ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Privigen 100 mg/ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)*

One ml contains:
Human normal immunoglobulin 100 mg
(purity of at least 98% IgG)

Each vial of 25 ml solution contains: 2.5 g human normal immunoglobulin
Each vial of 50 ml solution contains: 5 g human normal immunoglobulin
Each vial of 100 ml solution contains: 10 g human normal immunoglobulin
Each vial of 200 ml solution contains: 20 g human normal immunoglobulin
Each vial of 400 ml solution contains: 40 g human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG_1 67.8%
IgG_2 28.7%
IgG_3 2.3%
IgG_4 1.2%

The maximum IgA content is 25 micrograms/ml.

*Produced from the plasma of human donors.

Excipients with known effects:
Privigen contains approximately 250 mmol/L (range: 210 to 290) of L-proline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear or slightly opalescent and colourless to pale yellow.
Privigen is isotonic, with an approximate osmolality of 320 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults, and children and adolescents (0-18 years) in:
Primary immunodeficiency (PID) syndromes with impaired antibody production (see section 4.4).

- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré syndrome.
- Kawasaki disease.
- Chronic inflammatory demyelinating polyneuropathy (CIDP). Only limited experience is available of use of intravenous immunoglobulins in children with CIDP.

4.2 Posology and method of administration

Replacement therapy should be commenced and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Posology

The dose and dose regimen is dependent on the indication.
In replacement therapy the dose may need to be individualised for each patient depending on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency (PID) syndromes
The dose regimen should achieve a trough IgG level (measured before the next infusion) of at least 5 to 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 to 0.8 g/kg body weight (bw) given once, followed by at least 0.2 g/kg bw every 3 to 4 weeks.

The dose required to achieve a trough level of 5 to 6 g/l is of the order of 0.2 to 0.8 g/kg bw/month. The dosage interval when steady state has been reached varies from 3 to 4 weeks.
Trough levels should be measured and assessed in conjunction with the patient's clinical response. Depending on the clinical response (e.g. infection rate), adjustment of the dose and/or the dose interval may be considered in order to aim for higher trough levels.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase; multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections
The recommended dose is 0.2 to 0.4 g/kg bw every 3 to 4 weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
The recommended dose is 0.2 to 0.4 g/kg bw every 3 to 4 weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia (ITP)
There are two alternative treatment schedules:

- 0.8 to 1g/kg bw given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg bw given daily for 2 to 5 days.

The treatment can be repeated if relapse occurs.

Guillain-Barré syndrome
0.4 g/kg bw/day over 5 days.

Kawasaki disease
1.6 to 2.0 g/kg bw should be administered in divided doses over 2 to 5 days or 2.0 g/kg bw as a single dose.
Patients should receive concomitant treatment with acetylsalicylic acid.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)**
The recommended starting dose is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw over 1 to 2 consecutive days every 3 weeks.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy in primary immunodeficiency (PID)	starting dose: 0.4 - 0.8 g/kg bw	
	Thereafter: 0.2 - 0.8 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 5 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 5 - 6 g/l
Congenital AIDS	0.2 - 0.4 g/kg bw	every 3 to 4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough level above 5 g/l.
Immunomodulation		
Primary immune thrombocytopenia (ITP)	0.8 - 1 g/kg bw or 0.4 g/kg bw/d	on day 1, possibly repeated once within 3 days for 2 to 5 days
Guillain-Barré syndrome	0.4 g/kg bw/d	for 5 days
Kawasaki disease	1.6 – 2 g/kg bw or	in divided doses over 2 to 5 days in association with acetylsalicylic acid
	2 g/kg bw	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)*	starting dose: 2 g/kg bw	in divided doses over 2 to 5 days
	maintenance dose: 1 g/kg bw	every 3 weeks over 1 to 2 days

*The dose is based on the dose used in the clinical studies conducted with Privigen. The duration of treatment beyond 25 weeks should be subject to the physicians discretion based upon the patient response and maintenance response in the long-term. The dosing and intervals may have to be adapted according to the individual course of the disease.

Paediatric population
The posology in children and adolescents (0-18 years) is not different from that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Method of administration
For intravenous use.
Human normal immunoglobulin should be infused intravenously at an initial infusion rate of 0.3 ml/kg bw/hr for approximately 30 min. If well tolerated (see section 4.4), the rate of administration may gradually be increased to a maximum of 4.8 ml/kg bw/hr.

In PID patients who have tolerated the infusion rate of 4.8 ml/kg bw/hr well, the rate may be further increased gradually to a maximum of 7.2 ml/kg bw/hr.

If dilution prior to infusion is desired, Privigen may be diluted with 5% glucose solution to a final concentration of 50 mg/ml (5%). For instruction, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.4).
Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.
Patients with hyperprolinaemia type I or II.

4.4 Special warnings and precautions for use

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section 4.2 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 rate of infusion,
- in patients with hypogammaglobulinaemia 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.

Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially infusing the product slowly (0.3 ml/kg bw/hr);
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

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

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.

For patients suffering from diabetes mellitus and requiring dilution of Privigen to lower concentrations, the presence of glucose in the recommended diluent should be taken into account.

Hypersensitivity
True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactoid reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Haemolytic anaemia
IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration.

Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation and death have occurred.
The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; non-O blood group; and underlying inflammatory state. As this event was commonly reported in non-O blood group patients receiving high doses for non-PID indications, increased vigilance is recommended. Haemolysis has rarely been reported in patients given replacement therapy for PID.

IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis develop during or after an IVIg infusion, discontinuation of the IVIg treatment should be considered by the treating physician (see also section 4.8).

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl.
AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Thromboembolism
There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients 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 hypovolaemic patients, patients with diseases which increase blood viscosity).

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

Acute renal failure
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 containing various excipients such as sucrose, glucose and maltose, 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 should therefore be considered. Privigen does not contain sucrose, maltose or glucose.
In patients at risk of acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Transfusion-related acute lung injury (TRALI)
Noncardiogenic pulmonary edema may very rarely occur following treatment with IVIg products, including Privigen. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.
Monitor patients for pulmonary adverse reactions. TRALI may be managed using oxygen therapy with adequate ventilatory support.

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 antibodies, for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
Privigen is made from human plasma. 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) and for the non-enveloped viruses such as hepatitis A virus (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 Privigen 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.

Sodium content
Privigen is essentially sodium-free.

Paediatric population
Although limited data is available, it is expected that the same warnings, precautions and risk factors apply to the paediatric population. In post marketing reports it is observed that IVIG high-dose indications in children, particularly Kawasaki disease, are associated with an increased reporting rate of haemolytic reactions compared to other IVIG indications in children.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines
Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps, and varicella. After administration of this medicinal 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.

Paediatric population
Although limited data is available, it is expected that the same interactions may occur in the paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy
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. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Experimental studies of the excipient L-proline carried out in animals found no direct or indirect toxicity affecting pregnancy, embryonal or foetal development.

Breast-feeding
Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.

Fertility
Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

4.7 Effects on ability to drive and use machines

The ability to drive and operate machines may be impaired by some adverse reactions associated with Privigen. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally in connection with intravenous administration of human immunoglobulin including Privigen.

Rarely human normal immunoglobulins including Privigen 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 and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin including Privigen.

Reversible haemolytic reactions have been observed in patients, especially those with non-O blood groups in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment including Privigen (see section 4.4).

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

Very rarely: Transfusion related acute lung injury and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses.

Tabulated list of adverse reactions
Six clinical studies were performed with Privigen, which included patients with PID, ITP and CIDP. In the pivotal PID study, 80 patients were enrolled and treated with Privigen. Of these, 72 completed the 12 months of treatment. In the PID extension study, 55 patients were enrolled and treated with Privigen. The two ITP studies were performed with 57 patients each. The two CIDP studies were performed with 28 and 207 patients, respectively.

Most adverse drug reactions (ADRs) observed in the six clinical studies were mild to moderate in nature.

The following table shows an overview of the ADRs observed in the six clinical studies categorized according the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency. Frequencies were evaluated according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000). For spontaneous post-marketing ADRs, the reporting frequency is categorized as unknown.

Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

MedDRA System Organ Class (SOC)	Adverse Drug Reaction	Frequency
Infections and infestations	Aseptic meningitis	Uncommon
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia), leukopenia	Common
	Anisocytosis (including microcytosis), thrombocytosis	Uncommon
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Unknown
Nervous system disorders	Headache (including sinus headache, migraine, head discomfort, tension headache)	Very common
	Dizziness (including vertigo)	Common
	Somnolence, tremor	Uncommon
Cardiac disorders	Palpitations, tachycardia	Uncommon
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia), hypotension	Common
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon
	Transfusion related acute lung injury	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common
Gastrointestinal disorders	Nausea	Very common
	Vomiting, diarrhoea, abdominal pain	Common
Hepatobiliary disorders	Hyperbilirubinaemia	Common
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)	Common
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon
	Acute renal failure	Unknown
General disorders and administration site conditions	Pain (including back pain, pain in extremity, arthralgia, neck pain, facial pain) pyrexia (including chills), influenza like illness (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very common
	Fatigue, asthenia (including muscular weakness)	Common
	Injection site pain	Uncommon
Investigations	Decreased haemoglobin (including decreased red blood cell count, decreased haematocrit), Coombs` (direct) test positive, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase	Common

For safety with respect to transmissible agents and additional details on risk factors, see section 4.4.

Paediatric Population

In Privigen clinical studies with paediatric patients, the frequency, nature and severity of adverse reactions did not differ between children and adults. In post marketing reports it is observed that the proportion of haemolysis cases to all case reports occurring in children is slightly higher than in adults. Please refer to section 4.4 for details on risk factors and monitoring recommendations.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 1,000 donors. 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.

The safety and efficacy of Privigen was evaluated in 6 prospective, open-label, single-arm, multicenter studies performed in Europe (ITP, PID and CIDP studies) and the USA (PID study).

PID
The PID pivotal study included a total of 80 patients aged between 3 and 69 years old. 19 children (3 to 11 years), 12 adolescents (12 to 16 years) and 49 adults were treated with Privigen over 12 months. 1038 infusions were administered, 272 (in 16 patients) in the 3-week schedule and 766 (in 64 patients) in the 4-week schedule. The median doses administered for the 3-week and 4-week treatment schedules were almost identical to each other (428.3 vs. 440.6 mg IgG/ kg bw).The PID extension study included a total of 55 patients aged between 4 and 81 years old. 13 children (3 to 11 years), 8 adolescents (12 to 15 years) and 34 adults were treated with Privigen over 29 months. 771 infusions were administered and the median dose administered was 492.3 mg IgG/kg bw.

ITP
In the ITP pivotal study, in total 57 patients aged between 15 and 69 years old were treated with 2 infusions of Privigen for a total of 114 infusions. The scheduled dose of 1 g/kg bw per infusion was closely adhered to in all patients (median 2 g IgG/kg bw).

In the second ITP study, 57 patients with ITP (baseline platelet counts $\leq 30\times10^9$ / l) aged between 18 and 65 years were treated with Privigen at 1 g/kg bw. On day 3 patients could receive a second dose of 1 g/ kg bw, for patients with a platelet count of $< 50\times10^9$ / l on day 3 this second dose was mandatory. Overall, in 42 subjects (74 %) the platelet count increased at least once to $\geq 50\times10^9$ / l within 6 days after the first infusion, which was well within the expected range. A second dose in subjects with platelet counts $\geq 50\times10^9$ /l after the first dose provided a relevant additional benefit in terms of higher and longer-lasting increases in platelet counts compared to a single dose. In subjects with platelet counts $< 50\times10^9$ / l after the first dose, 30% showed a platelet response of $\geq 50\times10^9$ / l after the mandatory second dose.

CIDP

In the first CIDP study, a prospective multicenter open label trial (Privigen impact on mobility and autonomy PRIMA study), 28 patients (13 subjects who have previously received IVIG and 15 subjects not) were treated with a Privigen loading dose of 2g/kg bw given over 2-5 days followed by 6 maintenance doses of 1g/kg bw over 1-2 days every three weeks. Previously treated patients were withdrawn from IVIG until confirmed deterioration before start of Privigen. On the adjusted 10 point INCAT (Inflammatory Neuropathy Cause and Treatment) scale a clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was observed in 17 out of 28 patients. The INCAT responder rate was 60.7% (95% confidence interval [42.41, 76.4]). 9 patients responded after receiving the initial induction dose by week 4, 16 patients responded by week 10.

Muscle strength as measured by the MRC (Medical Research Council) Score improved in all patients by 6.9 points (95% confidence interval [4.11, 9.75], in previously treated patients by 6.1 points (95% confidence interval [2.72, 9.44]) and in untreated patients by 7.7 points (95% confidence interval [2.89, 12.44]). The MRC responder rate, an increase of at least 3 points, was 84.8% which was similar in previously treated (81.5% [58.95, 100.00]) and untreated (86.7% [69.46, 100.00]) patients.
In patients defined as INCAT non-responders, muscle strength improved by 5.5 points (95% confidence interval [0.6, 10.2]) as compared to INCAT responders (7.4 points (95% confidence interval [4.0, 11.7])

In a second prospective, multicenter randomized, placebo-controlled clinical study (Polyneuropathy and Treatment with Hizentra, PATH trial), 207 subjects with CIDP were treated with Privigen in the prerandomization phase of the study. Subjects all with IVIg pretreatment of at least 8 weeks and with an IVIg-dependence confirmed by clinically evident deterioration during an IVIg withdrawal phase of up to 12 weeks, received a Privigen loading dose of 2 g/kg bw followed by up to 4 Privigen maintenance doses of 1 g/kg bw every 3 weeks for up to 13 weeks.
Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥ 1 point at the adjusted INCAT score. Additional measures of CIDP improvement were an increase in R-ODS (Rasch-built Overall Disability Scale) score of ≥ 4 points, a mean grip strength increase of ≥ 8 kPa, or an MRC sum score increase of ≥ 3 points. Overall, 91 % of subjects (188 patients) showed improvement in at least one of the criteria above by week 13.
By adjusted INCAT score, the responder rate by week 13 was 72.9 % (151 / 207 patients), with 149 patients responding already by week 10. A total of 43 of the 207 patients achieved a better CIDP status as assessed by the adjusted INCAT score compared to their CIDP status at study entry.

The mean improvement at the end of the treatment period compared to reference visit was 1.4 points in the PRIMA (1.8 points in IVIg pretreated subjects) and 1.2 points in PATH study.

In PRIMA, the percentage of responders in the overall Medical Research Council (MRC) score (defined as an increase by ≥ 3 points) was 85 % (87 % in the IVIg-untreated and 82 % in IVIg-pretreated) and 57 % in PATH. The overall median time to first MRC sum score response in PRIMA was 6 weeks (6 weeks in the IVIg-untreated and 3 weeks in the IVIg-pretreated) and 9.3 weeks in PATH. MRC sum score in PRIMA improved by 6.9 points (7.7 points for IVIg-untreated and 6.1 points for IVIg-pretreated) and by 3.6 points in PATH.
The grip strength of the dominant hand improved by 14.1 kPa (17.0 kPa in IVIg-untreated and 10.8 kPa in IVIg pretreated subjects) in the PRIMA study, while in PATH the grip strength of the dominant hand improved by 12.2 kPa. For the non dominant hand similar results were observed in both PRIMA and PATH trials.

The efficacy and safety profile in the PRIMA and the PATH study in CIDP patients were overall comparable.

Paediatric population

No differences were seen in the pharmacodynamic properties between adult and paediatric study patients.

5.2 Pharmacokinetic properties

Absorption
Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution
It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination
IgG and IgG complexes are broken down in the cells of the reticuloendothelial system. The half-life may vary from patient to patient. The pharmacokinetic parameters for Privigen were determined in a clinical study in PID patients (see section 5.1). 25 patients (aged 13-69 years) participated in the pharmacokinetic (PK) assessment. In this study, the median half-life of Privigen in PID patients was 36.6 days. In an extension of this study, 13 PID patients (aged 3-65 years) participated in a PK sub-study. The results of this study show the median half-life of Privigen to be 31.1 days (see table below).

Pharmacokinetic parameters of Privigen in PID patients

Parameter	**Pivotal Study (N= 25) ZLB03_002CR Median (Range)**	**Extension Study (N=13) ZLB05_006CR Median (Range)**
C_{max} (peak, g/l)	23.4 (10.4-34.6)	26.3 (20.9-32.9)
C_{min} (trough, g/l)	10.2 (5.8-14.7)	12.3 (10.4-18.8) (3-week schedule) 9.4 (7.3-13.2) (4-week schedule)
$t_{½}$ (days)	36.6 (20.6-96.6)	31.1 (14.6-43.6)

C_{max}, maximum serum concentration; $C_{min,}$ trough (minimum level) serum concentration; $t_{½}$, elimination half-life

Paediatric population
No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients with PID. There are no data on pharmacokinetic properties in paediatric patients with CIDP.

5.3 Preclinical safety data

Immunoglobulins are a normal constituent of the human body. L-proline is a physiological, non-essential amino acid.

The safety of Privigen has been assessed in several preclinical studies, with particular reference to the excipient L-proline. 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. Non-clinical data reveal no special risk for humans based on safety pharmacology and toxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-proline, water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, diluents, or solvents except those mentioned in section 6.6.

6.3 Shelf life

3 years

Stability after first opening:
Once the vial has been broached, its contents should be used promptly. Because the solution contains no preservative, Privigen should be infused immediately.

Stability after dilution:
If the product is diluted to lower concentrations (see section 6.6), immediate use after dilution is recommended. The in-use stability of Privigen after dilution with a 5% glucose solution to a final concentration of 50 mg/ml (5%) has been demonstrated for 10 days at 30°C; however, the microbial contamination aspect was not studied.

6.4 Special precautions for storage

Do not store above 25 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after first opening of the medicinal product and after dilution, see section 6.3.

6.5 Nature and contents of container

25 ml of solution in a single vial (type I glass), with a stopper (elastomeric), a cap (aluminium crimp), a flip off disc (plastic), label with integrated hanger.

50 or 100 ml of solution in a single vial (type I or II glass), with a stopper (elastomeric), a cap (aluminium crimp), a flip off disc (plastic), label with integrated hanger.

200 or 400 ml of solution in a single vial (type II glass), with a stopper (elastomeric), a cap (aluminium crimp), a flip off disc (plastic), label with integrated hanger.

Pack sizes
1 vial (2.5 g/25 ml, 5 g/50 ml, 10 g/100 ml, 20 g/200 ml or 40 g/400 ml),
3 vials (10 g/100 ml or 20 g/200 ml).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Privigen comes as a ready-to-use solution in single-use vials. The product should be brought to room temperature (25°C) before use. A vented infusion line should be used for the administration of Privigen. Flushing of the infusion tubes with physiological saline or 5% glucose solution is permitted. Always pierce the stopper at its centre, within the marked area.

The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

If dilution is desired, 5% glucose solution should be used. For obtaining an immunoglobulin solution of 50 mg/ml (5%), Privigen 100 mg/ml (10%) should be diluted with an equal volume of the 5% glucose solution. Aseptic technique must be strictly observed during the dilution of Privigen.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CSL Behring GmbH
Emil-von-Behring-Strasse 76
D-35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBERS

EU/1/08/446/001
EU/1/08/446/002
EU/1/08/446/003
EU/1/08/446/004
EU/1/08/446/005
EU/1/08/446/006
EU/1/08/446/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 April 2008
Date of first renewal: 13 March 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/