WARNING:

THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including PRIVIGEN. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of oestrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

PRIVIGEN 25 ml solution for infusion for intravenous use

PRIVIGEN 50 ml solution for infusion for intravenous use

PRIVIGEN 100 ml solution for infusion for intravenous use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 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

Distribution of the IgG subclasses (approx. values):

IgG_1 ..... 69 %

IgG_2 ..... 26 %

IgG_3 ..... 3 %

IgG_4 ..... 2 %

The maximum IgA content is 25 micrograms/mL.

For the full list of excipients, see section 6.1.

Sugar free.

3. PHARMACEUTICAL FORM

Solution for infusion for intravenous use.

The solution is clear to slightly opalescent and colourless to pale yellow.

Osmolarity is 320 mOsmol/kg, the solution is thus isotonic.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PRIVIGEN is indicated for

Replacement therapy in:

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

- *Secondary immune defects (SID)* in patients with severe or recurring infections, ineffective antimicrobial treatment and either confirmed insufficient increase of

antibodies from vaccinations (PSAF*) or IgG serum levels of < 4 g/L.

*PSAF = Absence of a minimum two-fold increase of the IgG antibody concentration against pneumococci-polysaccharides and polypeptide antigen vaccine (PSAF = proven specific antibody failure).

Immunomodulation:

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

4.2 Posology and method of administration

Posology:

The dosage and intervals between infusions depend on the indication. In replacement therapy, the dosage should be individually adjusted depending on the clinical response.

The following dosages are given as a recommendation.

To ensure the traceability of the biologically manufactured medicinal products it is recommended to document the brand name and the lot number for each treatment.

- Replacement therapy in primary immunodeficiency syndromes (PID):

A dosage regimen must be selected, under which IgG trough levels (determination of IgG serum levels immediately prior to the next infusion) of at least 5 to 6 g/L are achieved. After initiation of treatment, 3 to 6 months are needed until a steady-state concentration is reached. The recommended initial 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. After the steady-state concentration has been reached, the dosing interval is 3 to 4 weeks. To establish the required dose and correct dosing interval, IgG trough levels should be determined.

- Secondary immune defects (SID):

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 connection with the incidence of infection. The dose should be adapted as needed to achieve optimum protection against infections. A dose increase may be necessary in patients with persistent infections; a dose reduction may be considered if the patient remains free of infections.

- 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 administered on 2 to 5 consecutive days. In the event of a second decrease in the platelet count, treatment can be repeated.

- Guillain-Barré syndrome:

0,4 g/kg BW/day for 5 days. Experience in children is limited.

- Kawasaki's disease:

1,6 to 2,0 g/kg BW spread over 2 to 5 days, or 2,0 g/kg BW as a single dose. Patients should receive acetylsalicylic acid as co-medication.

- Chronic inflammatory demyelinating polyneuropathy (CIDP):

The recommended starting dose is 2 g/kg BW and is, divided into several doses, administered on 2 to 5 consecutive days. Subsequently, every 3 weeks, maintenance doses of 1 g/kg BW are administered on one day or spread over 2 consecutive days.

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

- Multifocal motor neuropathy (MMN):

Starting dose: 2 g/kg BW for 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. If an insufficient response to the treatment is determined after 6 months, the treatment should be terminated. If the treatment is effective, the necessity of long-term treatment should be evaluated by the physician based on the patient's response. The dosage and the intervals may have to be adapted to the individual course of disease.

Dosage recommendations are summarised in the following table:

Therapeutic indication	**Dose**	**Injection interval**
Replacement therapy		
Primary immunodeficiency syndromes (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 immune defects (SID)	0,2 to 0,4 g/kg BW	every 3 to 4 weeks

<u>Immunomodulation</u> *Primary immune thrombocytopenia (ITP)*	0,8 to 1 g/kg BW or 0,4 g/kg BW/day	on the first day; treatment can be repeated once within 3 days over 2 to 5 days
Guillain-Barré syndrome	0,4 g/kg BW/day	over 5 days
Kawasaki's disease	1,6 to 2 g/kg BW	divided into several 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)	Initial dose: 2 g/kg BW	divided into several doses over 2 to 5 days
	Maintenance dose: 1 g/kg BW	every 3 weeks spread over 1 to 2 days
Persistent antibody deficiency syndrome.	0,5 g/kg BW	monthly, until antibody levels normalise
Multifocal motor neuropathy (MMN)	Starting dose: 2 g/kg BW	over 2 to 5 consecutive days every 2 to 4 weeks

	Maintenance dose: 1 g/kg BW or 2 g/kg BW	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 infusion rate of 0,3 ml/kg BW/hour (over approximately 30 minutes). If well tolerated, the infusion rate can be gradually increased to 4,8 ml/kg BW/hour.

In patients with immunodeficiency syndromes and good tolerability to PRIVIGEN replacement therapy, the infusion rate can be increased gradually to a maximum value of 7,2 ml/kg BW/hour.

Paediatric population

In the phase III main study on patients with primary immunodeficiency syndromes (PID) (n = 80), 19 patients aged 3 to 11 years and 15 aged 12 up to and including 18 years 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 up to and including 18 years. In the clinical study on 57 patients with chronic primary immune thrombocytopenia (ITP), 2 patients (15 and 16 years old) were treated. In the three studies, no dose adjustment for children was required. In children with chronic inflammatory demyelinating polyneuropathy (CIDP), literature reports indicate that intravenous immunoglobulins are effective. However, there are no available data on PRIVIGEN.

Instructions for handling:

PRIVIGEN is a ready-to-use solution. The product should be at room or body temperature prior to administration. For administration, a standard infusion set with an integrated filter should be used. 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, the rinsing of infusion tubes with physiological saline solution is permitted.

The solution must be clear or slightly opalescent. Solutions showing cloudiness or precipitates must not be used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of PRIVIGEN listed in section 6.1.

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

Hyperprolinaemia type I or II. Hyperprolinaemia is a very rare disease affecting only individual families worldwide.

4.4 Special warnings and precautions for use

Certain severe adverse reactions can be correlated with the infusion rate. It is imperative to adhere to the infusion rate recommended in the section "Posology/Administration: *Method of administration*". Patients must be monitored for the entire duration of the infusion and afterward and observed closely for the occurrence of symptoms of any kind.

Certain adverse reactions may occur more frequently in the following cases:

- a high rate of infusion,
- patients with hypo- or agammaglobulinaemia with or without IgA deficiency,
- patients receiving human immunoglobulin for the first time, or, in rare cases, when switching immunoglobulin preparations, 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 initially giving them the preparation as a slow injection (0,3 ml/kg BW/hour):
- patients are carefully monitored for symptoms of any kind throughout the entire duration of the infusion. In particular, patients initially receiving human immunoglobulin after switching from another immunoglobulin preparation, or who have had a prolonged break in treatment, should be monitored during the first infusion and for an hour thereafter, so as to identify possible adverse reactions. All other patients should be observed for a period of at least 20 minutes following 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, standard medical procedures for shock treatment must be applied.

A higher rate of adverse reactions can be expected at higher dosages. The lowest effective dose should therefore be sought for each individual patient and a careful monitoring routine must be established.

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

Hypersensitivity:

Genuine hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies. In patients with selective IgA deficiency without impairment of the other Ig classes, IVIg must not be used for Ig replacement.

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

Haemolytic anaemia:

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

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

The following risk factors are associated with the development of haemolysis: high doses, administered as a single dose or given in divided doses over several days (dividing IVIg administration into several single doses is not suitable for preventing possible haemolysis, as the half-life period of immunoglobulins is in the order of 3-4 weeks); blood group A, B or AB; concomitant primary inflammatory disease. As haemolysis has been frequently reported in patients of blood group A, B or AB concomitantly receiving high IVIg doses for non-primary immunodeficiency syndrome (PID)-indications, increased vigilance is recommended. Haemolysis has been only rarely reported in PID patients on replacement therapy.

A significantly increased risk of clinically relevant haemolysis exists for patients with blood group A, B or AB, cumulatively receiving ≥ (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 are shown during or after IVIg infusion, the treating physician should consider interrupting treatment with IVIg (see also section 4.8 "Undesirable effects").

Aseptic meningitis syndrome (AMS):

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

Thromboembolism:

There is clinical evidence to suggest an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebrovascular accident (stroke), pulmonary embolism and deep vein thrombosis. These are probably due to a relative increase in blood viscosity during immunoglobulin use in patients at risk. Therefore, particular caution is indicated when prescribing and infusing intravenous immunoglobulins in overweight patients and patients with pre-existing risk factors for thromboembolic events (such as advanced age, hypertension, diabetes mellitus, prior history of vascular disease or thrombotic episodes, acquired or congenital thrombophilia, prolonged immobility, severe hypovolaemia and diseases which increase blood viscosity).
In patients at risk of thromboembolic reactions, IVIg preparations should be administered at the lowest possible infusion rate and lowest possible dose.

Acute renal failure:

Cases of acute renal failure have been described in patients receiving intravenous immunoglobulin therapy. In most cases, risk factors have been identified, e.g. pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, obesity, nephrotoxic co-medications

or age over 65.

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

Although reports of renal dysfunction and acute renal failure have been associated with the use of many approved IVIg preparations with various excipients such as sucrose, glucose, and maltose, the percentage of preparations containing sucrose as a stabiliser was disproportionately high.

The use of sucrose-free IVIg preparations should therefore be considered in patients at risk.

PRIVIGEN contains no sucrose, glucose, or maltose.

In patients at risk of acute renal failure, IVIg preparations should be administered at the lowest possible infusion rate and lowest possible dose.

Transfusion-related acute lung injury (TRALI):

In very rare cases, non-cardiogenic pulmonary oedema may occur during treatment with IVIg preparations. TRALI is characterised by clinical signs, such as severe dyspnoea, pulmonary oedema, hypoxaemia, normal left ventricular function and fever. Symptoms usually appear within 1 to 6 hours after treatment. Patients should therefore be monitored for signs of adverse reactions in the lungs. TRALI can be treated using oxygen therapy with adequate ventilation.

Information on safety with respect to transmissible agents:

PRIVIGEN is made from human plasma. Standard measures to prevent infections that might result from using medicinal products made from human blood or plasma include donor selection, screening of individual donations and plasma pools for specific markers of infectivity and the introduction of effective manufacturing steps for viral inactivation/elimination (cf. also section "Properties/Effects"). Nevertheless, the possibility of transmission of infectious agents cannot be totally excluded when administering medicinal products made from human blood or plasma. This also applies to hitherto unknown or newly emerging viruses and other pathogens.

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

Clinical experience shows that transmission of hepatitis A infections or parvovirus B19 infections 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 the preparation name and batch number be documented each time PRIVIGEN is administered to establish a link between patient and product batch.

Children and adolescents:

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

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

4.5 Interaction with other medicines and other forms of interaction

Attenuated live virus vaccines:

The use of immunoglobulins may interfere with the efficacy of attenuated live 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 preparation, a waiting period of 3 months must be observed before vaccination with attenuated live virus vaccines. In the case of measles vaccinations, such interference may last up to one year. The antibody status should therefore be checked in patients receiving measles vaccine.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no controlled clinical data on the use of PRIVIGEN in pregnant women. Caution is therefore advised if used during pregnancy. IVIg products cross the placenta, especially during the last pregnancy trimester.

However, long-standing clinical experience with immunoglobulins indicates that no harmful effects are to be expected on the course of pregnancy, the foetus or neonate.

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

Lactation:

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

Fertility:

Clinical experience with immunoglobulins indicates that no harmful effects on fertility are expected.

4.7 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 can be impaired by certain adverse effects of PRIVIGEN. Patients in whom adverse effects occur during treatment should only resume driving or operating a machine when the adverse effects have resolved.

4.8 Undesirable effects

Summary of safety profile:

In association with the intravenous administration of human immunoglobulin, uncommon adverse reactions such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate back pain may occur.

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

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

In patients with blood groups A, B and AB, haemolytic reactions have been observed. In rare cases, haemolytic anaemia requiring transfusion may occur after high-dose IVIg therapy (see also section 4.4 "Warnings and precautions").

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

Very rarely, transfusion-related acute lung failure, thromboembolic episodes such as myocardial infarction, cerebrovascular accident (stroke), pulmonary embolism and deep vein thrombosis have occurred.

List of adverse drug reactions:

Six clinical studies have been conducted with PRIVIGEN, which included patients with primary immunodeficiency (PID), primary immune thrombocytopenia (ITP) and chronic inflammatory demyelinating polyneuropathy (CIDP). In the pivotal PID main study, 80 patients were included and treated with PRIVIGEN. Of these, 72 completed twelve months of treatment. In the PID extension study, 55 patients were included and treated with PRIVIGEN. The two ITP studies each included 57 patients. The two CIDP studies were conducted with 28 and 207 patients.

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

The ADRs observed in clinical studies and within the context of worldwide post-marketing use of PRIVIGEN are specified in the following list. Within the system organ classes mentioned, ADRs are listed according to frequency according to the following 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); Isolated cases (cannot be estimated from the available data). Within each frequency grouping, 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, decreased red blood cells, decreased haematocrit, increased blood lactate dehydrogenase level), leukopenia

Uncommon:

Anisocytosis (including microcytosis), thrombocytosis

Isolated cases:

Reduced neutrophil count

Immune system disorders:

Common:

Hypersensitivity

Isolated cases:

Anaphylactic shock

Nervous system disorders:

Very common:

Headache (39 %) (including sinus headache, migraine, head discomfort, tension headaches)

Common:

Light-headedness (including dizziness (vertigo))

Uncommon:

Somnolence, tremor, dysaesthesia

Cardiac disorders:

Uncommon:

Palpitations, tachycardia

Vascular disorders:

Common:

Hypertension, flushing (including hot flush, hyperaemia, night sweats), drop in blood pressure

Uncommon:

Thromboembolic events (including pulmonary embolism), vasculitis (including peripheral occlusive disease)

Isolated cases:

Transfusion-related associated acute lung injury

Respiratory, thoracic, and mediastinal disorders:

Common:

Dyspnoea (including chest pain, tightness in the chest/throat, painful breathing)

Isolated cases:

Respiratory insufficiency

Gastrointestinal disorders:

Very common:

Nausea (10,1 %)

Common:

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

Isolated cases:

Acute renal failure

General disorders and administration site conditions:

Very common:

Pain (19 %) (including back pain, limb pain, arthralgia, neck pain, facial pain), fever (17 %) (including chills), flu-like symptoms (14,7 %), (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)

Common:

Fatigue, asthenia (including muscle weakness)

Uncommon:

Injection-site pain

For information about viral safety and further particulars regarding serious adverse reactions and risk factors: see section 4.4 “Warnings and precautions”.

Paediatric population:

In clinical studies with PRIVIGEN on paediatric patients, there was no difference in the frequency, type and severity of adverse reactions compared with adult patients. 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. See section 4.4 "Warnings and precautions" for details on risk factors and monitoring recommendations.

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of PRIVIGEN is important. It allows continued monitoring of the benefit/risk balance of PRIVIGEN.

Healthcare professionals are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Gen-Eye (Pty) Ltd via email: pharmacovigilance@gen-eye.co.za or telephonically on 011 312 3812. Suspected adverse reactions can also be reported to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

An overdose may lead to volume 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

Pharmacological classification:

A 30.1 Antibodies

Mechanism of action:

Adequate PRIVIGEN doses can restore normal values when IgG levels are low. The mechanism of action in therapeutic indications other than replacement therapy is not yet fully understood, but includes immunomodulatory effects.

The manufacturing process for PRIVIGEN includes the following steps: precipitation of the IgG fraction from plasma by ethanol, followed by octanoic acid fractionation and pH4 incubation. Further purification steps include depth filtration, chromatography, immunoaffinity chromatography for 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 mainly contains immunoglobulin G (IgG) with a broad spectrum of functionally intact antibodies against infectious agents. Both the Fc and Fab functions of 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 leukocyte activation. Inhibition of immune complex-induced complement activation ("scavenging", an anti-inflammatory function of IVIgs) is retained in PRIVIGEN. PRIVIGEN does not lead to non-specific activation of the complement system or of prekallikrein.

PRIVIGEN contains immunoglobulin G antibodies, which are present in the average population. It is produced from the plasma of at least 1000 donors. The IgG subclass distribution roughly corresponds to that of unprocessed human plasma.

According to Ph.Eur., the anti-A isoagglutinin titre in intravenous immunoglobulin preparations 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 have been studied in 6 prospective, open-label, single-arm, multicentre studies that have been carried out in Europe (ITP, PID and CIDP studies), the US (PID study)

and multinationally (CIDP study). Additional safety and efficacy data have been collected in a prospective, open-label, single-arm, multicentre extension study with PID patients in the US.

Primary immunodeficiency syndromes (PID):

In the main study, 80 patients between 3 and 69 years with primary immunodeficiency syndrome received a PRIVIGEN infusion every 3 to 4 weeks for a maximum of one year at a median dosage between 200 and 888 mg/kg BW. This 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 infections (aSBI) was 0,08 per patient per year (the upper 97,5 % confidence interval 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 interval of 0,098).

Primary immune thrombocytopenia (ITP):

In the ITP study, 57 patients with chronic ITP aged between 15 and 69 years took part. At baseline, their platelet count was 20 × 10^9/L. Following 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 in 80,7 % of patients within 7 days after the first infusion. In 43 % of patients, this increase was reached even after one day before the second infusion. The mean time to reach this platelet count was 2,5 days. In patients responding to treatment, the platelet count remained at a level of ≥ 50× 10^9/L for a median duration of 15,4 days.

In the second ITP study, 57 patients with ITP (initial platelet count (baseline value) of ≤ 30× 10^9/L) aged 18 to 65 years were treated with a PRIVIGEN dose of 1 g/kg BW. On the third day of treatment, patients could receive a second dose of 1 g/kg BW. However, in patients with a platelet count below a value of < 50× 10^9/L on day 3, this dose was mandatory.

In 42 patients (74 %), the platelet count rose at least once within 6 days to a value of ≥ 50× 10^9/L after the first infusion.

The second dose in patients with a platelet count of ≥ 50× 10^9/L after the first infusion had a relevant additional benefit in the form of a higher peak platelet count (median of 261,5× 10^9/L [range: 130 - 738 × 10^9/L]) and a more sustained increase in the platelet count (median of 14,0 days [range: 8 - 28 days]) compared with the single infusion (median peak platelet count of 171,0× 10^9/L [range: 22 – 516 × 10^9/l], with a median duration of increase of 13,0 days [range: 3 to 30 days]).
After the mandatory second dose in patients with a platelet count of < 50× 10^9/L after the first dose, 30 % of patients showed a blood platelet response of ≥ 50× 10^9/L.

Chronic inflammatory demyelinating polyneuropathy (CIDP):

In the first CIDP study, the PRIMA multicentre, open-label study (PRIVIGEN impact on mobility and anatomy study), 28 patients with CIDP (13 patients with previous IVIg treatment and 15 patients without previous IVIg treatment with at least 2 months of newly diagnosed CIDP or with IVIg treatment interruption for at least 1 year and advanced disease deterioration in the 2 months prior to inclusion in the study) with initial doses of 2 g/kg BW, spread over 2-5 days. This was followed by 6 maintenance doses of 1 g/kg BW, spread over 1-2 days every 3 weeks.
In treatment-experienced patients, IVIg was discontinued prior to treatment with PRIVIGEN, until a deterioration in clinical symptoms was confirmed using the INCAT scale (Inflammatory Neuropathy Cause and Treatment). On this 10-point INCAT scale, a clinically relevant improvement of at least 1 point was observed in 17/28 patients (60,7 %, 95 % confidence interval 42,41; 76,4) between baseline and week 25 of treatment. Nine patients responded to treatment even after administration of the initial dose in week 4 of treatment and 16 by week 10 of treatment.

In a second clinical trial, a prospective, multicentre, randomised, placebo-controlled PATH study, 207 patients with CIDP were treated with PRIVIGEN (pre-randomisation phase). An IVIg dependency was confirmed for this in advance for all 207 patients with previous IVIg treatment of at least 8 weeks, prior to screening, by means of a clinically evident deterioration in the symptoms in the IVIg discontinuation phase of up to 12 weeks. All patients then received an initial dose of 2 g/kg of body weight PRIVIGEN, followed

by up to 4 maintenance doses of 1 g/kg of body weight PRIVIGEN every 3 weeks over a total period of up to 13 weeks.

A clinical improvement in the CIDP symptoms was observed in 91 % of patients (188 patients) up to week 13, with at least one of the following criteria: regression by ≥ 1 point on the adjusted INCAT scale, an "Inflammatory Rasch-built Overall Disability Scale" (IRODS) value elevated by ≥ 4 points, an average increase in the grip strength by ≥ 8 kPa or an increase in the Medical Research Council (MRC) total score by ≥ 3 points. Overall, there was an improvement in 91 % of patients (188 patients) up to 13 weeks, with at least one of the abovementioned criteria.

In line with the adjusted INCAT scale, the response rate up to week 13 was 72,9 % (151 of 207 patients). Of this, 149 patients responded to PRIVIGEN treatment as early as week 10. In total, 43 of the 207 patients achieved a better clinical CIDP status than the beginning of the study according to the adjusted INCAT scale.

The efficacy and safety profile in the PRIMA and PATH studies for CIDP patients was comparable overall. The average improvement in the CIDP symptoms in patients at the end of treatment, determined according to the adjusted INCAT scale, was 1,4; using the adjusted INCAT scale in the PRIMA study (1,8 points for patients pre-treated with IVIg), and 1,2 points in the PATH study, in comparison to the beginning of the treatment. The secondary endpoints (IRODS, grip strength and MRC) supported the findings from the primary efficacy measurement.

5.2 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. After approximately 3 to 5 days, the balance between intra and extravascular compartments is reached.

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 studies on patients with primary immunodeficiency syndrome (cf. section "Properties/Effects"). 25 patients (between 13 and 69 years) in the main study and 13 patients (between 9 and 59 years) in the extension study were involved in the pharmacokinetic studies (cf. the following table).

Pharmacokinetic parameters of PRIVIGEN in patients with primary immunodeficiency syndrome:

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 levels) 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 syndrome was 36,6 days in the main study and 31,1 days in the extension study.

5.3 Preclinical safety data

The safety of PRIVIGEN has been investigated in several preclinical studies, with particular emphasis placed on investigation of the excipient L-proline. L-proline is a physiological nonessential 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 were without pathological findings.

A few published studies on hyperprolinaemia revealed a possible risk with 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 similar studies on 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 components of the human body. In animals, tests on the acute toxicity, chronic toxicity and embryofoetal toxicity of immunoglobulins are not predictive, owing to interactions between immunoglobulins of heterogeneous species and the induction of antibodies to heterologous proteins. In local tolerance studies on rabbits with intravenous, paravenous, intraarterial and subcutaneous administration of PRIVIGEN was well tolerated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-proline

sodium hydroxide (corresponds to maximum 1 mmol/litre sodium)

hydrochloric acid

water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products or even physiological saline solution. Exception: dilution with 5 % glucose solution.

Effect on diagnostic methods:

After infusion of immunoglobulins, the transitory 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 erythrocyte alloantibodies (e.g. the Coombs test), reticulocyte count and haptoglobin tests.

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

6.3 Shelf life

Unopened: 36 months

After first opening: PRIVIGEN is intended for single use. As the solution contains no preservatives, PRIVIGEN should be utilised/used for infusion as soon as possible after opening the vial.

6.4 Special precautions for storage

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

Store the vial in the original package in order to protect from light.

Keep out of the reach of children.

6.5 Nature and contents of container

PRIVIGEN is presented as a solution for infusion.

The solution is clear or slightly opalescent and colourless to pale yellow.

Each glass infusion vial contains 25 ml, 50 ml or 100 ml solution for infusion.

Pack sizes: 1 vial per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]

Royal Palm Business Estate

Unit 7, 646 Washington Street

Halfway House, Midrand, 1685

Gauteng, South Africa

8. REGISTRATION NUMBER

To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

[1] Company Registration Number.: 2009/009360/07