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	on day 1, possibly repeated once within 3 days
	0.4 g/kg bw/d	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 2-5 days
	maintenance dose: 1 g/kg bw	every 3 weeks over 1-2 days

*The dose is based on the dose used in the clinical study conducted with Privigen. The duration of treatment beyond 24 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.

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 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-0 blood group; and underlying inflammatory state. As this event was commonly reported in non-0 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 (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.

Interference with serological testing
After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell allo-antibodies, for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
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.

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 may 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.

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 postmarketing 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.

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.

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

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions have been observed with human normal immunoglobulin.

Reversible haemolytic reactions have been observed in patients, especially those with non-0 blood groups in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also section 4.4).

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

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

For safety information with respect to transmissible agents, see section 4.4.

Tabulated list of adverse reactions
Four clinical studies with Privigen were performed, 2 in PID patients and 1 in ITP patients and 1 in CIDP patients respectively. In the pivotal PID, study 80 subjects were enrolled and treated with Privigen. Of these, 72 completed the 12 months of treatment. In the PID extension study 55 subjects were enrolled and treated with Privigen. The ITP and CIDP studies were performed in 57 and 28 patients respectively.

Most adverse reactions (ARs) observed in the 4 clinical studies were mild to moderate in nature. The ARs reported in the 4 studies are presented in the table below according to the MedDRA System organ classification (SOC and Preferred Term Level).
Frequencies have been evaluated according to the following convention: 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).

Frequency of Adverse Reactions (ARs) in clinical studies with Privigen

MedDRA System Organ Class (SOC)	**Adverse Reaction**	**Frequency**
Blood and lymphatic system disorders	Haemolysis, anaemia, leukopenia, anisocytosis	Uncommon
Nervous system disorders	Headache	Very common

MedDRA System Organ Class (SOC)	Adverse Reaction	Frequency
	Dizziness, head discomfort, somnolence, tremor, sinus headache, migraine, dysaesthesia	Uncommon
Ear and labyrinth disorders	Vertigo	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Hypertension	Common
	Hypotension, flushing, peripheral vascular disorder	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, oropharyngeal blistering, painful respiration, throat tightness	Uncommon
Gastrointestinal disorders	Nausea, vomiting	Common
	Diarrhoea, abdominal pain upper	Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorders	Urticaria, rash	Common
	Pruritus, skin disorder, night sweats	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
	Neck pain, pain in extremity, musculoskeletal stiffness, muscle spasms, musculoskeletal pain, myalgia, muscular weakness	Uncommon
Renal and urinary disorders	Proteinuria	Uncommon
General disorders and administration site conditions	Pyrexia, chills, fatigue, asthenia, influenza-like illness	Common
	Chest pain, general symptom, hyperthermia, pain, injection site pain	Uncommon
Investigations	Bilirubin conjugated increased, blood bilirubin unconjugated increased, Coombs` direct test positive, Coombs` test positive, blood lactate dehydrogenase increased, haematocrit decreased, blood pressure increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood pressure decreased, blood creatinine increased, body temperature increased, haemoglobin decreased	Uncommon

Please refer to section 4.4 for additional details on risk factors.

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 postmarketing 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.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 4 prospective, open-label, single-arm, multicenter studies performed in Europe (ITP, PID and CIDP studies) and the USA (PID study).

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.

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 CIDP study, a multicentre open label trial (Privigen impact on mobility and autonomy PRIMA study), patients (who have previously either received IVIG or not) were treated with a Privigen starting 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 an 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, 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])

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
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). The half-life may vary from patient to patient, particularly in PID.

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

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

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 except those mentioned in section 6.6.

6.3 Shelf life

3 years

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

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. 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/

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

CSL Behring AG
Wankdorfstrasse 10, 3000 Bern 22
Switzerland

Name and address of the manufacturer(s) responsible for batch release

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Privigen 100 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human normal immunoglobulin 100 mg
IgG purity ..... ≥ 98%
IgA.....≤ 25 micrograms

2.5 g/25 ml
5 g/50 ml
10 g/100 ml
20 g/200 ml
40 g/400 ml
Will be placed in the upper right corner of the main face of the box to give total content and volume of the container

3. LIST OF EXCIPIENTS

Excipients: L-proline, water for injections.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion (10%)

Contains 1 vial.
Contains 3 vials.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder:
CSL Behring GmbH
D-35041 Marburg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/446/001 5 g/50 ml
EU/1/08/446/002 10 g/100 ml
EU/1/08/446/003 20 g/200 ml
EU/1/08/446/004 2.5 g/25 ml
EU/1/08/446/005 10 g/100 ml (3 vial pack size)
EU/1/08/446/006 20 g/200 ml (3 vial pack size)
EU/1/08/446/007 40 g/400 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL

1. NAME OF THE MEDICINAL PRODUCT

Privigen 100 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains:
Human normal immunoglobulin 100 mg. IgG purity ≥ 98%. IgA ≤ 25 micrograms.

2.5 g/25 ml
5 g/50 ml
10 g/100 ml
20 g/200 ml
40 g/400 ml
Will be placed in the upper right corner of the label to give total content and volume of the container

3. LIST OF EXCIPIENTS

L-proline, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion (10%)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CSL Behring GmbH, D-35041 Marburg, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/446/001 5 g/50 ml
EU/1/08/446/002 10 g/100 ml
EU/1/08/446/003 20 g/200 ml
EU/1/08/446/004 2.5 g/25 ml
EU/1/08/446/005 10 g/100 ml (3 vial pack size)
EU/1/08/446/006 20 g/200 ml (3 vial pack size)
EU/1/08/446/007 40 g/400 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Privigen 100 mg/ml (10%) solution for infusion
Human normal immunoglobulin (IVIg)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or healthcare professional.
- If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What Privigen is and what it is used for

What Privigen is

Privigen belongs to the class of medicines called human normal immunoglobulins. Immunoglobulins are also known as antibodies and are blood proteins that help your body to fight infections.

How Privigen works

Privigen contains immunoglobulins that have been prepared from the blood of healthy people. The medicine works in exactly the same way as the immunoglobulins naturally present in human blood of healthy people.

What Privigen is used for

Privigen is used for the treatment of adults and children (0-18 years) in the following situations:

A) <u>to increase abnormally low immunoglobulin levels in your blood to normal levels (replacement therapy). There are five groups:</u>
   1. Patients who are born with a reduced ability or inability to produce immunoglobulins (primary immunodeficiencies (PID)).
   2. Patients with blood cancer (chronic lymphocytic leukaemia) who have low immunoglobulin levels in the blood (hypogammaglobulinaemia) and develop recurrent infections and for whom preventative antibiotics have failed.
   3. Patients with bone marrow cancer (multiple myeloma) who have low immunoglobulin levels in the blood and develop recurrent infections, if no immune response is obtained after vaccination against certain bacteria (pneumococci).
   4. Patients who have low immunoglobulin levels in the blood after transplantation of stem cells from another person.
   5. Patients with inborn AIDS (Acquired Immunodeficiency Syndrome) and recurrent infections.

B) <u>to treat certain inflammatory disorders (immunomodulation). There are 4 groups:</u>

1. Patients who do not have enough blood platelets (primary immune thrombocytopenia (ITP) and who are at high risk of bleeding or will have surgery in the near future.
2. Patients with Guillain-Barré syndrome. This is an acute disease that is characterised by inflammation of the peripheral nerves that causes severe muscle weakness mainly in the legs and upper limbs.
3. Patients with Kawasaki disease. This is an acute disease that primarily affects young children. It is characterised by inflammation of blood vessels throughout the body.
4. Patients with chronic inflammatory demyelinating polyneuropathy (CIDP). This is a chronic disease that is characterised by inflammation of the peripheral nerves that causes muscle weakness and/or numbness mainly in the legs and upper limbs.

2. What you need to know before you are given Privigen

➔ Read this section carefully. The information given should be taken into consideration by you and your doctor before you are given Privigen.

Do **NOT** take Privigen
- if you are allergic to human immunoglobulins or to proline.
- if you have developed antibodies against immunoglobulins of the type IgA in your blood.
- if you suffer from hyperprolinaemia (a genetic disorder causing high levels of the amino acid proline in the blood). This is an extremely rare disorder. Only a few families with this disease are known worldwide.

Warnings and precautions

Which circumstances increase the risk of having side effects?

➔ Tell your doctor or healthcare professional prior to treatment if any of the circumstances listed below applies to you:
- You receive this medicine in high doses either on 1 day or over several days and you have a blood group A, B or AB and/or you have an underlying inflammatory condition. In these circumstances, it has been commonly reported that immunoglobulins increase the risk of breakdown of red blood cells (haemolysis).
- You are overweight, are elderly, have diabetes, have been bedridden for a long time, have high blood pressure, have low blood volume (hypovolaemia), have problems with your blood vessels (vascular diseases), have an increased tendency for blood clotting (thrombophilia or thrombotic episodes) or have a disease or a condition which causes your blood to thicken (hyperviscous blood). In these circumstances, immunoglobulins may increase the risk of heart attack (cardiac infarction), stroke, blood clots in the lung (lung embolism), or blockage of a blood vessel in the leg, although only very rarely.
- You are diabetic. Although Privigen does not contain sugar, it may be diluted with a special sugar solution (5% glucose), which could affect your blood sugar level.
- You have or had previously problems with your kidneys or take medicinal products that may harm your kidneys (nephrotoxic medicinal products). In these circumstances, immunoglobulins may increase the risk of serious rapid loss of kidney function (acute renal failure) although only very rarely. Loss of kidney function with fatal outcome has occurred in isolated haemolysis-related cases.

What kind of monitoring is required during the infusion?

For your personal safety treatment with Privigen will take place under the supervision of your doctor or healthcare professional. You will usually be observed during the whole infusion and for at least 20 minutes thereafter. In certain circumstances, special precautions may be necessary. Examples of such circumstances are:
- you are receiving Privigen at a high infusion rate *or*
- you are receiving Privigen for the first time or after a long break in treatment (e.g. several months).

In these cases you will be closely observed during the whole infusion and for at least 1 hour afterwards.

When may slowing or stopping the infusion be required?

- You may be allergic (hypersensitive) to immunoglobulins without knowing it.
  However, true allergic reactions are rare. They may occur even if you have previously received human immunoglobulins and had tolerated them well. It may happen particularly if you have developed antibodies against immunoglobulins of the type IgA. In these rare cases allergic reactions such as a sudden fall in blood pressure or shock may occur (see also section 4 "Possible side effects").
  ➔ Tell your doctor or healthcare professional immediately if you notice such reactions during the infusion of Privigen. He or she will decide whether to decrease the infusion rate or to stop the infusion completely.

Blood tests

➔ Tell your doctor about your treatment with Privigen prior to any blood test.

After receiving Privigen, the results of certain blood tests (serological tests) may be impaired for a certain time.

Information on safety with respect to infections

Privigen is made from human blood plasma (this is the liquid part of the blood).
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses and other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus and parvovirus B19.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections, possibly because antibodies against these infections, which are contained in the product, are protective.

- It is strongly recommended that every time you are given a dose of Privigen the name and batch number of the product are recorded in order to maintain a record of the batches used.

Other medicines and Privigen

➔ Tell your doctor or healthcare professional if you are using, have recently used or might use any other medicines.

Vaccinations

➔ Tell your vaccinating doctor prior to a vaccination about your treatment with Privigen.

After receiving Privigen, the efficacy of certain vaccinations may be impaired. Affected are vaccinations with live attenuated virus vaccines such as vaccinations against measles, mumps, rubella and varicella. Such vaccinations should be postponed for at least 3 months after the last infusion of Privigen. In the case of measles vaccinations the impairment may persist for up to 1 year. Therefore, your vaccinating doctor should check the effectiveness of the measles vaccination.

Pregnancy and breast-feeding

➔ Tell your doctor or healthcare professional if you are pregnant, plan to become pregnant or are breast-feeding. Your doctor will decide whether you can receive Privigen during your pregnancy or while you are breast-feeding.

Medicines containing antibodies have been used in pregnant or breast-feeding women. Long-term experience has shown that no harmful effects during the course of the pregnancy or to the newborn are to be expected.
If you receive Privigen while you are breast-feeding the antibodies in this medicine will also be found in the breast milk. Thus, also your baby can receive the protective antibodies.

Driving and using machines

Patients may experience effects, such as dizziness or nausea, during treatment with Privigen that might affect the ability to drive and use machines. If this happens, you should not drive or use machines until these effects have disappeared.

Privigen contains proline

You must not take it if you suffer from hyperprolinaemia (see also section 2 “What you need to know before you are given Privigen”).
➔ Tell your doctor prior to treatment.

3. How to use Privigen

Privigen is intended solely for the infusion into a vein (intravenous infusion). It is usually administered by your doctor or healthcare professional. Your doctor will calculate the correct dose for you taking into account your weight, the specific circumstances listed under section 2 “Warnings and precautions” and response to treatment. The dose calculation for children and young patients is not different from that for adults. At the beginning of the infusion you will receive Privigen at a slow infusion rate. If you tolerate this well, your doctor can gradually increase the infusion rate.

If you receive more Privigen than you should

Overdose is very unlikely to occur because Privigen is usually administered under medical supervision. If, in spite of this, you receive more Privigen than you should, your blood may become too thick (hyperviscous). This may happen particularly if you are a patient at risk, for example if you are elderly or if you suffer from kidney disease.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Possible side effects may be reduced or even avoided by infusing Privigen at a slow infusion rate. Such side effects may occur even if you have previously received human immunoglobulins and tolerated them well.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations:
- severe hypersensitivity reactions such as a sudden fall in blood pressure or shock (e.g. you may feel light-headed, dizzy, faint on standing, cold in the hands and feet, sense an abnormal heart beat or chest pain, or have blurred vision) even when you have shown no hypersensitivity on previous infusions,
  ➔ Tell your doctor or healthcare professional immediately if you notice such signs during the infusion of Privigen. He or she will decide whether to decrease the infusion rate or to stop the infusion completely.

- formation of blood clots which may be carried off in the blood circulation (thromboembolic reactions) and which may result e.g. in myocardial infarction (e.g. when you have sudden chest pain or shortness of breath), stroke (e.g. when you have a sudden onset of muscle weakness, have loss of sensation and/or balance, decreased alertness or difficulty in speaking), blood clots in the arteries of the lungs (e.g. when you have chest pain, difficulty in breathing or are coughing up blood), deep vein thrombosis (e.g. when you have redness, feel warmth, pain, tenderness, or have a swelling of one or both legs),
  - ➔ Tell your doctor or healthcare professional immediately if you have any of the above symptoms. Anyone experiencing such symptoms should immediately be transported to a hospital emergency room for evaluation and treatment.
- temporary non-infectious meningitis (reversible aseptic meningitis),
  - ➔ Tell your doctor or healthcare professional immediately if you have a stiff neck together with one or more of the following symptoms: fever, nausea, vomiting, headache, abnormal sensitivity to light, mental disturbances.
- transient skin reactions,
- increase in blood creatinine level,
- acute renal failure,
- transient decrease in red blood cells (reversible haemolytic anaemia/haemolysis).

Other side effects presented in order of decreasing frequency:

Very Common (may occur with more than 1 in 10 infusions**):**
Headache

Common (may occur with up to 1 in 10 infusions):
High blood pressure (hypertension), upset stomach (nausea), vomiting, hives, rash, back pain, fever, chills, tiredness (fatigue), physical weakness (asthenia), flu-like illness.

Uncommon (may occur with up to 1 in 100 infusions):
Breakdown of red blood cells (haemolysis), temporary lowering of red blood cell count (anaemia), decreased number of white blood cells (leukopenia), irregularity of red blood cell shape (microscopic finding), dizziness, head discomfort, sleepiness, shiver (tremor), nasal sinus headache, migraine, abnormal sense of touch (dysaesthesia), vertigo, abnormal awareness of heartbeat, low blood pressure, flushing, lack of blood supply to the lower extremities causing e.g. pain when walking (peripheral vascular disorder), breathlessness, blisters in mouth and throat, painful breathing, throat tightness, diarrhoea, upper stomach pain, mild jaundice, itching, skin disorder, night sweats, pain (including neck pain, pain in extremity, chest pain, muscle pain, pain and stiffness of muscles and bones), muscle spasms, muscular weakness, protein in the urine (on testing), increase of body temperature, injection site pain, decrease in blood pressure, increase in blood pressure.

Routine laboratory tests may uncommonly reveal changes to liver or kidney functions as well as changes in blood count.

➔ If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet.

Please also refer to section 2 “What you need to know before you are given Privigen” for additional details on circumstances which increase the risk of side effect.

5. How to store Privigen

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the vial label after EXP. The expiry date refers to the last day of that month.

- Because the solution contains no preservative, your healthcare professional must infuse it immediately after opening the vial.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- Do not use this medicine if you notice that the solution is cloudy or has particles floating within the solution.

6. Contents of the pack and other information

What Privigen contains

- The **active substance** is human normal immunoglobulin (antibodies of the type IgG). Privigen contains 100 mg/ml (10%) human protein of which at least 98% is IgG.
  The approximate percentage of IgG subclasses is as follows:
  IgG_1 ..... 67.8%
  IgG_2 ..... 28.7%
  IgG_3 ..... 2.3%
  IgG_4 ..... 1.2%
  This medicine contains trace amounts of IgA (not more than 25 micrograms/ml).
  Privigen is essentially sodium free.
- The **other ingredients** (excipients) are the amino acid proline and water for injections.

What Privigen looks like and contents of the pack

Privigen is presented as a solution for infusion.
The solution is clear or slightly opalescent and colourless to pale-yellow.

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.

Marketing Authorisation Holder and Manufacturer

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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for healthcare professionals only:

Posology and method of administration

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 to 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 to 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	on day 1, possibly repeated once within 3 days
	0.4 g/kg bw/d	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 2-5 days
	maintenance dose 1 g/kg bw	every 3 weeks over 1-2 days

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, 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%).

Special precautions

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

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.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in the section below.

Special precautions for disposal and other handling

The product should be brought to room or body temperature before use. A vented infusion line should be used for the administration of Privigen. 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 is recommended. For obtaining an immunoglobulin solution of 50 mg/ml (5%), Privigen 100 mg/ml (10%) should be diluted with an equal volume of the glucose solution. Aseptic technique must be strictly observed during the dilution of Privigen.
Once the vial has been entered under aseptic conditions, its contents should be used promptly. Because the solution contains no preservative, Privigen should be infused as soon as possible.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.