

## **Privigen<sup>®</sup>**

### **Australia and New Zealand**

#### **NAME OF THE MEDICINE**

Normal immunoglobulin (Human) 10 % (100 g/L) – intravenous injection

#### **DESCRIPTION**

Privigen is a sterile, clear or slightly opalescent, colourless or pale yellow solution of human normal immunoglobulin for intravenous injection.

Privigen is a 10 % solution containing 100 mg/mL of total human plasma protein with a purity of at least 98 % immunoglobulin G (IgG). More than 90 % of the IgG consists of monomers and dimers, aggregates ( $\leq 2$  % - typically below 0.1 %) and albumin ( $\leq 3$  %). The distribution of the IgG subclasses is similar to that found in normal human plasma (approximate mean values: 67.8 % IgG<sub>1</sub>, 28.7 % IgG<sub>2</sub>, 2.3 % IgG<sub>3</sub>, 1.2 % IgG<sub>4</sub>).

Privigen has a nominal osmolality of 320 mOsmol/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.8. The product contains 250 mmol/L of L-proline as a stabiliser which is a physiological non-essential amino acid. Privigen contains no carbohydrate stabiliser (eg. sucrose, maltose) and no preservative, and it has a low sodium content.

The maximum IgA content is 0.025 mg/mL. Prekallikrein activator (PKA) levels are less than 10 IU/mL.

#### **PHARMACOLOGY**

##### **Pharmacodynamic properties**

Privigen contains mainly functionally intact IgG with a broad spectrum of antibodies against infectious agents. The Fc and Fab functions of the IgG molecule are retained.

The formulation of Privigen minimises the formation of IgG dimers. The minimisation of IgG dimers is important for the tolerability of the product.

Privigen contains the IgG antibodies present in the normal population. It is prepared from pooled plasma from not fewer than 1,000 donors. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of this product may restore abnormally low IgG levels to the normal range.

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

##### **Pharmacokinetic properties**

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid. After approximately 3-5 days, equilibrium is reached between the intra- and extravascular compartments.

The pharmacokinetic parameters for Privigen were determined in a clinical study in primary immunodeficiency disorder (PID) patients (see **CLINICAL TRIALS**). Twenty-five patients (aged 13 to 69 years) participated in the pharmacokinetic assessment (see table below). The median half-life of Privigen in PID patients was 36.6 days. This half-life may vary from patient to patient, in particular in patients with primary immunodeficiencies.

#### Pharmacokinetic Parameters of Privigen in 25 PID Patients

Parameter	Median (Range)
C <sub>max</sub> (peak, g/L)	23.4 (10.4-34.6)
C <sub>min</sub> (trough, g/L)	10.2 (5.8-14.7)
t <sub>1/2</sub> (days)	36.6 (20.6-96.6)

C<sub>max</sub>, maximum serum concentration; C<sub>min</sub>, trough (minimum level) serum concentration; t<sub>1/2</sub>, elimination half-life

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

### CLINICAL TRIALS

The safety and efficacy of Privigen was evaluated in two prospective, open-label, single-arm, multicenter studies in the indications of idiopathic thrombocytopenic purpura (ITP) and primary immunodeficiency disorder (PID).

#### Treatment of Primary Immunodeficiency Disorder (PID)

In the PID study, a total of 80 subjects between 3 and 69 years of age were treated with a median dose of 200 to 888 mg/kg body weight for a maximum of 12 months. The administration of Privigen every 3 or 4 weeks resulted in stable serum IgG trough levels throughout the treatment period with mean IgG trough levels ranging from 8.84 g/L to 10.27 g/L.

The primary endpoint was the annual rate of acute Serious Bacterial Infections (SBIs), defined as pneumonia, bacteraemia/septicaemia, osteomyelitis/septic arthritis, bacterial meningitis, and visceral abscess, per subject, per year. The observed annual rate of acute SBI was 0.08 infections per subject per year (upper 1-sided 97% CI 0.182), which met the predefined success rate of less than one acute SBI per subject, per year.

The secondary endpoints in the PID study included: rate of any infection (3.55 per subject year), days out of work/school/day care/unable to perform normal activities due to illness (7.94 days, per subject year), days of hospitalisation (2.31 days, per subject year), and use of antibiotics (87.4 days, per subject year).

#### Treatment of Immune Thrombocytopenic Purpura (ITP)

A total of 57 subjects aged 15 to 69 years with chronic ITP and a platelet count of  $\leq 20 \times 10^9/L$  were treated with 1 g/kg body weight of Privigen on each of the two consecutive days. A rise in platelet count to at least  $50 \times 10^9/L$  within 7 days after the first infusion was observed in 46 of the 57 subjects studied. The median time to achieve this platelet response was 2.5 days after the first infusion (primary endpoint). After day one (i.e. on day two prior to the second dosing) 43 % of the subjects reached this response. For those subjects who responded, the median duration of platelet count  $\geq 50 \times 10^9/L$  was 15.4 days (range: 1 to > 82 days).

## INDICATIONS

### Replacement therapy

- Primary immunodeficiency disorder (PID) syndromes 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 acquired immunodeficiency syndrome (AIDS) and recurrent infections.

### Immunomodulatory therapy

- Idiopathic thrombocytopenic purpura (ITP) in children or adults at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain-Barré syndrome (GBS)
- Kawasaki disease.

### Allogeneic bone marrow transplantation

## CONTRAINDICATIONS

- Hypersensitivity to the active substance or to the excipient
- Hypersensitivity to homologous immunoglobulins, especially in the very rare cases of IgA deficiency when the patient has antibodies against IgA
- Patients with hyperprolinaemia.

## PRECAUTIONS

Certain adverse reactions may occur more frequently in:

- cases of high rate of infusion
- patients with hypogammaglobulinaemia or agammaglobulinaemia with or without IgA deficiency
- patients who receive intravenous immunoglobulin (IVIg) 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.

True hypersensitivity reactions are rare. They can occur in the very rare cases of IgA deficiency with anti-IgA antibodies.

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

Reactions to IVIg tend to be related to the infusion rate and are most likely to occur during the first hour of the 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 body weight/hr)

- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve 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.

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. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis (see also **ADVERSE EFFECTS**).

There is clinical evidence of an association between IVIg administration and thromboembolic events which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

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 impairment, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.

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
- monitoring during infusion and for at least 20 minutes after infusion.

In cases of renal impairment, IVIg discontinuation should be considered. While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, 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 may be considered. Privigen does not contain sucrose or other sugars.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

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.

No effect on the ability to drive and use machines have been observed.

### **Pathogen safety**

Privigen manufacture includes standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. These include: donor selection,

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. These multiple, complementary manufacturing processes include two dedicated steps to reduce the possibility of pathogen transmission: virus filtration and incubation at pH 4.

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 (HBV), and hepatitis C (HCV), and for the non-enveloped viruses 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.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

### **Effects on fertility**

No fertility studies have been conducted in animals using Privigen or the excipient present in the formulation (L-proline).

### **Use in pregnancy**

Animal reproduction studies have not been conducted with Privigen. It is also not known whether Privigen can cause foetal harm when administered to pregnant women, or whether it can affect reproductive capacity. Privigen should be given to pregnant women only if clearly indicated.

### **Use in lactation**

Immunoglobulins are excreted into breast milk and may contribute to the transfer of protective antibodies to the neonate.

### **Paediatric use**

#### Treatment of PID

Privigen was evaluated in 19 children and 12 adolescents with PID. There were no apparent differences in the safety and efficacy profiles when compared to these profiles in adult patients. No paediatric specific dose was necessary to achieve the desired serum IgG levels. The use of Privigen has not been established in paediatric patients with PID under the age of three years.

#### Treatment of ITP

The use of Privigen has not been established in patients with ITP under the age of 15 years.

### **Use in the elderly**

Clinical studies of Privigen did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently to younger subjects.

### **Carcinogenicity**

No carcinogenicity studies have been conducted with Privigen.

## **Genotoxicity**

No genotoxicity studies have been conducted with Privigen. The excipient L-proline was not genotoxic in a standard array of genotoxicity tests.

## **Interactions with other medicines**

### Live attenuated virus vaccines

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella and varicella for a period of at least six weeks and up to three months. After administration of Privigen, an interval of three months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to one year. Therefore patients receiving measles vaccine should have their antibody status checked.

### Drug interactions

The interaction of Privigen with other drugs has not been established.

## **Effect on laboratory tests**

### 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 serological tests.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test).

## **ADVERSE EFFECTS**

Intravenously administered human normal immunoglobulins have a well-established history of safety and efficacy in humans.

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur.

Human normal immunoglobulins may rarely 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, have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also **PRECAUTIONS**).

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

Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses events have been reported (see also **PRECAUTIONS**).

Two clinical studies with Privigen were performed, one in patients with primary immunodeficiency disorder (PID) and one in patients with immune thrombocytopenic purpura (ITP). In the PID study 80 subjects were enrolled and treated with Privigen. Of these, 72 completed the twelve months of treatment. The ITP study was performed in 56 patients.

Most adverse events (AEs) observed in the two clinical studies were mild to moderate in nature.

All AEs reported in the two studies that appeared more than once, regardless of causality, are summarised and categorised according to the MedDRA System organ class and frequency in the table below. Frequency per infusion has been evaluated using the following criteria: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ).

Within each frequency grouping, AEs are presented in order of decreasing severity.

## Frequency of Adverse Events (AEs) in clinical studies with Privigen.

MedDRA System Organ Class	MedDRA preferred term	ADR frequency category
Blood and lymphatic system disorders	Anaemia, anisocytosis	Uncommon
Nervous system disorders	Headaches	Very common
	Dizziness, head discomfort, somnolence, tremor, sinus headache	Uncommon
Cardiac disorders	Palpitations	Uncommon
Vascular disorders	Flushing, increase in blood pressure (hypertension), decrease in blood pressure (hypotension)	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea, oropharyngeal blistering, painful respiration, throat tightness	Uncommon
Gastrointestinal disorders	Vomiting, nausea	Common
	Diarrhoea, abdominal pain upper	Uncommon
Hepatobiliary disorders	Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, skin disorders, night sweats, urticaria	Uncommon
Musculoskeletal and connective tissue disorders	Back pain	Common
	Neck pain, pain in extremity, musculoskeletal stiffness, muscle spasms, musculoskeletal pain, myalgia	Uncommon
Renal and urinary disorders	Proteinuria	Uncommon
General disorders and administration site conditions	Chills, fatigue, pyrexia	Common
	Chest pain, general symptom, asthenia, influenza like illness, hyperthermia, pain, injection site pain	Uncommon
Investigations	Bilirubin conjugated increased, blood bilirubin unconjugated increased, Coombs direct test positive, Coombs test positive, blood lactate dehydrogenase increased, haematocrit decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood pressure decreased, blood pressure increased, body temperature increased, haemoglobin decreased	Uncommon

For safety with respect to transmissible agents, see section **PRECAUTIONS/Pathogen safety**.

## DOSAGE AND ADMINISTRATION

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency of infusions
<b>Replacement therapy:</b>		
Primary immunodeficiency*	Starting dose: 0.4 to 0.8 g/kg body weight  thereafter: 0.2 to 0.8 g/kg body weight	every 2 to 4 weeks to obtain IgG trough level of at least 4 to 6 g/L.  3-6 months are required after the initiation of therapy for equilibration  2-4 weeks
Secondary immunodeficiency <ul style="list-style-type: none"> <li>• myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections</li> <li>• Children with AIDS</li> </ul>	0.2 to 0.4 g/kg body weight	every 3 to 4 weeks to obtain IgG trough level of at least 4 to 6 g/L

<b>Immunomodulatory therapy:</b>		
Idiopathic thrombocytopenic purpura	0.8 to 1 g/kg body weight  or  0.4 g/kg body weight /day	on day 1, possibly repeated once within 3 days  for 2 to 5 days  Treatment can be repeated if relapse occurs.
- Guillain-Barré syndrome	0.4 g/kg body weight /day	for 3 to 7 days  (experience in children limited)
- Kawasaki disease	1.6 to 2 g/kg body weight  or  2 g/kg body weight	in divided doses over 2 to 5 days in association with acetylsalicylic acid  in one dose in association with acetylsalicylic acid

<b>Allogeneic bone marrow transplantation (as part of the conditioning regimen and after transplantation):</b>		
- treatment of infections and prophylaxis of graft versus host disease	Starting dose: 0.5 g/kg body weight (dosage individually tailored)	every week from 7 days before to (up to) 3 months after transplantation
- persistent lack of antibody production	0.5 g/kg body weight	every month until antibody levels return to normal

\* In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response

## **Administration**

Privigen contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused portion should be discarded in accordance with local requirements. Use in one patient on one occasion only. Do not use if the solution has been frozen. The name and batch number of the product should be recorded every time Privigen is administered to a patient in order to maintain a link between the patient and the batch of the product.

Privigen should be infused intravenously. Patients naïve to human normal immunoglobulin, patients switched from an alternative IVIg product or patients who have not received IVIg for a long time should have vital signs and general status monitored regularly during and for the first hour after the first infusion. In such patients the initial infusion rate is 0.3 mL/kg body weight/hr. If well tolerated, the rate of administration may gradually be increased to 4.8 mL/kg body weight/hr. In a clinical study in PID patients, the maximum infusion rate was 7.2 mL/kg body weight/hr [see Clinical Trials section].

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

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 side effect.

In case of shock, the current medical standards for shock treatment should be implemented.

Privigen is packaged as a ready-to-use solution in single use vials. The product should be at room or body temperature before use. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have particulate matter. Do not shake. Slight yellow colouration is of no concern and the product can still be used. Do not use if turbid.

Privigen should always be administered by intravenous (IV) infusion using appropriate administration equipment. Privigen is packaged in a glass bottle that must be vented during use.

Always pierce the stopper at its centre, within the marked area. If desired, Privigen can be diluted with glucose 5% solution, using aseptic technique. Do not mix other medicinal products in the same infusion line.

## **OVERDOSAGE**

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with renal insufficiency.

## **PRESENTATION AND STORAGE CONDITIONS**

Privigen is presented as a 10 % (100 g/L) solution for intravenous injection. The solution is dispensed into a clear glass bottle and closed with a latex-free rubber stopper and aluminium crimp cap, with a plastic flip-off disk providing a tamper-evident seal.

The product is supplied in the following pack sizes:

Privigen 5 g:	50 mL solution in a 50 mL bottle AUST R 143273
Privigen 10 g:	100 mL solution in a 100 mL bottle AUST R 143337
Privigen 20 g:	200 mL solution in a 200 mL bottle AUST R 143368

Store below 25° C (Do not freeze). Do not shake. Keep the vial in the outer carton in order to protect from light.

Do not use after the expiry date printed on the carton and the label.

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**POISON SCHEDULE OF THE MEDICINE (Australia)**

S4

**MEDICINE CLASSIFICATION (New Zealand)**

Prescription Medicine

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