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MEA/EN MULTI MARKET MANUSCRIPT DATA SHEET

PRIVIGEN®

Revision date: October 2020
Reason for change:
MEA V2.0 local requirements updates.

Supersedes previous version(s):
CCDS V6.0 and V7.0

Revision date: October 2020
Reason for change: CCDS updates V8.0 **-** Additions and revisions based on data from the completed observational study IgPro10_5003 and the clinical study IgPro10_3004.

Note:

- Headers and footers will not be printed.

- SHADED TEXT: is used to highlight text which will not be printed. It is used for guidance and explanatory notes or text to be selected or deleted as appropriate

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

Composition

Active substance

Human normal immunoglobulin for intravenous administration (IVIg).

Human plasma protein with a minimum content of ≥98 % Immunoglobulin G (IgG).

IgG subclass distribution (approximate values): IgG_1 69%, IgG_2 26%, IgG_3 3% IgG_4 2%.

The maximum IgA content is 25 micrograms/mL.

The isoagglutinin titre is 1:8 for anti-A antibodies and 1:4 for anti-B antibodies (median measured by the direct agglutination test according to the European Pharmacopoeia (Ph.Eur.)).

Excipients

L-proline, sodium hydroxide (equivalent to maximum 1 mmol/L sodium), hydrochloric acid, water for injections.

Pharmaceutical form and active substance quantity per unit

Solution for infusion for intravenous use.

1 mL 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. The osmolarity is 320 mOsmol/kg and thus isotonic.

Indications/Uses

Replacement therapy in

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

- *Secondary immunodeficiencies (SID)* in patients with severe or recurrent infections, ineffective antimicrobial treatment, and either a confirmed inadequate increase of antibodies from vaccinations (PSAF*) or serum IgG levels of < 4 g/L.

*PSAF (proven specific antibody failure) = absence of at least a two-fold rise in the IgG antibody concentration against pneumococcal polysaccharide and polypeptide antigen vaccines.

Immunomodulation

- *Primary immune thrombocytopenia (ITP), to correct the platelet count in children or adults at high risk of bleeding or before surgery*
- *Guillain-Barré syndrome*
- *Kawasaki disease*
- *Chronic inflammatory demyelinating polyneuropathy (CIDP)*
- *Multifocal motor neuropathy (MMN)*

Allogeneic bone marrow transplantation

Dosage/Administration

Dosage

The dosage and intervals between infusions depend on the indication. In replacement therapy, the dosage should be individually adjusted according to the clinical response. The following dosages are given as recommendations.

To ensure the traceability of biological medicinal products, it is recommended that the brand name and the lot number are documented for each treatment.

Replacement therapy in primary immunodeficiency (PID) diseases

A dose regimen must be selected to achieve IgG trough levels (serum IgG levels determined immediately before the next infusion) of at least 5 to 6 g/L. After the start of treatment, 3 to 6 months are needed until a steady-state concentration is reached. 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 maintain an IgG trough level of 5 to 6 g/L is 0.2 to 0.8 g/kg bw/month. Once the steady-state concentration has been reached, the dosing interval is 3 to 4 weeks. IgG trough levels should be determined to establish the required dose and correct dosing interval.

Secondary immunodeficiencies (SIDs)
The recommended dose is 0.2 to 0.4 g/kg bw every 3 to 4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. The dose should be adapted as necessary to achieve optimum protection against infections. A dose increase may be required in patients with persistent infection; a dose reduction may be considered if the patient remains infection-free.

Primary immune thrombocytopenia (ITP)

For the treatment of an acute episode, 0.8 to 1 g/kg bw is administered on the first day. Treatment can be repeated once within 3 days; alternatively, 0.4 g/kg bw is given on 2 to 5 consecutive days. Treatment can be repeated in the event of another fall in the platelet count (see also section “Pharmacological Properties”).

Guillain-Barré syndrome

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

Kawasaki disease

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

Chronic inflammatory demyelinating polyneuropathy (CIDP)

The recommended starting dose is 2 g/kg bw given in divided doses on 2 to 5 consecutive days. Maintenance doses of 1 g/kg bw are then administered every 3 weeks, on one day or given over 2 consecutive days.

Long-term treatment beyond 25 weeks is guided by the response to maintenance therapy. The lowest effective maintenance dose and the dosage regimen have to be adapted according to the individual course of the disease.

Multifocal motor neuropathy (MMN)
Starting dose: 2 g/kg bw over 2 to 5 consecutive days.
Maintenance dose: 1 g/kg bw every 2 to 4 weeks or 2 g/kg bw every 4 to 8 weeks. Treatment should be discontinued if the therapeutic response seen after 6 months is insufficient. If treatment is effective, the physician should evaluate the necessity of long-term treatment based on the patient’s response. The dosage and the intervals may have to be adapted according to the individual course of disease.

Allogeneic bone marrow transplantation

Treatment with human immunoglobulin may be given as part of conditioning and after transplantation. For the treatment of infections and prophylaxis of graft-versus-host reactions, the dosage should be individually adjusted.

The starting dose is normally 0.5 g/kg bw/week, starting seven days before transplantation. Treatment is continued for up to 3 months after transplantation. If an antibody deficiency persists, a dose of 0.5 g/kg bw/month is recommended until the IgG antibody levels return to normal.

The dosage recommendations are summarised in the following table:

Therapeutic indication	**Dose**	**Injection interval**
Replacement therapy		
Primary immunodeficiency diseases (PID)	Starting dose: 0.4 to 0.8 g/kg bw	
	Maintenance dose: 0.2 to 0.8 g/kg bw	every 3 to 4 weeks, to achieve IgG trough levels of at least 5 to 6 g/L
Secondary immunodeficiencies (SID)	0.2 to 0.4 g/kg bw	every 3 to 4 weeks
Immunomodulation		
Primary immune thrombocytopenia (ITP)	0.8 to 1 g/kg bw	on the first day; treatment can be repeated once within 3 days
	or 0.4 g/kg bw/day	over 2 to 5 days
Guillain-Barré syndrome	0.4 g/kg bw/day	over 5 days

Kawasaki disease	1.6 to 2 g/kg bw	in several divided doses over 2 to 5 days, together with acetylsalicylic acid
	or 2 g/kg bw	as a single dose, together with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy (CIDP)	Starting dose: 2 g/kg bw	in several divided doses over 2 to 5 days
	Maintenance dose: 1 g/kg bw	every 3 weeks spread over 1 to 2 days
Allogeneic bone marrow transplantation Treatment of infections and prophylaxis of graft-versus-host disease	0.5 g/kg bw	weekly, from day 7 before and up to 3 months after transplantation
Persistent antibody deficiency syndrome.	0.5 g/kg bw	monthly, until antibody levels return to normal
Multifocal motor neuropathy (MMN)	Starting dose: 2 g/kg bw	over 2 to 5 consecutive days
	Maintenance dose: 1 g/kg bw or 2 g/kg bw	every 2 to 4 weeks every 4 to 8 weeks over 2 to 5 days

bw = body weight

Method of administration

Privigen must be administered intravenously.

Infusion rate

Privigen should be infused at an initial rate of 0.3 mL/kg bw/hour (for approximately 30 minutes). If well tolerated, the infusion rate can gradually be increased to 4.8 mL/kg bw/hour.

In patients with immunodeficiency diseases who tolerate Privigen replacement therapy, the infusion rate can gradually be increased to a maximum of 7.2 mL/kg bw/hour.

Children and adolescents
The dosage for children and adolescents (0 to 18 years) does not differ from that of adults, as the dosage for each indication is based on body weight and adjusted according to the clinical course of the relevant diseases.

Contraindications

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

Hypersensitivity to human immunoglobulins, especially in patients with IgA deficiency who have antibodies to IgA.

Hyperprolinaemia type I or II. Hyperprolinaemia is a very rare disease that affects only isolated families worldwide.

Warnings and precautions

Certain severe adverse reactions may be related to the infusion rate. It is essential to follow the infusion rates recommended in the section “Dosage/Administration: *Method of administration*”. Patients must be closely monitored for the entire duration of the infusion and thereafter, watching carefully for the appearance of any symptoms.

Certain adverse reactions may occur more frequently in:

- The case of a high rate of infusion,
- patients with hypogammaglobulinemia or agammaglobulinaemia, with or without IgA deficiency,
- patients receiving human immunoglobulin for the first time or, in rare cases, when switching immunoglobulin products or after a prolonged break in treatment.

Possible complications can often be avoided if it is ensured that patients:

- are not hypersensitive to human immunoglobulin, by starting the injection of the product at a slow rate (0.3 mL/kg bw/hour);
- are carefully monitored for any symptoms throughout the entire duration of the infusion. In particular, patients who are receiving human immunoglobulin for the first time, who have been switched from another immunoglobulin product or who have had a prolonged break in treatment should be monitored during the first infusion and

for an hour thereafter, in order to detect possible adverse reactions. All other patients should be observed for a period of at least 20 minutes after administration.

If an adverse reaction occurs, either the infusion rate must be reduced or the infusion discontinued. The treatment required depends on the nature and severity of the adverse reaction.

If shock symptoms occur, the standard medical treatment for shock must be initiated.

A higher rate of adverse reactions can be expected at higher dosages. Every effort should therefore be made to determine the lowest effective dose for the individual patient and establish a careful monitoring routine.

In all patients, treatment with IVIg requires adequate hydration before starting the IVIg infusion.

Hypersensitivity

True hypersensitivity reactions are rare. They may occur in patients with anti-IgA antibodies. IVIg must not be used for Ig replacement in patients with selective IgA deficiency but no disorder of the other immunoglobulin classes.

Rarely, human immunoglobulin may cause a drop in blood pressure with an anaphylactic reaction, even in patients who have previously tolerated treatment well.

Haemolytic anaemia

IVIg products may contain antibodies to blood group antigens. As haemolysis, such antibodies can induce *in vivo* binding of immunoglobulins to red blood cells. This can lead to a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Following treatment with IVIg, haemolytic anaemia may develop due to the increased sequestration of red blood cells.

In association with haemolysis, isolated cases of renal dysfunction/renal failure or disseminated intravascular coagulation and death have been reported.

The following risk factors are associated with the development of haemolysis: high doses, whether given as a single dose or in divided doses over several days (administering IVIg in several divided doses is not an appropriate measure to prevent possible haemolysis, as the half-life of immunoglobulins is in the order of 3-4 weeks); blood group A, B or AB; concomitant primary inflammatory disease. As haemolysis has frequently been reported in

patients with blood group A, B or AB, increased vigilance is recommended when these patients are concomitantly receiving high IVIg doses for non-primary immunodeficiency disease (PID) indications. Haemolysis has only rarely been reported in patients given replacement therapy for PID.

There is a significantly increased risk of clinically relevant haemolysis for patients with blood group A, B or AB who receive a cumulative dose ≥ (1-) 2 g/kg bw IVIg with a high isoagglutinin titre. Only rare cases of haemolysis have been reported with the use of IVIg products with a median anti-A titre ≤1:16 (measured by the direct agglutination test according to Ph.Eur.). Privigen has a median anti-A titre of 1:8 (see section “Mechanism of action/pharmacodynamics”).

IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis occur during or after IVIg infusion, the treating physician should consider interrupting IVIg treatment (see also section “Undesirable effects”).

Aseptic meningitis syndrome (AMS)

Cases of AMS have occurred during treatment with intravenous immunoglobulin. Discontinuing treatment led to remission of the AMS within a few days, without sequelae. The syndrome usually begins within a few hours to 2 days after the start of IVIg treatment. Cerebrospinal fluid tests are often positive with pleocytosis up to several thousand cells per mm^3 (mainly granulocytes) and elevated protein levels of up to several hundred mg/dL. AMS may occur more frequently on high-dose treatment with intravenous immunoglobulins (2 g/kg bw).

Thromboembolism

There is clinical evidence to suggest a relationship between IVIg administration and thromboembolic events such as heart attack, stroke, pulmonary embolism and deep vein thrombosis. These are probably due to a relative increase in blood viscosity with immunoglobulin use in at-risk patients. Particular caution should therefore be exercised when prescribing and infusing intravenous immunoglobulin in overweight patients and patients with pre-existing risk factors for thromboembolic events (such as advanced age, hypertension, diabetes mellitus, past medical history of vascular disease or thrombotic episodes, congenital or acquired thrombophilia, prolonged immobilisation, severe hypovolaemia and diseases which increase blood viscosity).

In patients at risk of thromboembolic reactions, IVIg products should be administered at the lowest possible dose that is practicable on clinical judgement and the lowest possible infusion rate.

Acute kidney injury

Cases of acute kidney injury have been reported in patients receiving intravenous immunoglobulin therapy. In most cases, risk factors have been identified, e.g. pre-existing chronic kidney disease, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medication or age over 65.

In the event of renal impairment, discontinuation of IVIg products should be considered.

Although reports of renal dysfunction and acute kidney injury have been associated with the use of many approved IVIg products containing various excipients such as sucrose, glucose, and maltose, the percentage of products containing sucrose as a stabiliser was disproportionately high. The use of sucrose-free IVIg products should therefore be considered in patients at risk. Privigen does not contain sucrose, glucose or maltose.

In patients at risk of acute kidney injury, IVIg products should be administered at the lowest possible dose that is practicable on clinical judgement and the lowest possible infusion rate.

Transfusion-related acute lung injury (TRALI)

In very rare cases, non-cardiogenic pulmonary oedema may occur on treatment with IVIg products. TRALI is characterised by clinical signs such as severe respiratory distress, pulmonary oedema, hypoxaemia, normal left ventricular function and fever. Symptoms usually appear within 1 to 6 hours of treatment.

Patients should therefore be monitored for signs of pulmonary adverse reactions. TRALI can be treated using oxygen therapy with adequate ventilatory support.

Information on safety with respect to transmissible agents

Privigen is made from human plasma. Standard measures to prevent infections resulting from the use of medicinal products produced from human blood or plasma include donor selection, screening of individual donations and plasma pools for specific infection markers, and the introduction of effective manufacturing steps for the inactivation/elimination of viruses (cf. also section “Pharmacological Properties”). Nevertheless, the possibility of transmitting infectious agents cannot be totally excluded when administering medicinal products made from human blood or plasma. This also applies to previously unknown or emerging viruses and other pathogens.

The measures taken are considered effective against enveloped viruses, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), as well as against non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19.

Clinical experience shows that transmission of hepatitis A or parvovirus B19 does not occur with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety.

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

Sodium content

Privigen contains less than 1 mmol sodium (23 mg) per vial, that is to say it is virtually 'sodium free'.

Children and adolescents

The data available on paediatric patients indicate that the same warnings, precautions, and risk factors apply equally to children and adolescents. Privigen should therefore be used in children and adolescents with appropriate caution and under strict observation of the specified warnings.

Interactions

Live attenuated virus vaccines

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella or varicella for a period of at least 6 weeks and up to 3 months. Following administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles vaccination, this impairment may last for up to one year. Patients receiving measles vaccine should therefore have their antibody status checked.

Although there are no corresponding interaction studies for children and adolescents, interactions analogous to those in adults are to be expected with live vaccines.

Pregnancy,lactation, Fertility

Pregnancy

There are no controlled clinical data on the use of Privigen in pregnant women. Caution is therefore advised with use during pregnancy. IVIg products cross the placenta, especially during the third trimester. However, long-term clinical experience with immunoglobulins indicates that no harmful effects on the course of the pregnancy, the fetus or the neonate are to be expected.

Animal studies with the excipient L-proline show no direct or indirect toxicity with respect to pregnancy, embryonic development, or fetal development.

Lactation

Immunoglobulins are excreted in breast milk and may contribute to protecting the neonate from pathogens with a mucosal portal of entry.

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

Effects on ability to drive and use machines

Privigen has a minor effect on the ability to drive or use machines.

The ability to drive or use machines may be impaired by certain adverse effects of Privigen. Patients who experience adverse reactions during treatment should wait for them to resolve before driving or operating machines.

Undesirable effects

Summary of safety profile

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

Human immunoglobulin may rarely cause hypersensitivity reactions with a sudden drop in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has not shown any hypersensitivity to previous administrations.

Cases of reversible aseptic meningitis and rare cases of transient skin reactions (including cutaneous lupus erythematosus – frequency unknown) have been reported with the use of human immunoglobulin.

Haemolytic reactions have been reported in patients with blood groups A, B and AB. In rare cases, haemolytic anaemia requiring transfusion may occur after high-dose IVIg therapy (see also section “Warnings and precautions”).

An increase in serum creatinine levels and/or acute kidney injury has been reported.

Very rarely, transfusion-related acute lung injury, thromboembolic episodes such as heart attack, stroke, pulmonary embolism, and deep vein thrombosis have occurred.

List of adverse drug reactions

Seven clinical trials have been conducted with Privigen, including patients with primary immunodeficiency (PID), primary immune thrombocytopenia (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP). In the pivotal PID main study, 80 patients were enrolled and treated with Privigen. Of these, 72 completed the twelve months of treatment. In the PID extension study, 55 patients were enrolled and treated with Privigen. A further clinical trial in Japan included 11 patients with PID. Two ITP studies each included 57 patients. Two CIDP studies were conducted with 28 and 207 patients.

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

The following list gives the ADRs observed in clinical trials and within the context of worldwide post-marketing surveillance of Privigen. Within each system organ class, the ADRs are listed according to the following frequency convention: very common (≥1/10); common (<1/10, ≥1/100); uncommon (<1/100, ≥1/1,000); rare (<1/1,000, ≥1/10,000); very rare (<1/10,000); Not known (cannot be estimated from the available data). Within each frequency grouping, the ADRs are presented in order of decreasing frequency.

Infections and infestations:
Uncommon: Aseptic meningitis

Blood and lymphatic system disorders:
Common: Anaemia, haemolysis (including haemolytic anaemia, decreased haemoglobin, positive Coombs' test, reduced red blood cells, decreased haematocrit, increased blood lactate dehydrogenase levels), leukopenia
Uncommon: Anisocytosis (including microcytosis), thrombocytosis
Not known: Reduced neutrophil count

Immune system disorders:
Common: Hypersensitivity
Not known: Anaphylactic shock

Nervous system disorders:
Very common: Headache (39%) (including sinus headache, migraine, head discomfort, tension headaches)
Common: dizziness (including vertigo)
Uncommon: Somnolence, tremor, dysaesthesia

Cardiac disorders:
Uncommon: Palpitations, tachycardia

Vascular disorders:
Common: Hypertension, flushing (including hot flushes, hyperaemia, night sweats), drop in blood pressure
Uncommon: Thromboembolic events (including pulmonary embolism), vasculitis (including peripheral occlusive disease)
Not known: Transfusion-related acute lung injury

Respiratory, thoracic, and mediastinal disorders:
Common: Dyspnoea (including chest pain, tightness in the chest/throat, painful breathing)
Not known: Respiratory insufficiency

Gastrointestinal disorders:
Common: Nausea, vomiting, diarrhoea, abdominal pain

Hepatobiliary disorders:
Common: Hyperbilirubinaemia, increased alanine aminotransferase, increased aspartate aminotransferase

Skin and subcutaneous tissue disorders:
Common: Skin diseases (including rash, pruritus, urticaria, maculopapular rash, erythema, skin peeling)

Musculoskeletal, connective tissue, and bone disorders:
Common: Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)

Renal and urinary disorders:
Uncommon: Proteinuria, increased creatinine blood levels
Not known: Acute kidney injury

General disorders and administration site conditions:
Very common: Pain (19%) (including back pain, limb pain, joint pains, neck pain, facial pain), fever (17%) (including chills), flu-like illness (14.7%), (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, tightness in the throat)
Common: Fatigue, asthenia (including muscle weakness)

Uncommon: Injection-site pain (including symptoms at infusion site)

In the PASS study, there was a 89% reduction in the incidence rate of probable haemolytic anaemia after implementing a risk-reduction measure- immunoaffinity chromatography as compared to the period before the institution of immunoaffinity chromatography . The incidence rate reduction was significant in patients treated with Privigen doses ≥0.75 g/kg bw. (Statistical significance based on an incidence ratio of 0.11, adjusted for inpatient/outpatient status, age, sex, Privigen dose, and indication for the use of Privigen; one-sided *p*-value <0.01.).

For information about viral safety and further particulars regarding serious adverse reactions and risk factors: see section “Warnings and precautions”.

Children and adolescents

In clinical studies with Privigen on paediatric patients with immunodeficiencies or ITP, there was no difference in the frequency, type, or severity of adverse reactions compared with adult patients. From a few post-marketing surveillance reports, it has been seen that the ratio of cases of haemolysis to all case reports is slightly higher in children than in adults. No cases of haemolysis or other serious adverse reactions were reported in a phase IV post-marketing safety study in children with CIDP. See section “Warnings and precautions” for details on risk factors and monitoring recommendations.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation is extremely important. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are requested to report any suspected new or serious adverse reaction via

To report any side effect(s):

Algeria: http://www.cnpm.org.dz/index.php

Tunisia : effets.indesirables@rns.tn or www.pharmacovigilance.rns.tn

Egypt:
The Egyptian Pharmaceutical Vigilance Center (EPVC)
Email: pv.followup@edaegypt.gov.eg,

Website: www.edaegypt.gov.eg,

Hotline:15301

Jordan:

Email: jpc@jfda.jo

JFDA reporting link on JFDA website www.jfda.com: https://primaryreporting.who-umc.org/JO

Tel: +962-6-5632000

Iraq

Please Contact The Iraqi Pharmacovigilance center

Mobile: 07807820490

E-mail: iraqiphvc@moh.gov.iq

Website: http://tec-moh-com/

United Arab Emirates:

Pharmacovigilance & Medical Device section

P.O.Box: 1853

Tel: 80011111

Email: pv@mohap.gov.ae

Drug Department

Ministry of Health & Prevention

Dubai, UAE

Saudi Arabia:

The National Pharmacovigilance Centre (NPC):

SFDA Call Center: 19999

E-mail: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa

Other GCC states:

Please contact the relevant competent Authority

Overdose

An overdose may lead to volume overload and hyperviscosity, particularly in patients at risk, including elderly patients and patients with cardiac or renal impairment.

Pharmacological Properties

ATC code

J06BA02

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, human immunoglobulin for intravenous administration.

Mechanism of action

Adequate doses of Privigen can restore low IgG levels to the normal range.

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

Pharmacodynamic properties

The manufacturing process for Privigen includes the following steps: ethanol precipitation of the IgG plasma fraction, followed by octanoic acid fractionation and incubation at pH4. Further purification steps include depth filtration, chromatography, immunoaffinity chromatography for the specific removal of anti-blood group A and B antibodies (isoagglutinins) and a filtration step that can separate particles up to a size of 20 nm.

Privigen contains mainly immunoglobulin G (IgG) with a broad spectrum of functionally intact antibodies against infectious agents. Both the Fc and Fab functions of the IgG molecules are retained. The ability of Fab regions to bind antigens has been demonstrated with biochemical and biological methods. Fc function has been tested using complement activation and Fc receptor-mediated leucocyte activation. Inhibition of immune complex-induced complement activation (“scavenging”, an anti-inflammatory function of IVIg) is retained in Privigen. Privigen does not give rise to non-specific activation of the complement system or of prekallikrein.

Privigen contains immunoglobulin G antibodies, that are present in the average population. It is produced from the plasma of at not fewer than 1000 donors. The IgG subclass distribution corresponds approximately to that of native human plasma.

According to Ph. Eur., the anti-A isoagglutinin titre in intravenous immunoglobulin products must be no more than 1:64. The Privigen isoagglutinin titre is 1:8 for anti-A and 1:4 for anti-B (median of 149 batches, measured by the direct agglutination test according to Ph. Eur.).

Clinical efficacy

The safety and efficacy of Privigen were evaluated in 7 prospective, multicentre, open-label, single-arm trials carried out in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP studies), the USA (PID and CIDP studies) and multinationally (CIDP study). Additional safety and efficacy data were collected in the USA in a prospective, multicentre, open-label, single-arm, extension study on patients with PID.

Primary immunodeficiency disease (PID)

In the main study, 80 patients aged between 3 and 69 with primary immunodeficiency disease received a Privigen infusion at a median dosage between 200 and 888 mg/kg bw every 3 to 4 weeks for a maximum of one year. This therapy achieved constant IgG trough levels over the entire treatment period, with mean concentrations of 8.84 g/L to 10.27 g/L. The rate of acute serious bacterial infection (aSBI) was 0.08 per patient per year (the upper 97.5% confidence limit was 0.182).

In the PID extension study with a total of 55 patients (45 of whom had already been treated in the main study and 10 of whom had been newly recruited), Privigen doses were administered as in the main study. The results of the main study were confirmed for mean IgG trough levels (9.31 g/L to 11.15 g/L), as well as the aSBI rate (0.018 per patient per year with an upper 97.5% confidence limit of 0.098).

Primary immune thrombocytopenia (ITP)

Fifty-seven patients aged between 15 and 69 years with chronic ITP took part in the ITP study. At baseline, their platelet count was 20×10^9/L. Following the administration of Privigen at a dosage of 1 g/kg bw on two consecutive days, the platelet count rose to at least 50×10^9/L within 7 days of the first infusion in 80.7% of the patients. In 43% of patients, this increase was seen after only one day, even before the second infusion. The mean time to reach this platelet count was 2.5 days. In patients who responded to treatment, the platelet count remained at a level of $\geq50\times10^9$/L for a mean duration of 15.4 days.

In the second ITP study, 57 patients aged 18 to 65 with ITP (baseline platelet count $\leq30\times10^9$/L) were treated with a Privigen dose of 1 g/kg bw. Patients could receive a second dose of 1g/kg bw on the third day of treatment. However, this second dose was mandatory in patients with a platelet count below 50×10^9/L on day 3.
In 42 patients (74%), the platelet count rose to a value of $\geq50\times10^9$/L at least once within 6 days of the first infusion.

The second dose in patients with a platelet count of $\geq50\times10^9$/L after the first infusion had a relevant additional benefit in terms of a higher peak platelet count (median 261.5×10^9/L [range: $130\text{-}738\times10^9$/L]) and a more sustained increase in the platelet count (median 14.0 days [range: 8-28 days]) compared with the single infusion (median peak platelet count of 171.0×10^9/L [range: $22\text{-}516\times10^9$/l], with a median duration of increase of 13.0 days [range: 3 to 30 days]).

In patients with a platelet count of $<50\times10^9$/L after the first dose, 30% showed a platelet response of $\geq50\times10^9$/L following the mandatory second dose.

Chronic inflammatory demyelinating polyneuropathy (CIDP)

In the first CIDP study, the multicentre, open-label PRIMA (Privigen impact on mobility and anatomy) study. 28 patients with CIDP (13 patients with previous IVIg treatment and 15 patients with at least 2 months of newly diagnosed CIDP but no previous IVIg treatment or with a break in IVIg treatment of at least 1 year and progressive disease that had deteriorated in the 2 months before enrolment in the study) were treated with starting doses of 2 g/kg bw in divided doses over 2-5 days. This was followed by 6 maintenance doses of 1 g/kg bw, given over 1-2 days every 3 weeks.

Previously treated patients stopped IVIg therapy before treatment with Privigen until a clinical deterioration had been confirmed using the Inflammatory Neuropathy Cause and Treatment (INCAT) scale. On this 10-point INCAT scale, a clinically relevant improvement of at least 1 point was observed between baseline and week 25 of treatment in 17/28 patients (60.7%, 95% confidence interval 42.41, 76.4). After administration of the starting dose, nine patients had already responded to treatment at week 4 and 16 patients by week 10.

In a second clinical trial,the prospective, multicentre, randomised, placebo-controlled PATH study, 207 patients with CIDP were treated with Privigen (in the pre-randomisation phase). The 207 patients, all with previous IVIg treatment of at least 8 weeks prior to screening, had an IVIg dependence confirmed by clinically evident symptomatic deterioration during the IVIg withdrawal phase of up to 12 weeks. All patients then received a Privigen starting dose of 2 g/kg of body weight, followed by up to 4 Privigen maintenance doses of 1 g/kg body weight every 3 weeks over a period of up to 13 weeks.

A clinical improvement in the CIDP symptoms was seen in 91% of patients (188 patients) by week 13, based on at least one of the following criteria: a reduction of ≥1 point on the adjusted INCAT scale, an increase of ≥ 4 points in the inflammatory Rasch-built overall disability scale (IRODS) , a mean increase in grip strength of ≥8 kPa or an increase in the Medical Research Council (MRC) sum score of ≥3 points. Overall, 91% (188) patients showed improvement in at least one of the above-mentioned criteria by week 13.

In line with the adjusted INCAT score, the response rate by week 13 was 72.9% (151 out of 207 patients), with 149 patients already responding to Privigen therapy by week 10. Based on the adjusted INCAT scale, 43 of the 207 patients achieved a better clinical CIDP status than at the start of the study.

The efficacy and safety profiles in the PRIMA and PATH studies on patients with CIDP were overall comparable. The mean improvement in the patients' CIDP symptoms on the adjusted INCAT scale at the end of treatment compared with the start of treatment was 1.4 points in the PRIMA study (1.8 points for patients pretreated with IVIg) and 1.2 points in the PATH study. The secondary endpoints (IRODS, grip strength and MRC) supported the findings from the primary efficacy measurement.

Efficacy in paediatric patients

In the phase III main study on patients with PID (n = 80), 19 patients aged 3 to 11 years and 15 aged 12 to 18 were treated. In an extension study on patients with PID (n = 55), there were 13 patients aged 3 to 11 years and 11 aged 12 to 18. In the clinical trial on 57 patients with chronic ITP, 2 patients (15 and 16 years old) were treated. No dose adjustment for children was required in the three studies.

Pharmacokinetic properties

Absorption

Normal human immunoglobulin is immediately and completely bioavailable in the recipient's bloodstream following intravenous administration.

Distribution

It is distributed relatively rapidly between plasma and extravascular fluid. Equilibrium between the intravascular and extravascular compartments is reached after approximately 3 to 5 days.

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 of Privigen were established in the two clinical trials on patients with primary immunodeficiency disease (cf. section "Pharmacological Properties"). 25 patients (aged between 13 and 69) in the main study, and 13 patients (aged 9 to 59) in the extension study were involved in the pharmacokinetic studies (cf. the following table).

Pharmacokinetic parameters of Privigen in patients with primary immunodeficiency disease

Parameter	**Main study (N=25) median (range)**	**Extension study (N=13) median (range)**
C_{max} (peak value) 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)

The half-life in patients with primary immunodeficiency disease was 36.6 days in the main study and 31.1 days in the extension study.

Preclinical data

The safety of Privigen has been investigated in several preclinical studies. Particular emphasis was placed on investigating the excipient L-proline. L-proline is a physiological non-essential amino acid. Studies on rats with daily L-proline doses of 1450 mg/kg bw revealed no evidence of teratogenicity or embryotoxicity. Genotoxicity studies with L-proline did not show any pathological findings.

A few published studies on hyperprolinaemia revealed a possible risk with the long-term use of high daily doses of L-proline, in terms of brain development in very young rats. However, no such adverse reactions were found in studies comparable to the clinical use of Privigen. Additional safety pharmacology studies with L-proline on adult and juvenile rats revealed no evidence of behavioural disorders.

Immunoglobulins are natural constituents of the human body. Animals testing of the acute toxicity, chronic toxicity and embryofetal toxicity of immunoglobulins is not meaningful, owing to interactions between immunoglobulins of heterogeneous species and the induction of antibodies to heterologous proteins. In local tolerability studies on rabbits, Privigen was well tolerated with intravenous, paravenous, intra-arterial and subcutaneous administration.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products, not even with physiological saline solution. The only exception is dilution with 5% glucose solution.

Effect on diagnostic methods

After infusion of immunoglobulins, the transient rise in various passively transferred antibodies in the patient's blood may lead to false positive serological test results.

Passive transmission of antibodies against erythrocyte antigens, e.g. A, B and D, may produce false results in some serological tests for red cell alloantibodies (e.g. the Coombs' test), reticulocyte count, and haptoglobin test.

For interactions with live attenuated vaccines, cf. section “Interactions”.

Shelf life

36 months

Privigen is stable up to the expiry date given under “EXP” on the label and carton. Do not use the product after the printed expiry date (EXP).

Shelf life after first opening:

Privigen is intended for single use. As the solution contains no preservatives, Privigen should be used/infused as soon as possible after opening the vial.

Special storage instructions

Do not store above 25 °C. Do not freeze.

Store the vial in the original packaging in order to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

Privigen is a ready-to-use solution. The product should be brought to room or body temperature prior to administration. A standard infusion set with an integrated filter should be used for the administration. The vial stopper must always be pierced at its centre, within the marked area. If necessary, Privigen can be diluted with 5% glucose solution under aseptic conditions. Privigen must not be mixed with physiological saline solution. However, rinsing of infusion tubes with physiological saline solution is permitted.

The solution must be clear or slightly opalescent. Do not use solutions that are cloudy or contain precipitates.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

Marketing Authorisation Number

Algeria: 14/13V 451/485

Tunisia:
Privigen 25ml: 13813021H
Privigen 50ml: 13813022H
Privigen 100ml: 13813023H

United Arab Emirates:
Privigen 25ml: : 26831-10-11085
Privigen 50ml: 26831-10-15691
Privigen 100ml: 26831-10-3204

Kuwait:
Privigen 25ml: 2277/Oct 10
Privigen 50ml: 3575/ Oct 10
Privigen 100ml: 775/ Oct 10

Egypt:
Privigen 50ml: EGY/BP/Mar.2017/0136/01
Privigen 25ml: EGY/BP/Oct.2016/00120/01

Saudi Arabia
Privigen 25 ml: 4-470-12
Privigen 50 ml: 3-470-12
Privigen 100 ml: 2-470-12

Yemen

Privigen 25 ml: 0010439

Privigen 50 ml: 0010444

Privigen 100 ml: 0010446

Qatar:

Privigen 25 ml: 21-5138

Privigen 50 ml: 21-5139

Privigen 100 ml: 21-5206

Jordan:

Privigen 25 ml: 7/B.P/2011

Privigen 50 ml: 4/B.P/2011

Privigen 100 ml: 5/B.P/2011

Packs

Solution in vials:

2.5 g/25 mL (B)

5 g/50 mL (B)

10 g/100 mL (B)

20 g/200 mL (B)

Not all pack sizes may be marketed

List I- Prescription medicine only

Marketing Authorisation Holder and manufacturing site

CSL Behring AG,
Wankdorfstrasse 10
3014 Bern
Switzerland

Date of revision of the text

October 2020

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.

• Do not repeat the same prescription without consulting your doctor.

• Keep all medicaments out of reach of children.

Council of Arab Health Ministers,

Union of Arab Pharmacists