason samples of three commercial batches were submitted to the Paul-Ehrlich-Institut, where it was analyzed with respect to the marketing authorisation application. Each batch complies with the product specification.

Discussion on chemical, pharmaceutical and biological aspects
Based on the submitted data, the marketing authorisation application for Privigen is recommended for approval based on quality grounds.

2.3 Non-clinical aspects

Introduction

There is a history of safe use and proven efficacy of IgG formulations in humans. Privigen belongs to a well known and characterized biological product family and it complies with all the Pharmacopoeial requirements (Ph. Eur. monograph 01/2006:0918)
Considering this and due to the xenoreactivity of human IgG, Privigen was not examined in the full battery of pharmaco-toxicology studies, according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).

Pharmacology

- Primary pharmacodynamics

The active ingredient of Privigen is human polyvalent normal immunoglobulin G (IgG); ATC code: J06BA02. The structural and functional integrity of the IgG molecules are maintained during the manufacturing process of Privigen. Primary pharmacodynamic evaluation with *in vitro* assays showed proper Fab and Fc function of Privigen. Fab function was assessed with ELISA type assays (anti HBs, anti parvo B19), or with haemagglutination (anti measles), nephelometry (anti streptolysin) or biological assays (anti-polio, anti-diphtheria toxin). With *in vitro tests* the main two Fc functions of IgG the complement activation (by complexed IgG by an erythrocyte lysis assay according to Ph. Eur.) and the interaction with Fcγ-receptor (with purified human neutrophils in a chemiluminescence assay) were measured.
Human normal immunoglobulin contains the IgG antibodies present in the normal population. The mechanism of action in indications other than replacement is not fully elucidated, but includes immunomodulatory effects. (CPMP/BPWG/859/95 rev.1)

- Safety pharmacology programme

Privigen belongs to a well known and characterized biological product family and it complies with all the Pharmacopeial requirements (European Pharmacopoeia monograph 01/2006:0918)

For this reason, the studies examining general pharmacodynamic effects are focused on the excipient L-proline. This is acceptable also according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).
L–proline is a nonessential neutral amino acid and a component of nutritional proteins; the daily intake with food is about 5.2 g. The normal L–proline plasma level is in the range of 266 ± 35 µmol/L. L–proline is formed from and metabolized to glutamate. L–proline belongs to a group of amino acid with low excitatory potential. Some neurological effects of L–proline are described in the literature:
For L-proline, no literature data were available in which the application route or duration was comparable to an i.v. infusion of the amino acid with Privigen, therefore, two non-clinical studies (1657/ZLB/02 and PSR 08/06) were performed

study No. 1657/ZLB/02:
A safety pharmacology study (Irwin test) in rats was conducted under conditions relevant for the clinical situation, i.e. a 7 hrs/day infusion, which simulates a high dose infusion of Privigen to patients. In this study L–proline was compared to glycine, a broadly used excipient in IVIG solutions that is neurologically active. Groups of ten male rats were intravenously infused with two doses of L–proline (579 and 1449 mg/kg bw/day) or glycine (378 and 945 mg/kg bw/day) for 7 hours during the first 4 days and during approximately 3 hours on day 5. The lower dose of L–proline corresponds to twice the maximum daily dose applied in the clinical studies with Privigen. A control group was infused with physiological saline and a second control group consisted of non-treated animals. Behavioral measurements (autonomic, sensorimotor functions, convulsive behaviour and excitability) were performed on Day 1 (during infusion) and Day 5 (during infusion and 10 min after the end of the infusion) according to Irwin and Moser. Rectal temperature was measured individually on Day 1 before and during infusion and on Day 5 before, during and 10 min after infusion.
L–proline did not significantly affect the behavior of animals during and after infusion at both doses tested.

study No. PSR 08/06:
This study in rats was designed to assess acute neurotoxicty of L-proline at very high L-proline serum concentrations, measuring clinical signs and L-proline serum concentrations after s.c. or i.p. bolus injections.
Groups of six female rats were subcutaneously injected with 2 g L-proline/kg bw or intraperitoneally with 2 and 4 g L-proline/kg bw, respectively. Animals of two control groups were subcutaneously and intraperitoneally injected with sodium chloride solution of the same osmolarity as the high-dose L-proline solution used. Clinical signs with special reference to neurotoxicity were assessed during 24 hours. Blood samples for measurement of L-proline serum concentrations were also collected.
After subcutanous injection of 2.0 g L-proline/kg bw which resulted in maximum serum concentrations of 12 mmol/L, no clinical signs were found. All other groups of animals including

control group animals showed comparable clinical signs primarily shortly after test article administration.
Following i.p. injection, a high variation in L-proline serum concentrations between animals within the same test article group was observed. Conclusions as to the toxicity of L-proline are therefore only drawn from results obtained after s.c. administration of L-proline.

No significant effects on behaviour (Irwin test) at doses of L-proline up to 5 times the maximum dose administered with Privigen in clinical studies were found except for a slight rise of body temperature after 5 days of treatment.
After single s.c. application of 2 g L-proline/kg bw/day to female rats, leading to much higher serum concentrations than achieved with an i.v. infusion scheme, no clinical signs of neurotoxicity, especially no signs of seizures, were observed. Thus, no neurological effects of L-proline as excipient of Privigen are therefore expected in patients at the recommended dosage regimen. This was in agreement with the two clinical trials with Privigen supporting this application (ZLB03_002CR and ZLB03_003CR) where no unexpected neurological adverse events were found.

According to the proposed labeling, Privigen is also indicated to be used in children.
In order to address literature data on putative effects of high doses of L-proline on brain development CSLB performed a **Morris water maze task- study in newborn rats** with subcutaneous administration of L-proline with daily L-proline doses up to 4 g/kg and an application scheme reflecting the clinical situation of ITP (daily dose on 2-5 consecutive days) and PID patients (once every 2-4 weeks). Privigen administration under the PID treatment schedule can be considered as a single dose ($t_{1/2}$ of L-proline approx. 5 hours). The daily animal doses were more than 10-12 times higher than the human dose used in ITP (1g/kg IVIg; corresponding to 287.5 mg/kg L-proline), more than 13-17 times higher than the human dose in PID (up to 800mg/kg IVIg; corresponding to 230 mg/kg bw L-proline) and more than 5-6 times higher than the human dose in Kawasaki disease (single dose of 2g/kg IVIg; corresponding to 575 mg/kg L-proline). Morris water maze performance was tested at postnatal days 54 to 71, and the treated rats showed no change in spatial memory acquisition or retention as compared to the control rats, which themselves showed good learning and reproducible performance. Previous published studies used L-proline subcutaneous injection twice a day from day 6 to day 28 of age in a row, but this does not reflect the application scheme of Privigen. The different application scheme is the reason for the different observations obtained in previous published studies.

Pharmacokinetics
Studies investigating the pharmacokinetics, metabolism and elimination of the IgGs contained in Privigen were not performed. This can be considered in line with the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95). Pharmacokinetic data of Privigen were assessed in clinical studies and found to be as expected for a native IgG and comparable to the pharmacokinetics of other IVIG products.
For the excipient L-proline toxicokinetic parameters were mainly investigated using satellite groups in toxicity studies. The dosing regimen in animals was the intravenous route with a dosing time of 7 hours/day thus simulating a human high-dose IVIG infusion. Toxicokinetics was assessed in rats up to daily doses of 1449 mg/kg bw/day which is 5 times the maximum daily dose investigated in clinical trials with Privigen and represents the maximum L-proline dose that can be administered to animals by the i.v. route.

Pharmacokinetic data of L-proline were collected during toxicology studies in rats intravenously administered with L-proline for 5 and 28 days, respectively, and from an embryo toxicity study with dosing from Day 6 to Day 17 of gestation.

- In a 5-day repeat-dose intravenous dose finding study **(Study No. 925/034)**, groups of male rats were administered daily for 7 hours with low and high dose L–proline (579 and 1449 mg/kg bw/day). There was a dose-dependent increase in the peak serum concentration of L–proline up to 13 – 14 times baseline levels, equivalent to approximately 4.0 mmol/L for the high dose group. Three hours after the start of the infusion 83 and 71% of peak concentrations were reached at low and high dose L–proline, respectively. There was no indication of accumulation of L–proline in serum in both the doses tested.

- In a 28-day repeated dose intravenous study **(Study No. 925/035),** groups of female and male rats were administered daily for 7 hours with low and high dose L–proline (579 and 1449 mg L–proline/kg bw/day) as in the study before. There was a dose–dependent increase in the peak serum concentrations of L–proline, up to 14 and 9 times baseline levels for males and females, respectively. Maximal serum levels of 3.1 - 4.1 mmol/L and 2.2 - 2.8 mmol/L L–proline were found at termination of the infusion on days of measurements at the high dose level for males and females, respectively, without a trend to an increase or decrease during the 4 weeks of the study. No accumulation of L–proline occurred at both doses as serum concentrations of L–proline were similar to baseline levels during the treatment period before daily infusions. As expected, total daily excretion of L–proline in urine was low.
- In a single dose pharmacokinetic study (**Study No. PSR 08/06**) groups of female rats were injected s.c. with 2.0 g L-proline/kg bw, or i.p. with 2.0 or 4.0 g L-proline/kg bw. Control groups received i.p. or s.c. injections of sodium chloride solution of the same osmolarity as the high-dose L-proline solution. Peak serum concentrations of 12 mmol/L (mean; 70 fold baseline) for s.c. treated animals and up to 18 and 43 mmol/L after i.p. administration were reached 15 min after injection. L-proline was eliminated quickly from the serum with baseline levels reached at 8 hrs after injection for all animals except one high-dose i.p administered animal. Following i.p. injection, a high variation in L-proline serum concentrations between animals within the same test article group was observed.
- In an intravenous teratogenicity study (**Study No. AA30034**) L–proline and glycine were compared. Groups of pregnant rats were administered from Days 6 – 17 of gestation over 7 hours/day with 300 mmol/L L–proline (42 mL/kg bw/day equivalent to 1449 mg/kg bw/day) or 300 mmol/L glycine (42 mL/kg bw/day equivalent to 945 mg/kg bw/day) or, as a control, physiological saline (42 mL/kg bw/day). Serum concentrations of L–proline and glycine were assessed on Days 6 and 17 of gestation before and at the end of the infusion. Mean maximal serum levels on Days G6 and G17 were 3.53 mmol/L and 2.57 mmol/ L–proline in the animals infused with L–proline, and 1.67 mmol/L and 1.23 mmol/L glycine in the animals infused with glycine, respectively. No accumulation of L–proline and glycine occurred. Serum concentrations of glycine were only marginally influenced by L–proline infusions and vice versa.

The mean C_{max} obtained at the highest dose tested in these rat studies are summarized and compared to C_{max} obtained in humans in the clinical studies including the ITP study where a daily human dose of 1 g IgG/kg bw was infused (data from studies ZLB03_002CR and ZLB03_003CR).

Mean Cmax of L-proline serum concentrations in animal studies compared to clinical studies

Rat Study Duration	L-proline: mean C_{max} at highest dose tested	Ratio of mean C_{max} obtained in rats and PID/ITP patients*
Safety Pharmacology and Pharmacokinetics; exploratory study - Single dose, s.c. **Study No. PSR 08/06**,	12 mmol/L	6.3/3.8
Repeat dose toxicity - 5 days **Study No. 925/034**,	4.0 mmol/L	2.1/1.3
Repeat dose toxicity - 28 days **Study No. 925/035**	3.1 – 4.1 mmol/L (males); 2.2 – 2.8 mmol/L (females)	1.6-2.2/1.0-1.3 1.2-1.5/0.7-0.9
Reproduction Toxicity (segment II) **Study No. AA30034**,	2.6 – 3.5 mmol/L	1.4-1.8/0.8-1.1

- Mean C_{max} of L-proline obtained transiently in clinical PID Study (ZLB03_002CR): 1.9 mmol/L.
- Mean C_{max} of L-proline obtained transiently in clinical ITP Study (ZLB03_003CR): 3.2 mmol/L.

Toxicology

- Single dose toxicity

Human immunoglobulins are naturally occurring proteins with a well-known safety and tolerability record. Constituents used during manufacturing are well known, widely used in marketed plasma derived products and controlled in Privigen. Because of the slightly acidic pH of the product (pH 4.8), toxicity assessment of Privigen focused on local tolerance: a local tolerance study with Privigen was conducted to assess putative local reactions in rabbits after i.v., i.a. and p.v. application (**Study No. 143.143.482**). In addition a local tolerance study in rabbits was conducted with s.c. administration of Privigen (**Study No. 143.143.552)**. The results of the studies are described in the "Local tolerance" section. This approach is acceptable, according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).

- Repeat dose toxicity (with toxicokinetics)

No repeat dose toxicity studies were performed with Privigen, since human immunoglobulins administered to animals can be expected to initiate the immunological response, which would interfere with the toxicity evaluation (CPMP/ICH/302/95).
Two repeat dose toxicity studies with L-Proline were conducted in rats by continuous i.v. infusion:

-Study No. 925/034: In a 5-day repeat-dose intravenous dose finding study, groups of male rats were administered daily for 7 hours with low and high dose L–proline (579 and 1449 mg/kg bw/day). Other groups of rats were infused with low and high dose glycine (378 and 945 mg glycine/kg bw/day) or with physiological saline. Serum concentrations of L–proline and glycine were assessed on Day 1 (before infusion, 3 hrs after the start of the infusion and at the end of infusion), on Day 2 (before infusion) and on Day 5 (before infusion, 3 hrs after the start of the infusion and at the end of infusion).
The high dose level represented the maximal daily dose that could be infused in the animals. There were no signs of toxicity in either dose group with glycine or L-proline. The No Observed Adverse Effect Level (NOAEL) was therefore the high dose level, i.e. 1449 mg L–proline/kg bw/day and 945 mg glycine/kg bw/day, respectively. The high dose was considered appropriate as upper dose in the final 28-day toxicity study.

-Study No. 925/035: In a 28-day repeated dose intravenous study, groups of female and male rats were administered daily for 7 hours with low and high dose L–proline (579 and 1449 mg L–proline/kg bw/day) as in the study before. Other groups of rats were infused with low and high doses of glycine (378 and 945 mg glycine/kg bw/day) or with physiological saline. Serum concentrations of L–proline and glycine were assessed on Days 1, 7, 14 and 28 before and at the end of the infusion. Urine was collected at termination during 24 hours.
The high dose group represented the maximal daily dose that could be infused in the animals and was well tolerated and not associated with any marked changes indicative of toxicity. There were no unscheduled deaths throughout the study. No treatment-related clinical signs were observed in any group and there were no treatment-related eye lesions. There was no obvious influence of treatment on the hematology and serum clinical chemistry parameters. There were no treatment-related effects on the urine parameters. No obvious effects of treatment with L–proline and glycine were observed in organ weights, or after macroscopic and microscopic examinations of the tissues. The only treatment-related changes were slight (not statistically significant) reductions in body weight gain and food consumption during the first two weeks of treatment, especially in males. These affected principally the animals treated with both doses L–proline, and glycine at 945 mg/kg/day, whereas glycine at 378 mg/kg/day was not affected. NOAELs of 1449 mg/kg/day for L–proline and 945 mg/kg/day for glycine could be established under the defined experimental conditions.

- Genotoxicity

Human IgGs cannot interact directly with DNA or chromosomes in intact human cells. Genotoxicity testing of Privigen is therefore not appropriate, according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95). The absence of direct genotoxicity has been demonstrated for L-proline in combination with nicotinamide and L-isoleucine using a variety of assays such as the Ames test, *in vitro* cytogenicity assay, a bacterial stress gene (Pro-

Tox) assay and a bone marrow micronucleus assay in mice. Published literature substantiates that L-proline is not mutagenic in the Ames test, a microsomal mutagenesis assay or a host-mediated assay.

- Carcinogenicity

Both Privigen and the excipient L-proline, are endogenously available. Carcinogenicity studies are not appropriate for human IgG**,** according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).

- Reproduction Toxicity

No reproductive and developmental toxicity studies were conducted with Privigen. For a human immunoglobulin preparation with its various non-relevant interactions within the animal models this approach is considered as acceptable, according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95).
A teratogenicity (segment II) study with L-proline was performed in rats. No indications of maternal- or embryo-toxicity or teratogenicity at the daily dose of 1449mg/kg bw tested were observed.
In the SPC section 4.6 Pregnancy and lactation, a wording in line with the EU Core SPC for Human Normal Immunoglobulin For Intravenous Administration (IVIg) (CPMP/BPWG/859/95 rev.2) has been included as proposed.

- Local tolerance

Privigen is formulated at a slightly acidic pH (pH 4.8). To evaluate whether this property of the product would affect tolerability upon s.c. infusion, a local tolerance study in rabbits was performed with Privigen in comparison to products of higher protein concentration and higher pH. A second local tolerance study in the rabbit was conducted to assess putative local reactions after i.v., i.a. and p.v. application of Privigen.

In the local tolerance study investigating s.c. application of various IG products (**Study No. 143.143.552**) female and male rabbits were s.c. treated with 0.5 mL Privigen (by injection) on one side and 2.5 mL/kg bw Privigen (by infusion) on the opposite side of the animals. The dose of 2.5 ml/kg corresponds to about three times the maximum human dose per infusion site when calculated according to body weight. Physiological saline served as a control and was applied to the same animals. Other groups of animals received IgPro20, IgPro16, IgPro18, three products with the same formulation as Privigen, but at 20%, 16% and 18% protein concentrations, respectively. Yet another group received the marketed SCIG Beriglobin P, a product of nearly physiological pH and 16% protein concentration. Finally the excipient solution without protein, i.e. a solution of L-proline (250 mmol/L L-proline, pH 4.8), was evaluated in another group of rabbits. Clinical observations were performed twice daily on the day of application and daily until 96 hrs after test article applications. No notable differences between s.c. bolus injection and s.c. infusion were found. The frequency and intensity of edema formation correlated with the protein concentration of the test articles and suggested a protein-dose dependent effect. Pain assessment did not reveal major differences between test articles and saline and no abnormalities were obtained upon histological examination of the application sites.

In the second local tolerance study (**Study No. 143.143.482**) i.v., p.v. and i.a. application of Privigen was investigated. Privigen (0.5 mL per injection) was shown not to cause any significantly increased (quantitative and qualitative) local reactions at the i.v. and i.a. application sites of the right ears of rabbits, in comparison with the left "control" ears treated similarly with saline. Effects were slightly pronounced after test article injection compared to saline in the p.v. group. After 8 days, there were no treatment-related pathology findings. It was concluded that a single administration of Privigen i.v., p.v. and i.a will be locally tolerated. p.v. administration of Privigen may cause slight irritations within the first 24 hours.

Ecotoxicity/environmental risk assessment

Each of the components of Privigen is a naturally occurring substance in humans, animals and plant species, which can be degraded in the environment. According to the Guideline EMEA/CHMP/SWP/4447/00 on the environmental risk assessment of medicinal products for human

use, the lack of an ERA is acceptable for this product. This product is not considered to be a risk for the environment.

Discussion on main safety non-clinical aspects

There is a history of safe use and proven efficacy of IgG formulations in humans. Considering this and due to the xenoreactivity of human IgG, Privigen was not examined in the full battery of pharmaco-toxicology studies. This is acceptable, according to the note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95)
Privigen is formulated at a slightly acidic pH (4.8) in the presence of 250 mmol/L L-proline as the unique stabilizer for the IgG in solution. L–proline is known to be well tolerated in humans, and there is a long history of safe parenteral administration of high doses as medicinal products for parenteral nutrition, also indicated for premature and/or newborn babies.
Nevertheless, pharmacological studies have shown that very high concentrations of L-proline can produce excitotoxicity after direct injection into the brain. The effects of acute administration of large doses of L-proline sufficient to produce higher mean plasma L-proline concentrations of up to 12 mmol/L were evaluated. No agent-specific adverse signs were observed.
Moreover, a number of other published studies have indicated that neonatal rats can develop transient acute signs of poisoning and slight lasting neurobehavioral and neurochemical effects after repeated subcutaneous administration of L-proline at doses that produce mean peak plasma concentrations of 14 mmol/L. This may reflect a special sensitivity of the neonate to repeated very high plasma L-proline
To further investigate the influence of high doses of L-proline on the CNS and the developing brain, CSLB performed a Morris water maze task- study in newborn rats, using different application schemes from the published studies, and reflecting the application scheme of L-Pro in Privigen. The treated rats showed no change in spatial memory acquisition or retention as compared to the control rats, which themselves showed good learning and reproducible performance. The results were thus reassuring and suggested a non-neurotoxic potential of L-Proline, administered as an excipient with Privigen, on the developing brain.

2.4 Clinical aspects

Introduction

The single-arm open-label, prospective, multi-centre Phase III studies submitted were performed to support the following 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 (CLL) with severe secondary hypogammaglobulinemia and recurrent infections
Children with congenital AIDS and recurrent infections

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

Allogeneic bone marrow transplantation

The posology is applied for as described in the core SPC for IVIg (CPMP/BWG/859/95 rev.1) and is individualised according to the clinical condition to be treated.

The studies are in line with the current Guideline (CPMP/BPWG/388/95 rev. 1) and encompass the following trials.

- **Study ZLB03_002CR** to assess safety and efficacy in 80 subjects with Primary Immunodeficiency Disease – PID
- **Study ZLB03_003CR** to assess safety and efficacy in 57 subjects with Idiopathic Thrombocytopenic Purpura – ITP.

In **Study ZLB03_002CR** a subset of 25 patients was evaluated for pharmacokinetics. Trough levels were determined in the entire population.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

PK properties of Privigen were determined in the study ZLB03_002CR performed in PID patients. All subjects had been receiving stable IVIg replacement therapy for at least 6 months prior to study start. Trough IgG levels were assessed for all subjects (N=80) before and during the 12-month study additional PK parameters were studied in a subset of 25 subjects using blood samples taken after the 7th infusion of the 3-week treatment schedule or after the 5th infusion of the 4-week treatment schedule. These parameters included serum concentrations of total IgG, IgG subclasses, and specific IgG. Based on serum concentrations of total IgG, the following PK parameters were determined: Cmax, Cmin (trough level), Tmax, AUC0-t, CLtot and t½.

The median steady state trough level of total IgG in 79 patients achieved after the administration of Privigen was 9.18 g/L and thus clinically adequate. These levels are above those required in the SPC CPMP/BPWG/859/95 rev.2 of 4-6 g/L and fulfil the current clinical requirements. The median trough levels observed with a 3 and 4 week dosing schedule do not differ noticeably.

The median terminal half-life of Privigen for total IgG was 36.6 days (min: 20.6; max: 96.6 days. This result is in keeping with the data from other IVIG products and from the literature. The half-life is known to be fairly long in PID patients with a wide inter-patient variability, thus the large range of 20.6 – 96.6 days and the deviation of the mean (43 days) from the median (36.6.days).

The median AUC levels for total IgG were 298.6 day x g/L for the 3 week dosing schedule and 366.7 day x g/L for the 4 week dosing schedule

The median Cmax was 23.4 g/L (min 10.4, max: 34.6) and the median Tmax 2.3 hours after the start of the infusion (min1.3 and max 26.3h).

The results obtained in this study are in keeping with those reported in the literature and with other studies using similar products, also complying with the current standards requested by the Guideline CPMP/BPWG/388/95-rev.1 for PID patients.

Pharmacodynamics

Not applicable. PD studies are not requested by the Guideline (CPMP/BPWG/388/95 rev. 1). The text of the core SPC (CPMP/BPWG/859/95 rev.1) under 5.1 Pharmacodynamic properties has been adopted:

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.
Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donations. It has a distribution of 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

Clinical efficacy

- Main studies

Study ZLB03_002CR - Primary Immunodeficiency (PID)
The study was a single-arm open-label, prospective, multi-centre Phase III study to assess safety and efficacy of Privigen in PID patients.

METHODS

Study participants and treatments
The ITT (and safety) population consisted of 80 patients, while the PP data set consisted of 70 patients. Privigen was administered as an intravenous infusion, every 3 or 4 weeks for a period of 12 months, using an individualized dose regimen of 200 to 800 mg IgG per kg of body weight
The patients received a total of 1038 infusions,

Outcomes/Endpoints and Results
The primary efficacy endpoint was to achieve an annual rate of acute serious bacterial infections (aSBIs) (pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, bacterial meningitis, visceral abscess) per subject (ITT population) of less than 1.
A total of 6 aSBIs in 80 patients over the course of a year resulted in an annual infection rate of 0.08 (the upper 1-sided 97.5% limit of the confidence interval was 0.182). Thus the goal set by the protocol was achieved and is clinically relevant.

The secondary efficacy endpoints encompassed days off work/school, days in hospital, antibiotic use, infectious episodes and general well-being.
In the ITT population 53/80 patients missed 570 days resulting in an annual rate of 7.94 days (7.65 for PP). The mean number of days the patients were hospitalised was 2 (SD 10 days for ITT), the median was 0 (range 0 – 84 days). The monthly average was 0.16 days. Of the 166 reported days of hospitalization 116 were attributed to only two subjects. These rates are comparable to other IVIgs in the same population. The median number of days with antibiotic use was 25 in the ITT and 32 in the PP population (range: 0 – 361), the mean was 78 and 81 days, respectively (SD 112 and 115). The majority of patients received antibiotics for AEs via the oral route; only 3.5% received antibiotics prophylactically.

Other infections (mainly sino-pulmonary) resulted in an annual infection rate of 3.55; 66 patients had 255 episodes of infection. This annual rate is comparable to data from the literature. Although the methods used to evaluate “other infections”, in the literature are heterogeneous, the data with regard to the proportion of subjects with any infection was 82.5% in the current study and 80.4% in equivalent studies.
In a subjective rating score approximately 70-80% of the patients felt “fair, well or very well” for each infusion regardless of dosing schedule.

Study ZLB03_003CR – Idiopathic thrombocytopenic purpura (ITP)
The study was a single-arm open-label, prospective, multi-centre Phase III study to assess safety and efficacy of Privigen in ITP patients.

METHODS

Study participants and treatments
Privigen was administered to the patients (n= 57, ITT and safety population; n=56, PP population) on two consecutive days, at a total treatment dose of 2 g/kg.
The patients received a total of 114 infusions.

Outcomes/Endpoints and Results

The primary efficacy endpoint was the therapy response rate, defined as the percentage of subjects with an elevation of platelet count to $\geq$ 50 x 10^9/L within 7 days. The endpoint is consistent with the requirements of the current CPMP Guideline on IVIg (CPMP/BPWG/388/95 rev.1)
The primary endpoint (70% with platelets $\geq$ 50 x 10^9/L within 7 days) was met: out of the 57 patients included in the study, the proportion of responders was 80.7% (46/57) in the ITT population; this is in keeping with the rates from the literature and for similar products.
The platelet response rate was higher in males than in females (95.7 vs 70.6%), this difference seems to be coincidental; both genders reach the required level of 70% response rate

The main secondary efficacy end points were:

- time to a platelet count > 50 x 10^9/L and duration of response:
The median maximum platelet count achieved was 154 x 10^9/L. The median time to reach this maximum level was 6 days. The median time to reach response was 2.5 days after start of study medication, 43% of the subjects reached response after 1 day and 75% of the subjects reached response after 5 days. The median interpolated duration of platelet response was 15.4 days.

- regression of haemorrhages:
The overall haemorrhage regression rate was 86.1%; out of the 15 patients who responded but had a worsening of bleeding status, 2/15 had not yet reached "response" at the time of worsening and 11/15 had values below 55 x 10^9/L at the time of the bleeding event, 2/15 had bleeding despite adequate platelet levels which were mild in character and of short duration. Given these explanations and the overall response rate of 80.7%, these isolated bleeding events in responders are acceptable.

According to the current NfG (CPMP/BPWG/859/95 rev.1) indications for use in Guillain Barre' syndrome, Kawasaki disease and allogeneic bone marrow transplantation can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes and in patients with ITP is established.

Clinical safety

In both efficacy clinical studies (PID **Study ZLB03_002CR** and ITP **Study ZLB03_003CR**) safety analyses were carried out on the safety data set (SDS), which was identical to the intention-to-treat (ITT) data set.

- Patients exposure

A total of 137 patients (80 PID, 57 ITP) were exposed to 1152 Privigen infusions (1038 PID, 114 ITP). The extent of exposure for PID patients varied from a single administration up to 17 infusions administered over a 12-month period; all 57 ITP patients received 2 infusions over 2 consecutive days. Data from all centres that participated in this study were pooled to provide an adequate number of subjects available for analysis; this more than fulfils the Guideline (CPMP/BPWG/388/95 rev.1) which requires 30 patients or 180 infusions.

- Adverse events

Safety variables comprised the rate, severity and relatedness of AEs (including treatment emergent = TEAE and temporally associated adverse events = TempAssocAEs), changes to baseline in routine laboratory parameters (chemistry, haematology, urinalysis), in viral safety markers, in physical

examination results, in vital sign during each infusion and also in serum concentrations of L-proline (excipient) before and after the first two infusions and prior to infusion 4 or 5.

The majority of subjects in both studies experienced at least one TEAE: 78 of 80 subjects (97.5%) in the PID study; 52 of 57 subjects (91.2%) in the ITP study. Headache was by far the most frequent TEAE in both studies (67.5% PID and 66.7% ITP). Pyrexia/hyperthermia was reported in 35% of subjects in the ITP study and in 28.8 % of subjects in the PID study. Other TEAEs occurring in more than 20% of subjects (PID study only) included cough (33.8), sinusitis (31.3), vomiting (26.3), diarrhoea (26.3), pain (23.8), nasopharyngitis (22.5), and back pain (21.3).

TEAEs by causal relationship (adverse drug reactions, ADRs)
Thirty-three (41.3%) PID patients and 46 (80.7%) ITP patients experienced a TEAE that was at least possibly related to study medication (equivalent to adverse drug reactions (ADRs)). Headache was the most frequent ADR reported for subjects in both studies (30.0% PID and 64.9% ITP). Pyrexia was the only other ADR reported in more than 20% of subjects (14 [24.6%] subjects, ITP study).
In the PID study, the overall rate of ADRs per infusion was 0.21. As expected due to the higher dose, the ADR rate per infusion was higher (1.53) in the ITP study; 70.7% of these ADRs were assessed as mild. The corresponding rate for serious ADRs was < 0.01 per infusion in both studies.

TempAssocAEs
In the PID study approx. 9% of the infusions were associated with a related AE occurring either within 48 or 72 hours after administration. This has also been described for other IVIG products in the same population. The nature of the TempAssocAE was mainly headache, chills, fatigue and nausea i.e. side effects that are commonly related to IVIG treatment. As would be expected rates for TempAssocAEs were highest within the first 3 infusions and reached a lower plateau after the fourth infusion. TempAssocAEs did not show any distinct pattern of being related to infusion rate, thus the statement in the SPC under Method of administration "*If well tolerated, the rate of administration may gradually be increased to 4.8 ml/kg bw/hr. In a clinical study in PID patients, the maximum infusion rate was 7.2 ml/kg bw/hr*." is considered adequate.
In the ITP study 50 (87.7%) subjects experienced at least one TempAssocAE and 46 (80.7%) experienced at least one at least possibly related TempAssocAE. Twenty-seven (84.4%) of the 32 subjects who received pre-medication and 23 (92.0%) of the 25 subjects who did not receive pre-medication experienced at least one TempAssocAE. The overall incidences of TempAssocAEs were comparable to those of all TEAEs, with headache being the most common.

Laboratory findings

For both studies viral testing and laboratory values did not reveal any new safety concerns. However, in the PID study the direct Coombs' test changed from negative at baseline to positive in 36 (46.8%) of 77 subjects during the course of the study. In the ITP study this occurred at a rate of 21%. It is likely that the difference in the timing of the blood sampling in the PID and ITP studies explain the difference in the rate of positive Coomb's testing. In the PID study, blood samples were taken immediately post-infusion, whereas in the ITP study the sampling was performed later to evaluate the course of the platelet response. Differences in blood groups or batches administered did not seem to play a role. It has previously been described that IVIG can cause transiently positive Coombs' test results at rates comparable to the current study. For both studies no evidence of haemolysis was observed.

Overall, no new safety signals could be discerned from the submitted data.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance System as described by the applicant mainly 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.

Risk Management Plan

The MAA submitted a risk management plan.

With regard to the issue of possible neurotoxicity of L-Proline arising from the pre-clinical studies a combination of intensified routine Pharmacovigilance activities and an appropriate wording of section 5.3 of the SPC were proposed. The outline of the intensified Pharmacovigilance activities was submitted by the applicant and a final protocol is to be submitted 1 month after Commission approval of the MAA.
To broaden the safety data base on the paediatric population, a special intensified Pharmacovigilance protocol has been proposed to uncover signals on relevant neurological effects. This dedicated Signal Detection will focus on spontaneous ADR reports, including cases from the scientific literature, concerning Kawasaki disease, the paediatric population and neurologic disorders after Privigen administration. Results of this dedicated signal detection will be documented internally and reported to the Qualified Person for Pharmacovigilance on a monthly basis. Any confirmed signal will be reported immediately according to all applicable rules (especially Notice to Applicants, Vol. 9A). Finally results will be filed regularly with each PSUR.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities** **(routine and additional)**	**Proposed risk minimisation activities** **(routine and additional)**
Important identified risks *Undesirable effects (by decreasing frequency):* • Headache (very common); • Nausea, vomiting, chills, fatigue, and pyrexia/fever (common).	*Routine activities:* **Routine pharmacovigilance** including ongoing signal detection and PSUR analysis. .	*Routine activities:* labelling in **SPC section 4.8**
Important potential risks Undesirable effects with frequency "uncommon", which are regarded signals, whose causal association to Privigen has not been confirmed: • Anaemia, anisocytosis; • Dizziness, head discomfort, somnolence, tremor; • Dyspnoea; • Diarrhoea; • Hyperbilirubinaemia; • Pruritus, skin disorder; • Back pain, neck pain, pain in extremity, musculoskeletal stiffness; • Proteinuria; • Chest pain, general symptom, asthenia, influenza like illness, hyperthermia, pain; • A number of terms (PTs) from	*Routine activities:* **Routine pharmacovigilance** including ongoing signal detection and PSUR analysis. .	*Routine activities:* labelling in **SPC section 4.8**

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
the MedDRA SOC "Investigations" (Bilirubin conjugated increased, blood bilirubin unconjugated increased, Coombs direct test positive, Coombs test positive, blood lactate dehydrogenase increased, haematocrit decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood pressure decreased, blood pressure increased, body temperature increased, haemoglobin decreased). • Other potential risk • Neurotoxicity of L proline in the paediatric population when used at high dose	See below (missing information)	*Routine minimisation activities* *Labelling in section 5.3* "Some published studies pertaining to hyperprolinaemia have shown that long-term, high doses of L-proline have effects on brain development in very young rats. However, in studies where the dosing was designed to reflect the clinical indications for Privigen, no effects on brain development were observed."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important missing information Need to: (1) Extend available safety database with a focus on neurological effects in the paediatric population, especially on the population where the highest single dose of Privigen is used (i.e. Kawasaki disease). (2) Identify and characterise more specific safety data on the use of Privigen in the following indications: • Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; • Children with congenital AIDS and recurrent infections; • Guillain-Barré syndrome; • Kawasaki disease; • Allogeneic bone marrow transplantation.	*Routine activities:* **Routine pharmacovigilance** including ongoing signal detection and PSUR analysis. Dedicated Signal Detection (monthly) on spontaneous ADR reports, including cases from the scientific literature, concerning Kawasaki disease, the paediatric population and neurological disorders after Privigen administration, according to a separate *'Pharmacovigilance Protocol'*. **Routine pharmacovigilance**	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Based on the submitted data, the marketing authorisation application for Privigen is recommended for approval based on quality grounds.

Non-clinical pharmacology and toxicology

Human normal immunoglobulin is a highly purified, unmodified human IgG product intended for intravenous administration (IVIG). Due to the xenoreactivity of human IgG, the normal intravenous immunoglobulin Privigen was subjected to a limited programme to determine its pharmacological and toxicological characteristics. Privigen contains a broad range of antibodies specificities and is able to support immune-functions which need an intact antibody molecule. The two repeated dose toxicity studies for L-proline in the rat gave no indications for negative effects and revealed that the excipient L-Proline has no evidence of bioaccumulation. The NOAEL of L-proline was the high dose tested (1449mg/kg). The pharmacokinetics of L-proline was qualitatively and quantitatively similar in the rat and humans. The rat can be considered to be a suitable animal model.

No repeat dose toxicity studies were performed with Privigen. This is acceptable since administration of Human normal immunoglobulin to animals can be expected to initiate the immunological response, which would interfere with the toxicity evaluation.
Two repeat dose toxicity studies (5-day and 28-day) with high doses of L-Proline were conducted in rats by continuous i.v. infusion. There were no unscheduled deaths or treatment related clinical signs. For L-proline, a NOAEL of 1449 mg/kg bw/day, the highest dose assessed, was defined.
Privigen is formulated at a slightly acidic pH (4.8) in the presence of 250 mmol/L L-proline as stabilizer for IgG in solution. In a study in rabbits Privigen was locally well tolerated after subcutaneous application and the local tolerance was similar to saline and higher when compared to other IVIG preparations at higher protein concentrations formulated at nearly physiological pH (6.8).. In addition, Privigen showed acceptable local tolerance after intravenous (i.v.), paravenous (p.v.) and intra-arterial (i.a.) application in a second local tolerance study.

The absence of direct genotoxicity has been demonstrated for L-proline in combination with nicotinamide and L-isoleucine using a variety of assays. A rat teratogenicity study using L-proline alone revealed no evidence of embryotoxicity or teratogenicity at the tested dose of 1449 mg L-proline/kg/day. Privigen did not cause significant local tolerance reactions. The questions of residual solvents were sufficiently addressed and gave no reasons for concern from the preclinical experience.
Due to the vast experience with immunoglobulin products, the protein nature of the product and the results of the submitted data, the limited programme to characterise Privigen is considered as acceptable.

Efficacy

Two studies were performed for the evaluation of clinical efficacy (one PID Study ZLB03_002CR, one ITP Study ZLB03_003CR). For the PID study the infection rates were examined and in the ITP study numbers of responders and thrombocyte levels were investigated.
The data were well presented and the study reports were of good quality. The study designs comply with the current standards requested by the Guideline (CPMP/BPWG/388/95 rev. 2).

Safety

In general, the safety profile of the product is in keeping with other IVIgs and no new safety could be discerned from the submitted data; the adverse reactions to IVIgs are well known and have been described in the SPC. With respect to viral safety, viral and prion clearance have been demonstrated. The discussion on the possible neurotoxicity of L-Proline has been addressed in the Section 5.3. of the SPC and has led to the proposal of intensified Pharmacovigilance activities.

The proposed PIL complies with the Directive 2001/83/EC as amended by Council Directive 2004/27/EC and adhere to the current EMEA QRD template and to the Notice to Applicants Volume 2C ("Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use"). None of the questions resulted in a legibility or comprehensibility of lower than 90%.

Risk-benefit assessment

Clinical context

Privigen is a concentrated (100 g/L) liquid immunoglobulin product for intravenous use (IVIg). The product is formulated with 250 mmol/L L-proline at pH 4.8. The IgA content is typically below 25 mg/L. Other serum proteins are present in trace amounts.
The claimed indications are: a) Replacement therapy in primary immunodeficiency syndromes, myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and children with congenital AIDS and recurrent infections; and b) Immunomodulation in idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count, Guillain Barré syndrome, Kawasaki disease and c) Allogeneic bone marrow transplantation. These are currently considered established indications and are listed in the core SPC for IVIg (CPMP/BPWG/859/95 rev.1).

Benefit

With respect to clinical efficacy, two clinical trials were performed, one (ZLB03_002CR) for *replacement therapy* in patients with Primary Immunodeficiency Disease (PID) and another (ZLB03_003CR) for *immuomodulation* in patients with Idiopathic Thrombocytopenic Purpura (ITP). The correct patient population (primary immunodeficiency syndromes (PID), and patients with idiopathic thrombocytopenic purpura (ITP)) was included in the studies; the doses administered to the PID and ITP patients were adequate to maintain protective IgG trough levels and platelet counts respectively. In the PID population relevant, serious bacterial infections were kept under the ≥1 year level.
According to the NfG for the clinical investigation of IVIg (CPMP/BPWG/388/95 rev.1), demonstration of efficacy in PID would apply to all types of primary immunodeficiencies due to deficiency of functional IgG.

Furthermore, according to the current NfG (CPMP/BPWG/859/95 rev.1):

- indications for replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and replacement therapy in children with congenital AIDS and recurrent infections can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes has been established.
- indications for use in Guillain Barré syndrome, Kawasaki disease and allogeneic bone marrow transplantation can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes and in patients with ITP is established.

In general, the results for the clinical pharmacokinetics, efficacy and safety obtained from the clinical studies are in keeping with those reported in the literature and in other studies with similar products. They also fully comply with the current standards requested by the European Note for Guidance for the clinical investigation of IVIg (CPMP/BPWG/388/95 rev. 1).

Risks

No new safety could be discerned from the submitted data; the adverse reactions to IVIgs are well known and have been described in the SPC. The discussion on the possible neurotoxicity of L-Proline has led to a rewording in Section 5.3. of the SPC and the proposal of intensified Pharmacovigilance activities. With respect to viral safety, viral and prion clearance have been demonstrated.

Balance

The overall benefit/risk assessment of Privigen is positive**.**

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Privigen in the treatment of

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 (CLL) with severe secondary hypogammaglobulinaemia and recurrent infections
- Children with congenital AIDS and recurrent infections

Immunomodulation

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

Allogeneic bone marrow transplantation

was favourable and therefore recommended the granting of the marketing authorisation.