NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Privigen® NZ (10% (100 g/L)), solution for intravenous infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin

Privigen® NZ is a 10% solution containing 100 g/L of 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 (≤2%–typically below 0.1%). The distribution of the IgG subclasses is similar to that of normal human plasma (approximate values: 69% IgG_1, 26% IgG_2, 3% IgG_3, 2% IgG_4).

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

Privigen® NZ is manufactured from human plasma donated by New Zealand's voluntary and non-remunerated donors.

Privigen® NZ contains 250 mmol/L of L-proline as a stabiliser which is a physiological non-essential amino acid. Privigen® NZ contains no carbohydrate stabiliser (e.g. sucrose, maltose) and no preservative, and it has a low sodium content of ≤1 mmol/L.

3 PHARMACEUTICAL FORM

Privigen® NZ is a sterile, clear or slightly opalescent, colourless or pale yellow solution for intravenous infusion.

Privigen® NZ has a nominal osmolality of 320 mOsm/kg and is approximately isotonic. The pH value of the ready-to-use solution is 4.8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults and children:

- Primary Immunodeficiency Diseases (PID).
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.
- Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment.

Immunomodulatory therapy in adults and children:

- Idiopathic Thrombocytopenic Purpura (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré Syndrome (GBS).
- Kawasaki disease.
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).
- Multifocal Motor Neuropathy (MMN).

- Myasthenia Gravis (MG) exacerbations.
- Lambert-Eaton Myasthenic Syndrome (LEMS).
- Stiff Person Syndrome (SPS).

4.2 Dose and method of administration

Dose

The recommended dosage and dosage regimen are summarised in **Table 1** and are given as a guideline. The dose and dose regimen are dependent on the indication.

In replacement therapy the dosage may need to be individualised for each patient depending on the pharmacokinetic and clinical response.

In immunomodulatory therapy adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state.

Table 1: Dosage recommendations and frequency of infusions

Indication	Dose	Frequency of infusions
Replacement therapy		
Primary immunodeficiency diseases	Starting dose: 0.4–0.8 g/kg bw Thereafter: 0.2–0.8 g/kg bw	Every 2–4 weeks to obtain IgG trough level of at least 4–6 g/L 3–6 months are required after the initiation of therapy for equilibration 2–4 weeks
Secondary immunodeficiency myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections	0.2–0.4 g/kg bw	Every 3–4 weeks to obtain IgG trough level of at least 4–6 g/L
Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment	0.2–0.4 g/kg bw	Every 3–4 weeks to obtain IgG trough level of at least 4–6 g/L

Immunomodulatory therapy		
Idiopathic thrombocytopenic purpura	0.8–1 g/kg bw or 0.4 g/kg bw/day	On day 1, possibly repeated once within 3 days Over 2–5 days Treatment can be repeated if relapse occurs
Guillain-Barré syndrome	0.4 g/kg bw/day	Over 5 days (experience in children limited)
Kawasaki disease	1.6–2 g/kg bw or 2 g/kg bw	In divided doses over 2–5 days in association with acetylsalicylic acid In one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyneuropathy	Starting dose: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 1 g/kg bw	Every 3 weeks over 1–2 days
Multifocal motor neuropathy	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–2 g/kg bw	Every 2–6 weeks
Myasthenia gravis exacerbations	Prior to surgery or during myasthenic crisis Induction: 1–2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–1 g/kg bw	Every 4–6 weeks
Lambert-Eaton myasthenic syndrome	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 0.4–1 g/kg bw	Every 2–6 weeks
Stiff person syndrome	Induction: 2 g/kg bw	In divided doses over 2–5 days
	Maintenance: 1–2 g/kg bw	Every 4–6 weeks

The use of Privigen® has not been established in patients with neurological indications under the age of 18 years.
bw = body weight

Paediatric population

The dose in children is not different from that of adults as the dose for each indication is given by body weight and adjusted to the clinical outcome.

Method of administration

Privigen® NZ should be infused intravenously.

Patients naive 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 section 5.1).

For neurological conditions the patient's response to treatment should be regularly monitored, and if the response is inadequate, stopping treatment should be considered based on the clinical judgement of the treating physician.

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 an adverse reaction, 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.

If desired, Privigen® NZ can be diluted with glucose 5% solution, using aseptic technique.

The name and batch number of the product should be recorded every time Privigen® NZ is administered to a patient in order to maintain a link between the patient and the batch of the product.

For further instructions, see sections 4.4 and 6.6.

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.

4.4 Special warnings and precautions for use

Privigen® NZ contains the excipient L-proline. Physicians should weigh the risk/benefit of Privigen® NZ 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 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.

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 Privigen® NZ manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Privigen® manufactured with the IAC step show statistically significant reductions of haemolytic anaemia (see section 4.8, section 5.1).

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).

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 mm^3, 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. Privigen® NZ does not contain sucrose, maltose or glucose.

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

Transfusion-Related Acute Lung Injury (TRALI)

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

Privigen® NZ 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.

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

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).

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

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® NZ, 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 Privigen® with other medicines has not been established.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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).

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).

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 in each study. 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	MedDRA Term	Frequency*
Infections and infestations	Aseptic meningitis	Uncommon
Blood and lymphatic system disorders	Anaemia, haemolysis (including haemolytic anaemia)[α], 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
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 blood cell 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥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 into Privigen® production.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Privigen® NZ is prepared from plasma from 1000 or more human donors. The manufacturing process for Privigen® NZ 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, section 5.1) and a virus filtration step that can remove particles to a size of 20 nm.

Mechanism of action

Privigen® NZ contains mainly IgG that are present in the normal human population and that show a broad spectrum of functionally intact antibodies against infectious agents. The Fc and Fab functions of the IgG molecule are retained. In replacement therapy adequate doses of Privigen® NZ may restore abnormally low IgG levels to within the normal range.

The IgG subclass distribution in Privigen® NZ corresponds approximately to that of native human plasma.

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

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

Pharmacodynamic effects

The efficacy of Privigen® has been evaluated in 5 Phase III clinical studies; 1 ITP study; 2 CIDP studies (PRIMA and PATH) and 2 PID studies.

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

Clinical trials have been conducted with Privigen®.

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).

A phase 3 study conducted in Japan assessed the PK and safety of Privigen® in 11 subjects with PID.

ITP

A total of 57 patients aged 15 to 69 years with chronic ITP and a platelet count of ≤20 x 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 x 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 ≥50 x 10^9/L was 15.4 days (range: 1 to >82 days).

Treatment of neurological disorders

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]). Fifty three percent (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.

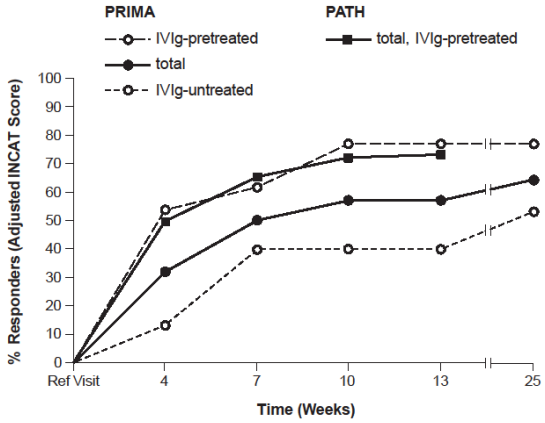
Following clinical deterioration during IVIg withdrawal, clinical improvement of CIDP was primarily defined by a decrease of ≥1 point in the adjusted INCAT score. Additional measures of CIDP improvement were a Rasch-built Overall Disability Scale (R-ODS) increase of ≥4 points, a mean grip strength increase 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 taking into account differences in duration of treatment, etc.

Privigen® has comparable characteristics to other IVIg products that have been used in the management of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Multifocal Motor

Neuropathy (MMN), Myasthenia Gravis (MG), Lambert-Eaton Myasthenic Syndrome (LEMS) and Stiff Person Syndrome (SPS). In addition, the adverse reactions reported in the literature for IVIg when used in these indications 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 these indications.

There are several randomised controlled clinical trials in the literature examining the efficacy and safety of the use of IVIg in the treatment of patients with CIDP, MMN and MG. Whilst the evidence for the efficacy of IVIg in the management of CIDP and acute exacerbations of MG is clear, data for the treatment of MMN is not as definitive. Clinical trials for the use of IVIg for MMN showed an increase in muscle strength but no impact on the disability scale.

The efficacy and safety of IVIg in the treatment of patients with stiff person syndrome and LEMS has only been demonstrated in a single randomised controlled clinical trial for each condition.[1,2]

The clinical trial data in these indications demonstrates that response to IVIg treatment may be variable or inadequate.

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

In an observational hospital-based cohort PASS, the risk of haemolytic anaemia following Privigen® therapy was evaluated in patients with various immunological conditions from 1 January 2008 to 30 April 2019. The risk of haemolytic anaemia was assessed prior (baseline) and after the implementation of a risk minimisation measure, the introduction of the IAC step in the Privigen® manufacturing process. The IAC step was shown to produce a 2-titre step (75%) 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.

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 patients experienced a moderate anaphylactic reaction equating to 0.4% of all Privigen® administrations.

Paediatric population

No differences were seen in the pharmacodynamic properties between adult and paediatric study patients.

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.

ITP

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

CIDP, MMN, MG, LEMS and SPS

The use of Privigen® has not been established in patients with neurological indications under the age of 18 years. In CIDP patients no differences were observed in the pharmacodynamic properties and safety profile between adult and paediatric study patients.

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.

5.2 Pharmacokinetic properties

Absorption

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution

It is distributed relatively rapidly between plasma and extravascular fluid. After approximately 3–5 days, equilibrium is reached between the intra- and extravascular compartments.

Elimination

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system. The half-life may vary from patient to patient, particularly in patients with primary immunodeficiencies.

The pharmacokinetic parameters for Privigen® were determined in a clinical study in PID patients (see section 5.1). Twenty-five patients (aged 13 to 69 years) participated in the pharmacokinetic assessment (see **Table 3**).

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)
$t_{½}$ (days)	36.6 (20.6–96.6)

C_{max}, maximum serum concentration.
C_{min}, trough minimum serum concentration.
$t_{½}$, elimination half-life.

The median half-life of Privigen® in PID patients was 36.6 days.

Paediatric population

No differences were seen in the pharmacokinetic parameters between adult and paediatric study patients with PID. There are no data on pharmacokinetic properties in paediatric patients with CIDP.

5.3 Preclinical safety data

Immunoglobulins are normal constituents of the human body. L-proline is a physiological, non-essential amino acid.

The safety of Privigen® has been investigated in several preclinical studies with particular reference to the excipient L-proline. Studies in rats given daily L-proline doses of 1450 mg/kg bw did not show any evidence of teratogenicity or embryotoxicity. Genotoxicity studies of L-proline did not show any pathological findings.

Some published studies pertaining to hyperprolinaemia have shown that long-term, high doses of L-proline have effects on brain development in very young rats. However, in studies where the dosing was designed to reflect the clinical indications for Privigen®, no effects on brain development were observed. Further safety-pharmacology studies of L-proline in adult and juvenile rats did not reveal behavioural disorders.

Immunoglobulins are natural components of the human body. Data from animal testing of acute and chronic toxicity and embryofoetal toxicity of immunoglobulins are inconclusive on account of interactions between immunoglobulins from heterogeneous species and the induction of antibodies to heterologous proteins. In local tolerability studies in rabbits in which Privigen® was administered intravenously, paravenously, intra-arterially, and subcutaneously, the product was well tolerated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-proline, water for injections

6.2 Incompatibilities

This medicine must not be mixed with other medicines, diluents, or solvents except those mentioned in section 6.6, and should be administered by a separate infusion line.

6.3 Shelf life

3 years

Shelf life after first opening:

Use in one patient on one occasion only. Privigen® NZ contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle.

6.4 Special precautions for storage

Store below 25°C (Do not freeze).

Do not use if the solution has been frozen.

Do not shake.

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

For storage conditions after first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Privigen® NZ 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.

Pack sizes

One bottle of 50 mL solution containing 5 g human normal immunoglobulin.
One bottle of 100 mL solution containing 10 g human normal immunoglobulin.
One bottle of 200 mL solution containing 20 g human normal immunoglobulin.
One bottle of 400 mL solution containing 40 g human normal immunoglobulin.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Privigen® NZ is packaged as a ready-to-use solution in single use bottles.

The product should be at room or body temperature before use. Privigen® NZ should always be administered by intravenous (IV) infusion using appropriate administration equipment. Privigen® NZ is packaged in a glass bottle that must be vented during use. Privigen® NZ must not be mixed with physiological saline. The infusion line may, however, be primed or flushed with physiological saline (0.9% sodium chloride).

Always pierce the stopper at its centre, within the marked area.

If desired, Privigen® NZ can be diluted with glucose 5% solution, using aseptic technique.

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.

Any unused portion should be discarded appropriately.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

09 March 2023

10 DATE OF REVISION OF THE TEXT

09 March 2023

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REFERENCES

1. Bain PG, Motomura M, Newsom-Davis et al. Effects of intravenous immunoglobulin on muscle weakness and calcium-channel autoantibodies in the Lambert-Eaton myasthenic syndrome. Neurology 1996;47:678–83.
2. Dalakas MC, Fujii M, Li M, et al. High-dose Intravenous Immune Globulin for Stiff-Person Syndrome. N Eng J Med 2001;345:1870–6.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	New registration