CSL Behring

Name of the medicinal product

Privigen ™

Human normal immunoglobulin

Solution for infusion (10%)

For intravenous use only

Composition

a. Active substance

Human immunoglobulin for intravenous use (IVIg)*.

Human plasma protein containing at least 98% immunoglobulin G (IgG).

Distribution of the IgG subclasses (average 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.

b. Excipients

L-proline, water for injections.

Privigen contains trace amounts of sodium (≤ 1 mmol/l).

Privigen contains no preservatives.

Privigen contains no carbohydrate stabiliser (e.g. sucrose, maltose).

Pharmacotherapeutic group

Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration.

ATC code:

J06BA02

Pharmaceutical form and active substance content per unit

Solution for intravenous infusion.

1 ml of solution contains: 100 mg human plasma protein with an IgG content of at least 98% (10% solution).

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

The pH value of the ready-to-use solution is 4.6 to 5.0 [4.8].

Therapeutic indications

Replacement therapy in

- *Primary immunodeficiency syndromes (PID)* such as:
  - congenital agammaglobulinaemia and hypogammaglobulinaemia
  - common variable immunodeficiency
  - severe combined immunodeficiency
  - Wiskott-Aldrich syndrome

- *Myeloma* or *chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections*

- *Children with congenital AIDS and recurrent infections*

Immunomodulation

- *Immune thrombocytopenic purpura (ITP) in children or adults at high risk of bleeding or prior to surgical interventions to correct the platelet count*
- *Guillain-Barré syndrome*
- *Kawasaki disease*
- *Chronic inflammatory demyelinating polyneuropathy (CIDP)*

Allogeneic bone marrow transplantation

Dosage/Administration

Dosage

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

Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough IgG level (measured before the next infusion) of at least 5 to 6 g/l. Three to 6 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) followed by at least 0.2 g/kg bw every 3 to 4 weeks.

The dose required to achieve a trough level of 5 to 6 g/l is of the order of 0.2 to 0.8 g/kg bw/month. The dosage interval when steady state has been reached varies from 3 to 4 weeks. Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in myelomas or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with congenital AIDS and recurrent infections

The recommended dosage is 0.2 to 0.4 g/kg bw every 3 to 4 weeks.

Immune thrombocytopenic purpura

For the treatment of an acute episode, 0.8 to 1 g/kg bw on day one, which may be repeated once within 3 days, or 0.4 g/kg bw daily for 2 to 5 days. The treatment can be repeated if relapse occurs (see also section “Properties/Effects”).

Guillain-Barré syndrome

0.4 g/kg bw/day over 5 days. Experience in children is limited.

Kawasaki disease

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

Chronic inflammatory demyelinating polyneuropathy (CIDP)

The recommended starting dose is 2 g/kg bw divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg bw given on one day or divided over 2 consecutive days every 3 weeks.

The long-term therapy over 25 weeks depends on the patient`s response to the maintenance therapy. The lowest effective maintenance dose and the dosage regimen are to adjust according to the individual course of the disease.

Allogeneic bone marrow transplantation

Human immunoglobulin therapy can be used as part of the conditioning regimen and after transplantation. To treat infections and prevent graft-versus-host disease, the dosage should be individually adjusted.

The starting dosage is usually 0.5 g/kg bw/week, commencing seven days before the transplant. The treatment is continued for up to 3 months after the transplant. If the lack of antibody production persists, a dosage of 0.5 g/kg bw/month is recommended until IgG antibody levels return to normal.

The dosages recommendations are summarised in the following table:

Indications	**Dose**	**Intervals between injections**
<u>Replacement therapy in</u> *primary immunodeficiency syndromes*	starting dose: 0.4-0.8 g/kg bw thereafter: 0.2-0.8 g/kg bw	 every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l
secondary immunodeficiency syndromes	0.2-0.4 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 5-6 g/l
children with congenital HIV infection and recurrent infections	0.2-0.4 g/kg bw	every 3-4 weeks
<u>Immunomodulation</u> *Immune thrombocytopenic purpura*	0.8-1 g/kg bw or 0.4 g/kg bw/day	on the first day; the therapy may be repeated once within 3 days over 2-5 days
Guillain-Barré syndrome	0.4 g/kg bw/day	over 5 days
Kawasaki disease	1.6-2 g/kg bw or 2 g/kg bw	divided into several doses given over 2-5 days in conjunction with acetylsalicylic acid as a single dose in conjunction with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2-5 days every 3 weeks over 1-2 days

Allogeneic bone marrow transplantation		
– treatment of infections and prevention of graft-versus-host disease	0.5 g/kg bw	weekly, from day 7 before up to 3 months after the transplant
– persistent lack of antibody production	0.5 g/kg bw	monthly, until antibody levels return to normal

bw = body weight

Use of the product in paediatric population

In the phase III pivotal study on patients with primary immunodeficiency diseases (n = 80), 19 patients between 3 and 11 years of age and 15 patients from 12 up to and including 18 years of age were treated. In an extension study of patients with primary immunodeficiency diseases (n = 55), 13 patients between 3 and 11 years of age and 11 between 12 and including 18 years of age were treated.

In the clinical study on 57 patients with chronic immune thrombocytopenic purpura 2 paediatric patients (15 and 16 years of age) were treated. No dose adjustment for children was required in these three studies.

Literature reports indicate that intravenous immunoglobulins are effective in children with CIDP. However, no data is available on Privigen in this respect.

Method of administration

Privigen should be infused intravenously.

Rate of infusion

The product should initially be infused at a rate of 0.3 ml/kg bw/hr (for approximately 30 min). If well tolerated, the infusion rate can be gradually increased to 4.8 ml/kg bw/hr. In patients with immunodeficiency syndrome who have tolerated substitution treatment with Privigen well, the infusion rate may be gradually increased to a maximal value of 7.2 ml/kg bw/hr.

Contraindications

Hypersensitivity to the active substance or the excipient (see section “Composition”).

Hypersensitivity to human immunoglobulins, especially in patients with IgA deficiency where the patient has anti-IgA antibodies.
Hyperprolinaemia. Hyperprolinaemia is a very rare disease, which affects only a few families worldwide.

Warnings and precautions for use

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section "Dosage/Administration: *Method of administration*" must be closely followed. Patients must be closely monitored and carefully-observed for any symptoms throughout the infusion period and thereafter.

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, switched from an alternative IVIg product or when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction. In case of shock, standard medical treatment for shock should be implemented.

Higher doses may be associated with increased rates of adverse effects. Therefore, the lowest effective dose should be sought in individual patients and careful monitoring routine is to establish.

In all patients, IVIg administration requires adequate hydration prior to the initiation of the infusion.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies. IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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

Haemolytic anaemia

IVIg products can contain blood group antibodies (e.g. anti-A and anti-B) 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 show statistically significant reductions of haemolytic anaemia (see section “Undesirable effects”).

Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation in some cases leading to 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; blood group A, B and AB (non-0 blood group) and underlying inflammatory state. As this event was commonly reported in patients with blood group A, B or AB (non-0 blood group) 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 IVIg infusion, discontinuation of IVIg treatment should be considered by the treating physician (see also section "Undesirable effects").

Aseptic meningitis syndrome (AMS)

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

AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulins in at-risk patients. Therefore 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, a history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, severe hypovolaemia, diseases which increase blood viscosity).

In patients at risk for thromboembolic reactions, IVIg products should be administered at the minimum rate of infusion and minimum 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 e.g. pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products containing various excipients such as sucrose, glucose and maltose those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose should therefore be considered. Privigen does not contain sucrose, maltose or glucose.

In patients at risk of acute renal failure, IVIg products should be administered at the minimum rate of infusion and minimum dose practicable based on clinical judgement.

Transfusion-related acute lung injury (TRALI)

Noncardiogenic pulmonary edema may very rarely occur following treatment with IVIg products. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Pathogen safety

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 (see also section “Properties/Effects”). 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 (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and for the non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins, and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is recommended that every time Privigen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Sodium content

Privigen is essentially sodium-free (Privigen has a low sodium content of ⩽ 1 mmol/l).

Paediatric population

Although limited data is available, it is expected that the same warnings, precautions and risk factors apply to the paediatric population.

Interactions

Live attenuated virus vaccines

After treatment with immunoglobulins, the efficacy of live attenuated vaccines, such as measles, mumps, rubella and chickenpox vaccines, may be impaired for a period of at least 6 weeks and up to 3 months. An interval of 3 months should elapse before vaccination with live attenuated vaccines. In the case of measles vaccinations, the decrease in efficacy may persist for up to a year. Patients given measles vaccine should therefore have their antibody status checked.

Paediatric population

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

Pregnancy, breast-feeding and fertility

Pregnancy

Controlled clinical data on the use of Privigen in pregnant women are not available. Caution should therefore be exercised with regard to administration during pregnancy. IVIg products have been shown to cross the placenta, increasingly during the third trimester.

Extensive clinical experience of immunoglobulins suggests that no harmful effects on the course of the pregnancy, or on the foetus and the newborn child 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.

Effect on driving and the operation of machines

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

Undesirable effects

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

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

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

Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB (non-0-blood groups) in immunomodulatory treatment. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see section “Warnings and precautions”).

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

Very rarely: transfusion related acute lung injury and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis have occurred.

Tabulated list of adverse reactions

Seven clinical studies were performed with Privigen, which included patients with PID, ITP and CIDP 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. 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 in the seven studies, categorized according to MedDRA System Organ Class (SOC and Preferred Term Level (PT)) and frequency. Frequencies per infusion were evaluated according to the following conventions: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10), Uncommon (≥ 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 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, 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, muscuskeletal 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, pharyngolarngeal pain, oropharyngeal blistering, throat tightness)	Very Common
	Fatigue, asthenia (including muscular weakness)	Common
	Injection site pain (including infusion site discomfort)	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

* The frequency is calculated based on studies completed prior to implementation of the Immuno-Affinity Chromatography isoagglutinin reduction step (IAC) into Privigen production. In a Post-Authorization Safety Study (PASS) assessing: "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", 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) showed a 89% statistically significant reduction in the overall rate of probable 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).

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 prekallikrein.

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 7 prospective, open, single-arm, multicentre studies carried out in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP study), and in the US (PID and CIDP study). Further data on safety and efficacy were collected in a prospective, open, single-arm, multicentre extension study with PID patients performed in the US.

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 x 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 x 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 ≥50 x 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 ≥50 × 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 ≥50×10^9/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 × 10^9/l on day 3 receiving a mandatory second infusion, the lowest median platelet count (8.0×10^9/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.

CIDP

In the first CIDP study, a prospective multicenter open label trial PRIMA (Privigen impact on mobility and autonomy study), 28 patients with CIDP (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 CIDP 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.

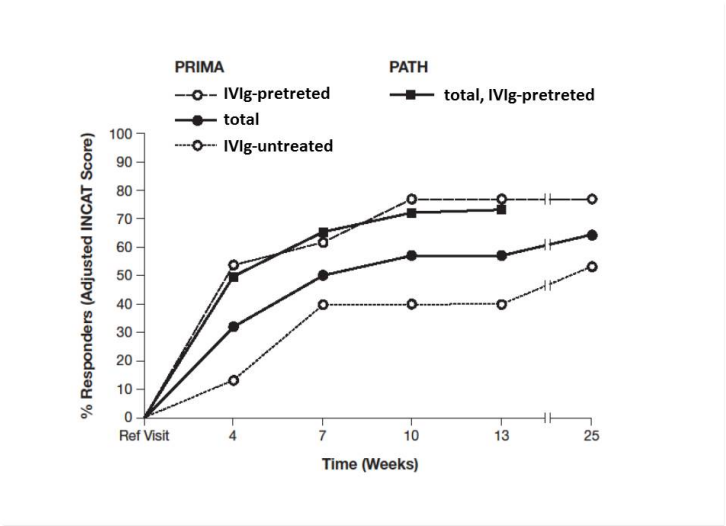
Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥ 1 point at the adjusted INCAT score. Additional measures of CIDP improvement were an R-ODS increase of ≥ 4 points, a mean grip strength increase of ≥ 8 kPa, or an MRC sum score 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 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 ≥ 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 CIDP patients were overall comparable.

Paediatric population

No differences were observed in the pharmacodynamic properties and safety profile 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)
$t_{½}$ (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; $t_{½}$, 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 CIDP.

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 embryofoetal 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.

<u>Shelf life of the product after opening:</u>

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

Manufactured by:

CSL Behring AG

Bern, Switzerland

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