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 ..... 69 %
IgG_2 ..... 26 %
IgG_3 ..... 3 %
IgG_4 ..... 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 syndromes (PID) with impaired antibody production (see section 4.4).
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l.

* PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

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 (in conjunction with acetylsalicylic acid; see section 4.2.).
- Chronic inflammatory demyelinating polyneuropathy (CIDP). Only limited experience is available of use of intravenous immunoglobulins in children with CIDP.
- Multifocal motor neuropathy (MMN)

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 clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.
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 6 g/l or within the normal reference range for the population age. 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 IgG of 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.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Secondary immunodeficiencies (as defined in 4.1)
The dose regimen should achieve a trough IgG level (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. The recommended dose is 0.2 – 0.4 g/kg bw every three to four weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

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 (possible repeat of dosing in case of relapse).

Kawasaki disease
2.0 g/kg bw should be administered 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 treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long term treatment should be subject to the physicians discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal Motor Neuropathy (MMN)
Starting dose: 2 g/kg given over 2-5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle. If insufficient treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long term treatment should be subject to the physician's discretion based upon the patient response. The dosing and intervals may have to be adapted according to the individual course of the disease.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy		
Primary immunodeficiency syndromes (PID)	starting dose: 0.4 - 0.8 g/kg bw	
	maintenance dose: 0.2 - 0.8 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies (as defined in 4.1)	0.2 - 0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Immunomodulation		
Primary immune thrombocytopenia (ITP)	0.8 - 1 g/kg bw	on day 1, possibly repeated once within 3 days
	or	
	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	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
Multifocal Motor Neuropathy (MMN)	starting dose : 2 g/kg bw	over 2 to 5 consecutive days
	maintenance dose:	
	1 g/kg bw	every 2 to 4 weeks
	or	or
	2 g/kg bw	every 4 to 8 weeks over 2 to 5 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 physician's 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.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration
For intravenous use.
Privigen 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 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 gradually increased 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 (human immunoglobulins) or to any of the excipients listed in section 6.1 (see also section 4.4).
Patients with selective IgA deficiency who developed antibodies to IgA as administering an IgA-containing product can result in anaphylaxis.
Patients with hyperprolinaemia type I or II.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 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 (see section 4.5.).
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.

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

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. The Privigen manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Privigen manufactured with the IAC step show statistically significant reductions of haemolytic anaemia (see section 4.8, section 5).
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. 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 bw) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

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 based on clinical judgement.

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.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals.

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 based on clinical judgement.

Transfusion-related acute lung injury (TRALI)
In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours of a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

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.

Sodium content
This medicinal product contains less than 2.3 mg sodium per 100 ml, equivalent to 0.12% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

Loop diuretics
Avoidance of concomitant use of loop diuretics.

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

Privigen has minor influence on the ability to drive and use machines, e.g. dizziness (see section 4.8). 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.

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 (including cutaneous lupus erythematosus – frequency unknown) have been observed with human normal immunoglobulin.

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

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

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

Tabulated list of adverse reactions

Seven 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. Another clinical study included 11 PID patients in Japan. Two ITP studies were performed with 57 patients each. Two CIDP studies were performed with 28 and 207 patients, respectively.

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

The following table shows an overview of the ADRs observed in the seven 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 Reaction**	**Frequency per patient**	**Frequency per infusion**
Infections and infestations	Aseptic meningitis	Uncommon	Rare
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia)[β], leukopenia	Common	Uncommon
	Anisocytosis (including microcytosis)	Uncommon	Uncommon
	Thrombocytosis		Rare
	Decreased neutrophil count	Unknown	Unknown
Immune system disorders	Hypersensitivity	Common	Uncommon
	Anaphylactic shock	Unknown	Unknown
Nervous system disorders	Headache (including sinus headache, migraine, head discomfort, tension headache)	Very common	Very common
	Dizziness (including vertigo)	Common	Uncommon
	Somnolence	Uncommon	Uncommon
	Tremor		Rare
Cardiac disorders	Palpitations, tachycardia	Uncommon	Rare
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia)	Common	Uncommon

MedDRA System Organ Class (SOC)	Adverse Reaction	Frequency per patient	Frequency per infusion
	Hypotension		Rare
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon	Rare
	Transfusion related acute lung injury	Unknown	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common	Uncommon
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Common	Common
	Abdominal pain		Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Common	Rare
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)	Common	Uncommon
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon	Rare
	Acute renal failure	Unknown	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	Common
	Fatigue	Common	Common
	Asthenia (including muscular weakness)		Uncommon
	Injection site pain (including infusion site discomfort)	Uncommon	Rare
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	Uncommon

[β] The frequency is calculated based on studies completed prior to implementation of the Immunoaffinity Chromatography isoagglutinin reduction step (IAC) into Privigen production. In a Post-Authorization Safety Study (PASS): "Privigen Use and Haemolytic Anaemia in Adults and Children and the Privigen Safety Profile in Children with CIDP – An Observational Hospital-Based Cohort Study in the US", assessing data of 7,759 patients who received Privigen identifying 4 haemolytic anaemia cases after IAC versus 9,439 patients who received Privigen identifying 47 haemolytic anaemia cases prior to IAC (baseline), an 89% statistically significant reduction in the overall rate of probable haemolytic anaemia was demonstrated based on an incidence rate ratio of 0.11 adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use (one-sided p-value <0.01). Probable cases of haemolytic anaemia were defined by an International Classification of Disease (ICD)-9 or ICD-10 hospital discharge code specific for haemolytic anaemia. Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD-9 or ICD-10

discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia.

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 and thus help against infections.
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 7 prospective, open-label, single-arm, multicenter studies performed in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP studies), and the US (PID and CIDP studies).
Additional safety data were collected in a Post-Authorization Safety Study (PASS), an observational multicentre trial in patients with various immunological conditions performed in the US.

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.

Post-Authorisation Safety Study (PASS)
In an observational hospital-based cohort Post-Authorisation Safety Study (PASS), the risk of haemolytic anaemia following Privigen therapy was evaluated in patients with various immunological conditions from 1 January 2008 to 30 April 2019. The risk of haemolytic anaemia was assessed prior (baseline) and after the implementation of a risk minimisation measure, the introduction of the Immunoaffinity Chromatography (IAC) step in the Privigen manufacturing process. Probable cases of haemolytic anaemia were defined by an ICD-9 or ICD-10 hospital discharge code specific for haemolytic anaemia. (Possible cases of haemolytic anaemia consisted of an unspecified transfusion reaction identified via ICD-9 or ICD-10 discharge codes or via review of hospital charge descriptions in temporal association with a haptoglobin, a direct antiglobulin test or indirect antiglobulin performed in the workup of haemolytic anaemia).

A statistically significant rate reduction of 89% of haemolytic anaemia (based on an incidence rate ratio of 0.11; adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use; one-sided p-value <0.01) was observed after implementation of the IAC step compared to baseline:

	Baseline	**IAC**
Period[ϕ]	1. January 2008- 31. December 2012	1. October 2016- 30. April 2019
Median anti-A titers[£]	1:32	1:8
Median anti-B titers[£]	1:16	1:4
Probable haemolytic anaemia[α] cases	47	4
Patient number (n)	n=9439	n=7759
Crude incidence rate of probable haemolytic anaemia [α] per 10.000 patient-days at risk	0.74 95% CI[&]: 0.54-0.98	0.08 95% CI: 0.02-0.20
Incidence rate reduction of probable haemolytic anaemia [α] versus baseline	-	89%
Adjusted[§] incidence rate ratio for haemolytic anaemia versus baseline	-	0.11 95% CI: 0.04-0.31, one-sided p-value: <0.01

[ϕ] The exclusion of human blood plasma donors with high anti-A titres performed between 1. October 2013 and 31. December 2015 as the initial risk minimisation measure for haemolytic anaemia indicated a 38% reduction in probable haemolytic anaemia incidence versus baseline and was subsequently replaced by the IAC step in the Privigen manufacturing process, as provided above.
[£] Median isoagglutinin titers measured by direct testing method according to Ph.Eur

[α] Probable haemolytic anaemia case: defined by an ICD-9 or ICD-10 hospital discharge code specific for haemolytic anaemia and the occurrence during the time interval from the first infusion up to 30 days after the last infusion, if >1 Privigen infusions were administered
[&] Confidence interval
[§] Adjusted for: in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use

The reduction in probable haemolytic anaemia incidence rate after IAC implementation versus baseline was especially pronounced in patients treated with Privigen doses ≥0.75 g/kg bw.

Additionally, 28 paediatric patients with CIDP <18 years of age were identified throughout the entire study period from 1 January 2008 to 30 April 2019. No paediatric patients with CIDP given a total of 486 Privigen administrations experienced haemolytic anaemia, AMS, acute renal failure, severe anaphylactic reaction or a thromboembolic event. Two patients experienced a moderate anaphylactic reaction, equating to 0.4% of all Privigen administrations.

Paediatric population
No differences were observed in the pharmacodynamic properties and safety profile 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
Hydrochloric acid (for pH-adjustment)
Sodium hydroxide (for pH adjustment)

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 latest renewal: 28 November 2017

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

or

CSL Behring (Australia) Pty Ltd
189-209 Camp Road
Broadmeadows, Vic 3047, Australia

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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, hydrochloric acid, sodium hydroxide.
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

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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, hydrochloric acid, sodium hydroxide.

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

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):</u>
   1. Patients who are born with a reduced ability or inability to produce immunoglobulins (primary immunodeficiencies (PID)).
   2. Patients with an acquired immunodeficiency (SID) who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of <4 g/l.

B) <u>To treat certain inflammatory disorders (immunomodulation). There are 5 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.
5. Patients with multifocal motor neuropathy (MMN). This is a slowly progressive disease of the motor nerves with weakness of arms and legs.

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 type I or II (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").
- In very rare cases transfusion-related acute lung injury (TRALI) can occur after receiving immunoglobulins. This will lead to non-heart related accumulation of fluid in the air spaces of the lungs (non-cardiogenic pulmonary oedema). You will recognize TRALI by severe difficulty in breathing (respiratory distress), bluish skin (cyanosis), abnormally low level of oxygen in the blood (hypoxia), decrease in blood pressure (hypotension) and increased body temperature (fever). Symptoms typically appear during or within 6 hours after receiving treatment.
  ➔ 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 having any blood tests.

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.

The concomitant use of medicines that increase the excretion of water from your body (loop diuretics) should be avoided during treatment with Privigen. Your doctor will decide whether you should use or continue treatment with loop diuretics.

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 and 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.

Sodium content
This medicine contains less than 2.3 mg sodium (main component of cooking/table salt) in 100 ml. This is equivalent to 0.12% of the recommended maximum daily dietary intake of sodium for an adult.

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) which might increase the risk of developing blood clots. This may happen particularly if you are a patient at risk, for example if you are elderly or if you suffer from a heart or kidney disease. Tell your doctor if you are known to have medical problems.

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 anaphylactic 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),
- chest pain, chest discomfort, painful respiration due to transfusion related lung injury (TRALI)
  - ➔ 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.
- increase in blood creatinine level,
- proteinuria,
- acute renal failure,
- transient decrease in red blood cells (reversible haemolytic anaemia/haemolysis), anaemia, leukopenia, anisocytosis (including microcytosis).

Side effects observed in controlled clinical studies and in post-marketing experience are presented in o rder of decreasing frequency:

Very Common (may occur with more than 1 in 10 patients**):**
Headache (including sinus headache, migraine, head discomfort, tension headache), pain (including ba ck pain, pain in extremity, pain in joints and bones (arthralgia), neck pain, facial pain), fever (includin g chills), flu-like illness (including runny nose (nasopharyngitis), sore throat (pharyngolaryngeal pain), blisters in mouth and throat (oropharyngeal blistering), throat tightness.

Common (may occur with up to 1 in 10 patients):
Temporary lowering of red blood cell count (anaemia), breakdown of red blood cells (haemolysis including haemolytic anaemia)$^{\beta}$, decreased number of white blood cells (leukopenia), hypersensitivity, dizziness (including vertigo), high blood pressure (hypertension), flushing (including hot flush, hyperaemia), hypotension (including decreased blood pressure), breathlessness (dyspnoea including chest pain, chest discomfort, painful breathing), upset stomach (nausea), vomiting, loose stools (diarrhea), stomach pain, skin disorder (including rash, itching (pruritus), hives (urticaria), maculopapular rash, redness of the skin (erythema), peeling of the skin (skin exfoliation)), pain in the muscles (including muscle cramps and rigidity), tiredness (fatigue), physical weakness (asthenia), weakness in the muscles, .

Routine laboratory tests may commonly reveal changes to liver functions (hyperbilirubinaemia) as well as changes in blood count (e.g. Coombs' (direct) test positive), increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase).

Uncommon (may occur with up to 1 in 100 patients):
Temporary non-infectious meningitis (reversible aseptic meningitis), irregularity of red blood cell shape (microscopic finding), presence of high platelet counts in the blood (thrombocytosis), sleepiness, shiver (tremor), palpitations, tachycardia, thromboembolic events, lack of blood supply to the lower extremities causing e.g. pain when walking (peripheral vascular disorder), presence of an excess of serum proteins in the urine (proteinuria including increased blood creatinine), injection site pain (including infusion site discomfort).

In isolated cases (post-marketing experience), the following have been observed in patients treated with Privigen: abnormally low level of specific white blood cells called neutrophils (decreased neutrophils counts), anaphylactic shock, painful respiration due to transfusion related lung injury (TRALI) and acute renal failure.

[β] The haemolytic anaemia cases after controlled clinical study completion were observed at significantly reduced frequency due to enhancements in the Privigen manufacturing process.

➔ 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 effects.

Reporting of side effects
If you get any side effects, talk to your doctor or healthcare professional. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

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 contains 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 ..... 69 %
IgG_2 ..... 26 %
IgG_3 ..... 3 %
IgG_4 ..... 2 %
This medicine contains trace amounts of IgA (not more than 25 micrograms/ml).

- The **other ingredients** (excipients) are the amino acid proline, water for injections, and hydrochloric acid or sodium hydroxide (for pH adjustment).

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:

België/Belgique/Belgien
CSL Behring NV
Tél/Tel: +32 15 28 89 20

България
МагнаФарм България
Тел: +359 2 810 3949

Česká republika
CSL Behring s.r.o.
Tel: +420 702 137 233

Danmark
CSL Behring ApS
Tlf: +45 4520 1420

Deutschland
CSL Behring GmbH
Tel: +49 69 30584437

Eesti
CSL Behring GmbH
Tel: +49 69 30584437

Ελλάδα
CSL Behring ΕΠΕ
Τηλ: +30 210 7255 660

Luxembourg/Luxemburg
CSL Behring NV
Tél/Tel: +32 15 28 89 20

Magyarország
CSL Behring Kft.
Tel: +36 1 213 4290

Malta
AM Mangion Ltd.
Tel: +356 2397 6333

Nederland
CSL Behring BV
Tel: +31 85 111 96 00

Norge
CSL Behring AB
Tlf: +46 8 544 966 70

Österreich
CSL Behring GmbH
Tel: +43 1 80101 2463

Polska
CSL Behring Sp. z o.o.
Tel.: +48 22 213 22 65

España
CSL Behring S.A.
Tel: +34 933 67 1870

France
CSL Behring SA
Tél: +33 1 53 58 54 00

Hrvatska
Marti Farm d.o.o.
Tel: +385 1 5588297

Ireland
CSL Behring GmbH
Tel: +49 69 30517254

Ísland
CSL Behring AB
Sími: +46 8 544 966 70

Italia
CSL Behring S.p.A.
Tel: +39 02 34964 200

Κύπρος
CSL Behring ΕΠΕ
Τηλ: +30 210 7255 660

Latvija
CSL Behring GmbH
Tel: +49 69 30584437

Lietuva
CSL Behring GmbH
Tel: +49 69 30584437

Portugal
CSL Behring Lda
Tel: +351 21 782 62 30

România
Prisum International Trading srl
Tel: +40 21 322 01 71

Slovenija
NEOX s.r.o
Tel: +386 41 42 0002

Slovenská republika
CSL Behring s.r.o.
Tel: +421 911 653 862

Suomi/Finland
CSL Behring AB
Puh/Tel: +46 8 544 966 70

Sverige
CSL Behring AB
Tel: +46 8 544 966 70

United Kingdom
CSL Behring UK Ltd.
Tel: +44 1444 447405

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Detailed information on this medicine is available on the European Medicines Agency website: 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		
Primary immunodeficiency syndromes (PID)	starting dose: 0.4 - 0.8 g/kg bw	
	maintenance dose: 0.2 - 0.8 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies (as defined in 4.1)	0.2 - 0.4 g/kg bw	every 3 to 4 weeks to obtain IgG trough levels of at least 6 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	2 g/kg bw	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)*	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2 to 5 days every 3 weeks over 1 to 2 days
Multifocal Motor Neuropathy (MMN)	starting dose : 2 g/kg bw maintenance dose: 1 g/kg bw or 2 g/kg bw	over 2 to 5 consecutive days every 2 to 4 weeks or every 4 to 8 weeks over 2 to 5 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 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.