





### Tabulated list of adverse reactions

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

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

The following table shows an overview of the ADRs in the six studies, categorized according to MedDRA System Organ Class (SOC and Preferred Term (PT)) and frequency. Frequencies per infusion were evaluated according to the following conventions: Very common ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). 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	Adverse Reaction MedDRA Preferred Term	ADR frequency category
Infections and infestations	Aseptic meningitis	Uncommon
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia), leukopenia	Common
	Anisocytosis (including microcytosis), thrombocytosis	Uncommon
	Decreased neutrophil count	Unknown
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Unknown
Nervous system disorders	Headaches (including sinus headache, migraine, head discomfort, tension headache)	Very Common
	Dizziness (including vertigo)	Common
	Somnolence, tremor	Uncommon
Cardiac disorders	Palpitations, tachycardia	Uncommon
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia), hypotension	Common
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon
	Transfusion related acute lung injury	Unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common
Gastrointestinal disorders	Nausea	Very Common
	Vomiting, diarrhoea, abdominal pain	Common
Hepatobiliary disorders	Hyperbilirubinaemia	Common
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)	Common
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon
	Acute renal failure	Unknown
General disorders and administration site conditions	Pain (including back pain, pain in extremity, arthralgia, neck pain, facial pain), pyrexia (including chills), influenza like illness (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very Common
	Fatigue, asthenia (including muscular weakness)	Common
	Injection site pain	Uncommon
Investigations	Decreased haemoglobin (including decreased red blood cell count, decreased haematocrit), Coombs' (direct) test positive, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase	Common

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

### 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 "Warnings and precautions" 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.

### Overdose

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

### Properties / Effects

#### Mechanism of Action/Pharmacodynamics

Privigen is prepared from plasma from 1000 or more human donors. The manufacturing process for Privigen includes the following steps: ethanol precipitation of the IgG plasma fraction, followed by octanoic acid fractionation and incubation at pH 4. Subsequent purification steps comprise depth filtration, chromatography, immunoaffinity chromatography to specifically reduce blood group A and B antibodies (isoagglutinins A and B) and a filtration step that can remove particles to a size of 20 nm.

Privigen contains mainly IgG that are present in the normal human population and that show a broad spectrum of functionally intact antibodies against infectious agents. In the replacement therapy adequate doses of Privigen may restore abnormally low IgG levels to the normal range and thus help against infections.

The IgG subclass distribution in Privigen corresponds roughly to that of native human plasma. Both the Fc and the Fab functions of the IgG molecules are preserved. The ability of the Fab parts to bind antigens was demonstrated with biochemical and biological methods. The Fc function was tested with complement activation and with Fc receptor-mediated leukocyte activation. The inhibition of immune complex-induced complement activation ("scavenging", an anti-inflammatory function of IVIGs) is preserved in Privigen. Privigen does not lead to non-specific activation of the complement system or of prekalikrein.

The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

### Clinical Efficacy

The safety and efficacy of Privigen was investigated in 6 prospective, open, single-arm, multicentre studies carried out in Europe (ITP, PID and CDP studies) and in the USA (PID study). Further data on safety and efficacy were collected in a prospective, open, single-arm, multicentre extension study with PID patients performed in the USA.

#### PID

In the pivotal study, 80 patients between 3 and 69 years of age with PID were given a Privigen infusion at a median dose of 200–888 mg/kg bw every 3 to 4 weeks for at most 1 year. With this treatment, constant IgG trough levels were achieved over the whole of the treatment period, the mean concentrations being 8.84 g/l to 10.27 g/l. The incidence of acute, severe bacterial infections (aSBI) was 0.08 per patient per year (the upper 97.5% confidence limit was 0.182). As in the pivotal study, Privigen dosages were administered in the PID extension study to a total of 55 patients (of which 45 had already been treated in the pivotal study and 10 were newly recruited patients). The results of the pivotal study were confirmed for the average IgG trough levels (9.31 g/l to 11.15 g/l) and the rate of aSBI (0.018 per patient per year with an upper 97.5% confidence interval of 0.098).

#### ITP

57 patients aged between 15 and 69 years with chronic ITP took part in the ITP study. Their platelet count at the start was  $20 \times 10^9/l$ . After administration of Privigen at a dose 1 g/kg bw on two consecutive days, the platelet count rose to at least  $50 \times 10^9/l$  within 7 days of the first infusion in 80.7% of the patients. In 43% of the patients, this increase occurred after just one day, before the second infusion. The mean time until this platelet count was reached was 2.5 days. In patients who responded to the treatment, the platelet count remained  $\geq 50 \times 10^9/l$  for a mean period of 15.4 days.

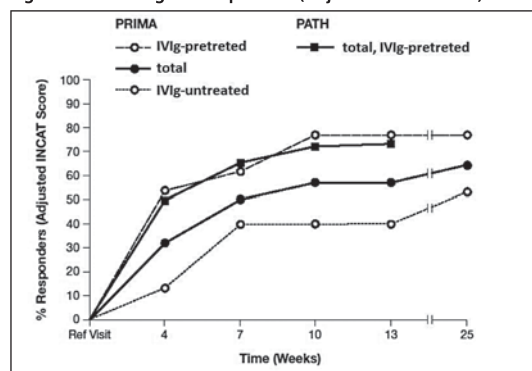
In the second ITP study on patients aged between 18 and 65 years, in 42 subjects (74%) the platelet count increased at least once to  $\geq 50 \times 10^9/l$  within 6 days after the first infusion, which was well within the expected range and similar to response rates were reported for other IVIGs in this indication (70%). A second dose in subjects with platelet counts  $\geq 50 \times 10^9/l$  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  $< 50 \times 10^9/l$  on day 3 receiving a mandatory second infusion, the lowest median platelet count ( $8.0 \times 10^9/l$ ) was observed already at the baseline. In this group, only 30% of subjects were observed with platelet response after the mandatory second dose. Consequently, it was more difficult to increase platelet counts with one infusion in these subjects.

#### CDP

In the first CDP study, a prospective multicenter open label trial PRIMA (Privigen impact on mobility and autonomy study), 28 patients with CDP (13 subjects with and 15 without IVIg pre-treatment) were treated with a loading dose of 2 g/kg bw given over 2–5 days followed by 6 maintenance doses of 1 g/kg bw given over 1–2 days every 3 weeks. Previously treated patients were withdrawn from IVIg before treatment with Privigen until the deterioration of clinical symptoms was confirmed on the basis of the INCAT scale (Inflammatory Neuropathy Cause and Treatment). On the adjusted 10 point INCAT scale a clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was observed in 17/28 patients (60.7%, 95% confidence interval 42.41, 76.4). Nine patients responded already after receiving the initial induction dose to the treatment at week 4 and 16 by week 10.

In a second clinical study, a prospective, multicenter randomized, placebo-controlled PATH [Polyneuropathy and Treatment with Hizentra] study, 207 subjects with CDP were treated with Privigen in the prerandomization phase of the study. Subjects all with IVIg pretreatment of at least 8 weeks and 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 CDP was primarily defined by a decrease of  $\geq 1$  point at the adjusted INCAT score. Additional measures of CDP improvement were an R-ODS increase of  $\geq 4$  points, a mean grip strength increase of  $\geq 8$  kPa, or an MRC sum score increase of  $\geq 3$  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 CDP status as assessed by the adjusted INCAT score compared to their CDP status at study entry. The comparability of the response rates and mean adjusted INCAT scores for the IVIg pretreated subjects in both PRIMA and PATH study are shown in the Figure 1 below.

Figure 1. Percentage of Responders (Adjusted INCAT Score)



IVIg: intravenous immunoglobulin; Ref Visit: reference visit

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  $\geq 3$  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 studies, PRIMA and PATH.

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

### Paediatric population

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

### Pharmacokinetics

Privigen is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively quickly between plasma and extravascular fluid. Equilibrium between the intravascular and extravascular compartments is reached after approximately 3 to 5 days.

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 both clinical studies in patients with primary immunodeficiency syndrome (see section "Properties/Effects"). 25 patients (aged 13 to 69 years) in the pivotal study and 13 patients (aged 9 to 59 years) in an extension of this study participated in the pharmacokinetic (PK) assessment (see table below).

### Pharmacokinetic parameters of Privigen in patients with primary immunodeficiency syndrome

Parameter	Pivotal study (N=25) Median (range)	Extension study (N=13) Median (range)
$C_{max}$ (peak level) in g/l	23.4 (10.4–34.6)	26.3 (20.9–32.9)
$C_{min}$ (trough level) in g/l	10.2 (5.8–14.7)	9.75 (5.72–18.01)
$t_{1/2}$ (half-life) in 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;  $t_{1/2}$ , elimination half-life.

In the pivotal study the median half-life of Privigen in primary immunodeficiency patients was 36.6 days and 31.1 days in the extension of this study.

### 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 CDP.

### Preclinical data

The safety of Privigen has been investigated in several preclinical studies with particular reference to the excipient L-proline. L-proline is a physiological, non-essential amino acid. Studies in rats given daily L-proline doses of 1450 mg/kg bw did not show any evidence of teratogenicity or embryotoxicity. Genotoxicity studies of L-proline did not show any pathological findings.

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. Further safety-pharmacology studies of L-proline in adult and juvenile rats did not reveal behavioural disorders.

Immunoglobulins are natural components of the human body. Data from animal testing of acute and chronic toxicity and embryofetal toxicity of immunoglobulins are inconclusive on account of interactions between immunoglobulins from heterogeneous species and the induction of antibodies to heterologous proteins. In local tolerability studies in rabbits in which Privigen was administered intravenously, paravenously, intra-arterially, and subcutaneously, the product was well tolerated.

### Other information

#### Incompatibilities

This medicine must not be mixed with other medicinal products nor with physiological saline. However, dilution with 5% glucose solution is permitted.

#### Influence on diagnostic tests

After infusion of immunoglobulins, the transient increase in the various passively transmitted antibodies in the patient's blood can lead to false-positive results in serological tests.

The passive transmission of antibodies to erythrocyte antigens, e.g. A, B and D, can lead to incorrect results in some serological tests for erythrocyte isoantibodies (e.g. Coombs' test), determinations of the reticulocyte count, and the haptoglobin test.

For interactions with attenuated live vaccines, see section "Interactions".

#### Shelf life and special precautions for storage

Privigen is stable until the expiry date stated on the vial label and the outer carton after "EXP". After the imprinted expiry date (EXP) the medicine must not be used. Do not store above 25 °C. Do not freeze. Do not use if Privigen has been frozen. Do not shake. Keep out of the sight and reach of children. Keep the vial in the outer carton in order to protect from light.

#### Shelf life of the product after opening

Privigen is intended for single use. Because the solution contains no preservative, Privigen should be used / infused immediately once opened.

#### Instructions for use and handling

Privigen is a ready-to-use solution. The product should be at room or body temperature before use. A vented infusion line with integrated filter should be used for the administration of Privigen. Always pierce the stopper at its centre, within the marked area. 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. Privigen must not be mixed with physiological saline. However, after-rinsing of the infusion tubes with physiological saline is permitted. The solution must be clear or slightly opalescent. Do not use solutions that are cloudy or have particulate matter. Any unused product and waste material should be disposed of in accordance with local requirements.

#### Packs

Solution in vials:

- 2.5 g / 25 ml
- 5 g / 50 ml
- 10 g / 100 ml
- 20 g / 200 ml

#### Packed by Benta SAL

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#### Under license from

CSL Behring AG, Bern, Switzerland

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Note: Privigen® is a registered trademark of CSL Behring AG in many countries.

- This is a medicament
- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
  - Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
  - The doctor and the pharmacist are the experts in medicines, their benefits and risks.
  - Do not by yourself interrupt the period of treatment prescribed for you.
  - Do not repeat the same prescription without consulting your doctor.
  - Keep all medicaments out of reach of children.

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