1. Name of the Medicinal Product

Privigen®

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

*Produced from the plasma of human donors.

Excipients with known effects:
Privigen contains approximately 250 mmol/L of L-proline.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion.

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

4. Clinical Particulars

4.1 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

4.2 Posology and method of administration

Dosage
The dosage and dosage regimen is dependent on the indication. In replacement therapy the dosage may need to be individualized 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. 3 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 24 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**
Replacement therapy in *primary immunodeficiency diseases*	– 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 diseases	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
Immunomodulation *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 – persistent lack of antibody production	0.5 g/kg bw 0.5 g/kg bw	weekly, from day 7 before up to 3 months after the transplant 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 a 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.

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 (Coomb's 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-0 blood group; and underlying inflammatory state. As this event was commonly reported in non-0 blood group patients receiving high doses for non-PID indications, increased vigilance is recommended. Haemolysis has rarely been reported in patients given replacement therapy for PID.

IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. 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 (see section 4.8).
The syndrome usually begins within several hours to 2 days following IVIg treatment. Symptoms may include severe headache, nuchal rigidity, drowsiness, fever, photophobia, nausea, and vomiting. 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 and/or rapid infusion (see sections 4.2 and 4.4).

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.

Patients with a recurrence of AMS in association with IVIg treatment should be monitored for the emergence or worsening of symptoms potentially progressing to brain oedema (cerebral oedema). Brain oedema (cerebral oedema) carries the risk of a fatal outcome.

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. 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
	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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il
and emailed to the Registration Holder's Patient Safety Unit at: PV-IL@cslbehring.com

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 1000 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 ≥ 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 after the first dose, 30% showed a platelet response of ≥ 50×10^9 /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

[ʒ] 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

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
The expiry date of the product is indicated on the packaging materials.

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

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, see section 6.3.

6.5 Nature and contents of container
Packs
Solution in vials:
- 2.5 g/25 ml
- 5 g/50 ml
- 10 g/100 ml

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 center, 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 medical product and waste material should be disposed of in accordance with local requirements.

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