

Intragam NexGen[®]

(Human normal immunoglobulin 10%) – Solution for intravenous infusion

1 NAME OF THE MEDICINE

Human Normal Immunoglobulin 10%

2 and 3 QUALITATIVE AND QUANTITATIVE COMPOSITION and PHARMACEUTICAL FORM

Intragam NexGen is a sterile, clear or slightly opalescent, colourless or pale yellow solution of human normal immunoglobulin for intravenous infusion.

Intragam NexGen 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 of normal human plasma (approximate values: 69% IgG₁, 26% IgG₂, 3% IgG₃, 2% IgG₄).

Intragam NexGen has a nominal osmolality of 320 mOsm/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.6–5.0. The product contains 250 mmol/L of L-proline as a stabiliser which is a physiological non-essential amino acid. Intragam NexGen contains no carbohydrate stabiliser (e.g. sucrose, maltose) and no preservative, and it has a low sodium content of ≤ 1 mmol/L.

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

Intragam NexGen is manufactured from human plasma collected by Malaysia National Blood Centre. Privigen[®] is manufactured from human plasma collected outside Malaysia by CSL Plasma.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Replacement therapy in

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

- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Children with congenital AIDS and recurrent infections

Immunomodulation

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

Allogeneic bone marrow transplantation

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The dosage and dosage regimen is dependent on the indication. In replacement therapy the dosage may need to be individualised for each patient depending on the clinical response.

The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough IgG level (measured before the next infusion) of at least 5 to 6 g/L. Three to 6 months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 to 0.8 g/kg body weight (bw) followed by at least 0.2 g/kg bw every 3 to 4 weeks.

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

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

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

Immune thrombocytopenic purpura

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

Guillain-Barré syndrome

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

Kawasaki disease

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

Chronic inflammatory demyelinating polyneuropathy (CIDP)

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

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

Allogeneic bone marrow transplantation

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

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

The dosages recommendations are summarised in the following table:

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

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

bw = body weight

Use of the product in paediatric population

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

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

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

Method of administration

Intragam NexGen should be infused intravenously.

Rate of infusion

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

Instructions for use and handling

Intragam NexGen is a ready-to-use solution. The product should be at room or body temperature before use. A vented infusion line with integrated filter should be used for the administration of Intragam NexGen. Always pierce the stopper at its centre, within the marked area.

If dilution is desired, 5% glucose solution should be used. For obtaining an immunoglobulin solution of 50 mg/mL (5%), Intragam NexGen 100 mg/mL (10%) should be diluted with an equal volume of the 5% glucose solution. Aseptic technique must be strictly observed during the dilution of Intragam NexGen.

Intragam NexGen must not be mixed with physiological saline. However, after-rinsing of the infusion tubes with physiological saline is permitted.

The solution must be clear or slightly opalescent. Do not use solutions that are cloudy or have particulate matter.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or the excipient.

Hypersensitivity to human immunoglobulins, especially in patients with IgA deficiency where the patient has anti-IgA antibodies.

For patients with hyperprolinaemia type I and type II see section 4.4 Special warnings and precautions for use.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intragam NexGen contains the excipient L-proline. Physicians should weigh the risk/benefit of Intragam NexGen in patients with hyperprolinaemia type I and type II on an individual basis.

Certain severe adverse reactions may be related to the rate of infusion. Reactions to IVIg tend to be related to the infusion rate and are most likely to occur during the first hour of the infusion. The recommended infusion rate given in section 4.2 Dose and method of administration must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion
- in patients with hypogammaglobulinaemia or agammaglobulinaemia, with or without IgA deficiency
- in patients who receive human immunoglobulin for the first time or, in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

Potential complications can often be avoided by ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially infusing the product slowly (0.3 mL/kg body weight/hr)
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

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

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion
- avoidance of concomitant use of loop diuretics

Hypersensitivity

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

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

Haemolytic Anaemia

IVIg products can contain blood group antibodies (e.g. anti-A and anti-B) which may act as haemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. The Intragam NexGen manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Privigen manufactured with the IAC step show statistically significant reductions of haemolytic anaemia (see section 4.8 Adverse effects (Undesirable effects), section 5.1 Pharmacodynamic properties- Clinical trials).

Isolated cases of haemolysis-related renal dysfunction/renal failure or disseminated intravascular coagulation and death have occurred.

The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; blood group A, B and AB (non-O blood group), and underlying inflammatory state. As this event was commonly reported in blood group A, B or AB (non-O blood group) patients receiving high doses for non-PID indications, increased vigilance is recommended.

Haemolysis has rarely been reported in patients given replacement therapy for PID.

IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. If signs and/or symptoms of haemolysis develop during or after an IVIg infusion, discontinuation of the IVIg treatment should be considered by the treating physician (see also section 4.8 Adverse effects (Undesirable effects)).

Aseptic Meningitis Syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several grams/L, but negative culture results.

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

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of 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).

In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable based on clinical judgement.

Acute Renal Failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal impairment, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65 years.

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

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

For patients suffering from diabetes mellitus and requiring dilution of Intragam NexGen to lower concentrations, the presence of glucose in the recommended diluent should be taken into account.

Transfusion-Related Acute Lung Injury (TRALI)

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

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

Pathogen safety

Intragam NexGen 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 such as hepatitis A (HAV) and parvovirus B19.

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

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

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

Use in the elderly

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

Paediatric use

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

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.

Treatment of CIDP

The use of Privigen has not been established in patients with CIDP under the age of 18 years.

For further information regarding the safety profile for use in paediatric patients with CIDP see section 5.1 Pharmacodynamic properties- Clinical trials (Post-Authorisation Safety Study).

Effects on laboratory tests

Interference with serological testing

After infusion 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. Direct Agglutination Test (DAT), direct Coombs' test).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 Intragam NexGen, 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.

Medicine interactions

The interaction of Intragam NexGen with other medicines has not been established.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been conducted in animals using Intragam NexGen or the excipient present in the formulation (L-proline). Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

Use in pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

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

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

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

Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB (non-O blood groups) in immunomodulatory treatment.

Haemolysis has been reported rarely in patients given replacement therapy for PID. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see section 4.4 Special warnings and precautions for use- Haemolytic anaemia).

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

Very rarely: transfusion related acute lung injury and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses events have been reported (see section 4.4 Special warnings and precautions for use).

Tabulated list of adverse reactions

Seven clinical studies were performed with Privigen, which included patients with PID, ITP and CIDP. In the pivotal PID study, 80 patients were enrolled and treated with Privigen. Of these, 72 completed the 12 months of treatment. In the PID extension study, 55 patients were enrolled and treated with Privigen. Another study in 11 PID patients was conducted in Japan.

Two ITP studies were performed with 57 patients each. Two CIDP studies were performed with 28 and 207 patients, respectively.

Most adverse drug reactions (ADRs) observed in the 7 clinical studies were mild to moderate in nature.

Table 2 shows an overview of the ADRs observed in the 7 clinical studies categorised according to MedDRA System organ class, preferred term level and frequency.

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

Table 2: Frequency of Adverse Drug Reactions (ADRs) in clinical studies with Privigen

MedDRA System Organ Class	Adverse Reaction	Frequency*
Infections and infestations	Aseptic meningitis	Uncommon
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia) ^a , leukopenia	Common
	Anisocytosis (including microcytosis), thrombocytosis	Uncommon
	Decreased neutrophil count	Unknown
Immune system disorders	Hypersensitivity	Common
	Anaphylactic shock	Unknown
Nervous system disorders	Headache (including sinus headache, migraine, head discomfort, tension headache)	Very common
	Dizziness (including vertigo)	Common
	Somnolence, tremor	Uncommon
Cardiac disorders	Palpitations, tachycardia	Uncommon
Vascular disorders	Hypertension, flushing (including hot flush, hyperaemia), hypotension	Common
	Thromboembolic events, vasculitis (including peripheral vascular disorder)	Uncommon
	Transfusion related acute lung injury	Unknown

Respiratory, thoracic and mediastinal disorders	Dyspnoea (including chest pain, chest discomfort, painful respiration)	Common
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, abdominal pain	Common
Hepatobiliary disorders	Hyperbilirubinaemia	Common
Skin and subcutaneous tissue disorders	Skin disorder (including rash, pruritus, urticaria, maculo-papular rash, erythema, skin exfoliation)	Common
	Exfoliative dermatitis	Unknown
Musculoskeletal and connective tissue disorders	Myalgia (including muscle spasms, musculoskeletal stiffness, musculoskeletal pain)	Common
Renal and urinary disorders	Proteinuria, increased blood creatinine	Uncommon
	Acute renal failure	Unknown
General disorders and administration site conditions	Pain (including back pain, pain in extremity, arthralgia, neck pain, facial pain), pyrexia (including chills), influenza like illness (including nasopharyngitis, pharyngolaryngeal pain, oropharyngeal blistering, throat tightness)	Very common
	Fatigue, asthenia (including muscular weakness)	Common
	Injection site pain (including infusion site discomfort)	Uncommon
Investigations	Decreased haemoglobin (including decreased red cell blood count, decreased haematocrit), Coombs' (direct) test positive, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood lactate dehydrogenase	Common

*Frequencies were evaluated according to the following conventions: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$). For spontaneous post-marketing ADRs, the reporting frequency is categorised as unknown.

α The frequency is calculated based on studies completed prior to implementation of the immunoaffinity chromatography isoagglutinin reduction step (IAC) into Privigen production. A reduction in the frequency of haemolytic anaemia was observed following the implementation of the IAC step (see section 5.1 Pharmacodynamic properties- Clinical trials).

Paediatric population

In Privigen clinical studies with paediatric patients, the frequency, nature and severity of adverse reactions did not differ between children and adults.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Regulatory Agency (NPRA).

4.9 OVERDOSE

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The manufacturing process for Intragam NexGen includes the following steps: ethanol precipitation of the IgG plasma fraction, followed by octanoic acid fractionation and incubation at pH 4. Subsequent purification steps comprise depth filtration, anion exchange chromatography, immunoaffinity chromatography to specifically reduce blood group A and B antibodies (isoagglutinins A and B, see section 4.8 Adverse effects (Undesirable effects), section 5.1 Pharmacodynamic properties- Clinical trials) and a virus filtration step that can remove particles to a size of 20 nm.

Mechanism of action

Intragam NexGen contains mainly IgG that are present in the normal human population and that show a broad spectrum of functionally intact antibodies against infectious agents. Intragam NexGen is prepared from plasma from 1000 or more human donors. The IgG subclass distribution in Intragam NexGen corresponds approximately to that of native human plasma. The Fc and Fab functions of the IgG molecule are retained.

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

In replacement therapy adequate doses of Intragam NexGen may restore abnormally low IgG levels to within the normal range.

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

Clinical trials

The safety and efficacy of Privigen was evaluated in 5 prospective, open-label, single-arm, multicentre studies carried out: in Europe (ITP, PID and CIDP studies), Japan (PID and CIDP studies) and in the US (PID and CIDP studies).

Additional safety data were collected in a Post-Authorisation Safety Study (PASS), an observational retrospective cohort study in patients with various immunological conditions performed in the US.

Treatment of Primary Immunodeficiency Syndromes (PID)

In the PID study, a total of 80 patients between 3 and 69 years of age were treated with a median dose of 200 to 888 mg/kg body weight (bw) 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 (SBI), 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).

An open-label, single-arm phase 3 study conducted in Japan assessed the PK and safety of Privigen in 11 subjects with PID.

Treatment of Immune Thrombocytopenic Purpura (ITP)

A total of 57 patients 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 bw 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 patients 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 patients reached this response. For those patients who responded, the median duration of platelet count $\geq 50 \times 10^9/L$ was 15.4 days (range: 1 to >82 days).

Treatment of neurological disorders

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

In the first CIDP study, a prospective multicentre open-label trial (PRIMA-Privigen Impact on Mobility and Autonomy study), 28 patients with CIDP (13 patients were and 15 patients were not on IVIg treatment at study screening) received a loading dose of 2 g/kg bw given over 2–5 days followed by up to 7 maintenance doses of 1 g/kg bw over 1–2 days every 3 weeks. Patients on IVIg treatment at study screening were withdrawn from IVIg treatment until confirmed deterioration had occurred before the start of Privigen treatment. On the adjusted 10-point INCAT (Inflammatory Neuropathy Cause and Treatment) scale a clinically meaningful improvement of at least 1-point from baseline to treatment week 25 was observed

in 17 out of 28 patients. The INCAT responder rate therefore, was 60.7% (95% confidence interval [42.41, 76.43]). 53% (9/17) of the responding patients responded after receiving the initial induction dose at week 4 and 94% (16/17) of patients responded by week 10.

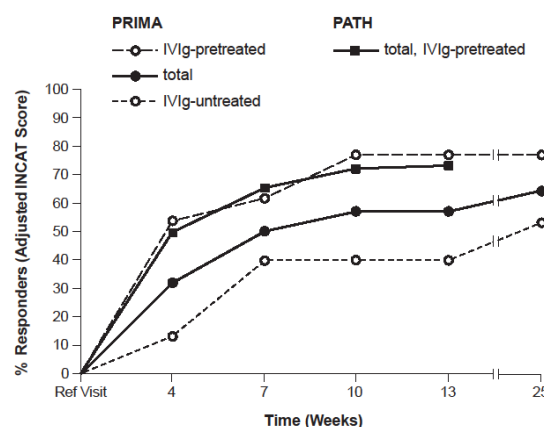
In the second CIDP clinical study, a prospective, multicentre, randomised, placebo-controlled study (PATH-Polyneuropathy and Treatment with Hizentra®), 207 subjects with CIDP received Privigen in the pre-randomisation phase of the study. All subjects had previously received IVIg treatment for at least 8 weeks prior to entering the study. IVIg-dependence was confirmed by clinically evident deterioration during an IVIg withdrawal phase of up to 12 weeks. In subjects who were IVIg-dependent 207 received a Privigen loading dose of 2 g/kg bw, followed by up to 4 Privigen maintenance doses of 1 g/kg bw every 3 weeks for up to 13 weeks.

Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥ 1 point in the adjusted INCAT score. Additional measures of CIDP improvement were a Rasch-built Overall Disability Scale (R-ODS) increase of ≥ 4 points, a mean grip strength increase of ≥ 8 kPa, or a Medical Research Council (MRC) sum score increase of ≥ 3 points. Overall, 91% of subjects (188 patients) showed improvement in at least one of the criteria above by week 13.

By adjusted INCAT score, the responder rate by week 13 was 72.9% (151 / 207 patients), with 149 patients responding already by week 10. A total of 43 of the 207 patients achieved a better CIDP status as assessed by adjusted INCAT score compared to their CIDP status at study entry.

The comparability of the response rates by adjusted INCAT score between the PRIMA and PATH studies are shown in **Figure 1**.

Figure 1. Percentage of Responders (Adjusted INCAT Score)



IVIg: intravenous immunoglobulin; Ref Visit: reference visit; IVIg-pretreated: patients on IVIg treatment at study screening; IVIg-untreated: patients naive or not on IVIg treatment for ≥ 1 year at study screening.

The mean improvement at the end of the treatment period in adjusted INCAT score compared to reference visit was 1.4 points in the PRIMA study (1.8 points in IVIg-pretreated subjects) and 1.2 points in PATH study.

In PRIMA, the percentage of responders based on MRC score (defined as an increase by ≥ 3 points) was 85% (87% in the IVIg-untreated and 82% in IVIg-pretreated) and 57% in PATH. The overall median time to first MRC sum score response in PRIMA was 6 weeks (6 weeks in the IVIg-untreated and 3 weeks in the IVIg-pretreated) and 9.3 weeks in PATH. MRC sum score in PRIMA improved by 6.9 points (7.7 points for IVIg-untreated and 6.1 points for IVIg-pretreated) and by 3.6 points in PATH. The grip strength of the dominant hand improved by 14.1 kPa (17.0 kPa in IVIg-untreated and 10.8 kPa in IVIg-pretreated subjects) in the PRIMA study, while in PATH the grip strength of the dominant hand improved by 12.2 kPa. For the non dominant hand similar results were observed in both studies, PRIMA and PATH.

Overall the efficacy and safety profiles of Privigen in the PRIMA and the PATH studies in CIDP patients were comparable.

Privigen has comparable characteristics to other IVIg products that have been used in the management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). In addition, the adverse reactions reported in the literature for IVIg when used in this indication were comparable with those reported for other indications. It is therefore expected that Privigen will have a comparable efficacy and safety profile to other IVIg products in the management of this indication.

There are several randomised controlled clinical trials in the literature demonstrating the efficacy and safety of the use of IVIg in the treatment of patients with CIDP. The evidence for the efficacy of IVIg in the management of CIDP is clear.

Post-Authorisation Safety Study (PASS) in patients with various immunological conditions

In an observational hospital-based retrospective cohort PASS, the risk of haemolytic anaemia following Privigen therapy was evaluated in patients with various immunological conditions across 2 time periods. The risk of haemolytic anaemia was assessed prior (baseline) and after the implementation of a risk minimisation measure, the introduction of the IAC step in the Privigen manufacturing process. The IAC step was shown to produce a 2-titre step reduction of isoagglutinins, from a median anti-A of 32 to 8 and from a median anti-B of 16 to 4.

Of the 9439 patients who received Privigen prior to the introduction of the IAC step, 47 cases of haemolytic anaemia were identified. Following the introduction of IAC, 7759 patients received Privigen, with 4 cases of haemolytic anaemia. A statistically significant reduction of

89% in the rate of haemolytic anaemia (based on an incidence rate ratio of 0.11; adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use; one-sided p-value <0.01) was observed after implementation of the IAC step compared to baseline.

The reduction in probable haemolytic anaemia incidence rate after IAC implementation versus baseline was especially pronounced in patients treated with Privigen doses ≥ 0.75 g/kg bw. These calculations are estimated from the demographic characteristics.

Additionally, 28 paediatric patients with CIDP <18 years of age were identified throughout the entire study period from 1 January 2008 to 30 April 2019. None of the paediatric patients given a total of 486 Privigen administrations experienced haemolytic anaemia, AMS, acute renal failure, severe anaphylactic reaction or a thromboembolic event. Two out of 28 patients experienced a moderate anaphylactic reaction equating to 7.1% of the patients, and 0.4% of all 486 Privigen administrations.

Clinical trials have been conducted with Privigen.

5.2 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 Syndromes (PID) patients (see section 5.1 Pharmacodynamic properties-Clinical trials). Twenty-five patients (aged 13 to 69 years) participated in the pharmacokinetic assessment (see **Table 3**). The median half-life of Privigen in PID patients was 36.6 days. This half-life may vary from patient to patient, particularly in patients with primary immunodeficiencies.

Table 3: Pharmacokinetic parameters of Privigen in 25 PID patients

Parameter	Median (Range)
C _{max} (peak, g/L)	23.4 (10.4–34.6)
C _{min} (trough, g/L)	10.2 (5.8–14.7)
t _{1/2} (days)	36.6 (20.6–96.6)

C_{max}, maximum serum concentration.

C_{min}, trough minimum serum concentration.

t_{1/2}, elimination half-life.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

No carcinogenicity studies have been conducted with Intragam NexGen.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Refer to Section 4.2 Dose and method of administration.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

Shelf life of the product after opening:

Intragam NexGen is intended for single use. Because the solution contains no preservative, Intragam NexGen should be used / infused immediately once opened.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C (Do not freeze).

Do not shake.

Keep the bottle in the outer carton in order to protect from light.

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

6.5 NATURE AND CONTENTS OF CONTAINER

Intragam NexGen is presented as a 10% (100 g/L) solution for intravenous infusion. 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 disc providing a tamper-evident seal.

The product is supplied in the following pack size:

- One bottle of 50 mL solution containing 5 g human normal immunoglobulin.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

No data available

CAS Number

9007-83-4

7 NAME AND ADDRESS OF THE MANUFACTURER

CSL Behring (Australia) Pty Ltd
189–209 Camp Rd
Broadmeadows VIC 3047

Product Registration Holder

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Distributed by

National Blood Centre
Kuala Lumpur
Malaysia

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