NEW ZEALAND DATA SHEET

1. PRODUCT NAME

GAMUNEX®, Normal Immunoglobulin (Human), 10%, 100 mg/mL, Solution for Intravenous or Subcutaneous Administration

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Normal Immunoglobulin (Human), 10%

One ml contains:
Normal immunoglobulin (human) .....100 mg
(purity of at least 98% IgG)

One vial of 10 mL contains: 1 g
One vial of 25 mL contains: 2.5 g
One vial of 50 mL contains: 5 g
One vial of 100 mL contains: 10 g
One vial of 200 mL contains: 20 g

Distribution of the IgG subclasses (average values):
IgG_1 ..... 62.8%
IgG_2 ..... 29.7%
IgG_3 ..... 4.8%
IgG_4 .....2.7%

1 ml GAMUNEX® contains 100 mg protein with an IgG content of at least 98%. GAMUNEX® contains trace levels of fragments and IgA (≤ 0.084 mg/mL) and IgM.

Produced from plasma of human donors.

GAMUNEX® contains 0.16–0.24 M glycine. The pH of GAMUNEX® is 4.0 – 4.5. GAMUNEX® contains no preservative.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for intravenous or subcutaneous administration

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

The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsmol/kg solvent, which is close to physiological osmolality (285 - 295 mOsmol/kg).

NEW ZEALAND DATA SHEET

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in:

- Primary Immunodeficiency (PI) diseases.
- Symptomatic Hypogammaglobulinaemia secondary to underlying disease or treatment.

Immunomodulation in:

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

4.2 Dose and method of administration

GAMUNEX® is recommended for administration by intravenous infusion for all indications. GAMUNEX® can also be administered by subcutaneous infusion for replacement therapy in primary immunodeficiency indications only. Safety and efficacy of subcutaneous administration has not been demonstrated for other indications.

The buffering capacity of GAMUNEX® is 35.0 mEq/L (0.35 mEq/g protein). A dose of 1000 mg/kg body weight therefore represents an acid load of 0.35 mEq/kg body weight. The total buffering capacity of whole blood in a normal individual is 45–50 mEq/L of blood, or 3.6 mEq/kg body weight. Thus, the acid load delivered with a dose of 1000 mg/kg of GAMUNEX® would be neutralized by the buffering capacity of whole blood alone, even if the dose was infused quickly via syringe push.

Dose

Replacement therapy in Primary Immunodeficiency (PI) diseases

Intravenous (IV)

GAMUNEX® doses between 300 and 600 mg/kg (3 and 6 mL/kg), which represented the dose range for 92% of the subjects in the larger efficacy trial, may be used for infection prophylaxis. The dose should be individualized taking into account dosing intervals (e.g. 3 or 4 weeks) and GAMUNEX® dose (between 300 and 600 mg/kg). A target serum IgG trough level (i.e. prior to the next infusion) of at least 5 g/L has been proposed in the literature, however no randomized controlled trial data are available to validate this recommendation. See section 5.1 Pharmacodynamic effects: Clinical efficacy and safety.

Subcutaneous (SC)

The weekly SC GAMUNEX® dose for replacement therapy in primary immunodeficiency diseases may be initiated with a dose comparable to the IVIg replacement dose adjusted for previous IV treatment interval. The dose and dosage interval must be individualised based on measured IgG trough levels and ongoing clinical response.

Replacement therapy in symptomatic secondary hypogammaglobulinaemia

The recommended dose is 200 to 400 mg/kg every 3 to 4 weeks, to obtain a trough level of at least 5 to 6 g/L.

Idiopathic Thrombocytopaenic Purpura (ITP)

GAMUNEX® may be administered at a total dose of 2 g/kg, divided in two doses of 1 g/kg (10 mL/kg) given on two consecutive days or into five doses of 0.4 g/kg (4 mL/kg) given on five consecutive days. If after administration of the first of two daily 1 g/kg (10 mL/kg) doses, an adequate increase in the platelet count is observed at 24 hours, the second dose of 1g/kg body weight may be withheld. Likewise, subsequent 0.4 g/Kg doses maybe withheld when an adequate increase in platelet count is observed.

The high dose regimen (1 g/kg × 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Guillain Barré Syndrome (GBS)

400 mg/kg (4 mL/kg) on three to seven consecutive days. The treatment should commence within 14 days of the onset of symptoms.

Only limited experience is available of use of intravenous immunoglobulins in children with Guillain Barré Syndrome.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Loading dose: 2 g/kg (20 mL/kg) in divided doses over 2 to 4 consecutive days.

Maintenance dose: 1 g/kg administered over 1 day (10 mL/kg) or divided into two doses of 500 mg/kg (5 mL/kg) given on two consecutive days, every 3 weeks.

Only limited experience is available of use of intravenous immunoglobulins in children with CIDP.

Clinical studies of GAMUNEX® did not include sufficient numbers of subjects aged 65 and over to determine a precise treatment effect.

Kawasaki disease

1.6 to 2 g/kg (16 to 20 mL/kg) as a single infusion or in divided doses over 2 to 5 days.

Method of administration

If dilution is required, GAMUNEX® may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline.

GAMUNEX® should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if turbid and/or if discoloration is observed.

For intravenous or subcutaneous administration, GAMUNEX® should be at room temperature during administration.

Intravenous (IV)

It is recommended that GAMUNEX® should initially be infused at a rate of 0.01 mL/kg per minute (1 mg/kg per minute) for the first 30 minutes. If well-tolerated, the rate may be gradually increased to a maximum of 0.08 mL/kg per minute (8 mg/kg per minute). If side effects occur, the rate may be reduced, or the infusion interrupted until symptoms subside. The infusion may then be resumed at the rate which is comfortable for the patient.

For patients judged to be at increased risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX® (human normal immunoglobulin intravenous, 10% Caprylate/Chromatography Purified) at a rate less than 8 mg/kg/min (0.08 mL/kg/min). No prospective data are presently available to identify a maximum safe dose, concentration, and rate of infusion in patients determined to be at increased risk of acute renal failure. In the absence of prospective data, recommended doses should not be exceeded and the concentration and infusion rate should be the minimum level practicable. Reduction in dose, concentration, and/or rate of administration in patients at risk of acute renal failure has been proposed in the literature in order to reduce the risk of acute renal failure.

Only 18 gauge needles should be used to penetrate the stopper for dispensing product from 10mL vial sizes; 16 gauge needles or dispensing pins should only be used with 25 mL vial sizes and larger. Needles or dispensing pins should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

GAMUNEX®-C vial size	Gauge of needle to penetrate stopper
10 mL	18 gauge
25, 50, 100, 200 mL	16 gauge

Content of vials may be pooled under aseptic conditions into sterile infusion bags and infused within 8 hours after pooling. Protect from light.

If dilution is required, GAMUNEX® may be diluted with 5% dextrose in water (D5/W). Do not dilute with saline.

It is recommended to infuse GAMUNEX® using a separate line by itself, without mixing with other intravenous fluids or medications the subject might be receiving. The GAMUNEX® infusion line can be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection.

Avoid simultaneous administration of GAMUNEX® and Heparin through a single lumen delivery device due to GAMUNEX®, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX® was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin. See table below.

Additional Solutions	Dilution	Line Flush	Delivery Device Flush
5% Dextrose in water	Yes	Yes	Yes
0.9% Sodium Chloride	No	Yes	Yes
Heparin	No	No	No

Subcutaneous (SC)

Subcutaneous infusion for home treatment should only be used for replacement therapy in patients with PI and should be initiated by a physician experienced in the guidance of patients for home treatment. Provide the patient with instructions on subcutaneous infusion for home treatment, if the physician believes that home administration is appropriate for the patient. Include the type of equipment to be used along with its maintenance, proper infusion techniques, selection of appropriate infusion sites (e.g., abdomen, thighs, upper arms, and/or lateral hip), maintenance of a treatment diary, and measures to be taken in case of adverse reactions in the patient instructions.

It is recommended that GAMUNEX® should be infused at a rate of 20 mL/hr per infusion site.

In clinical study 060001, the mean volume administered per infusion site was 34 mL (17-69 mL) and the majority of infusions were administered at a rate of 20 mL/hr per site. Multiple simultaneous infusion sites were enabled by administration tubing and Y-site connection tubing. Most subjects utilized 4 infusion sites per infusion with abdomen and thighs being the most commonly used sites.

Prior to use, allow the solution to reach ambient room temperature. GAMUNEX® should be inspected visually for discoloration and particulate matter prior to administration. DO NOT SHAKE. Do not use if the solution is cloudy or has particulates. Check the product expiration date on the vial. Do not use beyond the expiration date.

1. Use aseptic technique when preparing and administering GAMUNEX® for injection.
2. Remove the protective cap from the vial to expose the central portion of the rubber stopper.
3. Wipe the rubber stopper with alcohol and allow to dry.
4. Using a sterile syringe and needle, prepare to withdraw GAMUNEX® by first injecting air into the vial that is equivalent to the amount of GAMUNEX® to be withdrawn. Then withdraw the desired volume of GAMUNEX®. If multiple vials are required to achieve the desired dose, repeat this step. (Figure 1)
5. Follow the manufacturer's instructions for filling the pump reservoir and preparing the pump, administration tubing and Y-site connection tubing, if needed. Be sure to prime the administration tubing to ensure that no air is left in the tubing or needle by filling the tubing/needle with GAMUNEX®.
6. Select the number and location of injection sites. (Figure 2)
7. Cleanse the injection site(s) with antiseptic solution using a circular motion working from the center of the site and moving to the outside. Sites should be clean, dry, and at least two inches apart. (Figure 3)
8. Grasp the skin between two fingers and insert the needle into the subcutaneous tissue. (Figure 4)
9. Repeat priming and needle insertion steps using a new needle, administration tubing and a new infusion site. Secure the needle in place by applying sterile gauze or transparent dressing over the site. (Figure 5)
10. If using multiple, simultaneous injection sites, use Y-site connection tubing and secure to the administration tubing.
11. Infuse GAMUNEX® following the manufacturer's instructions for the pump. (Figure 6)

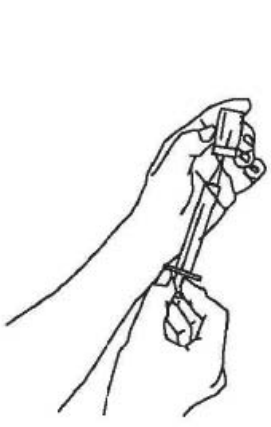


Figure 1

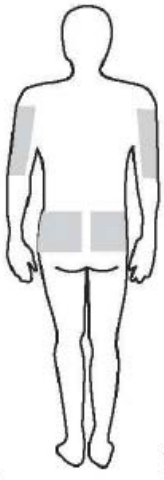
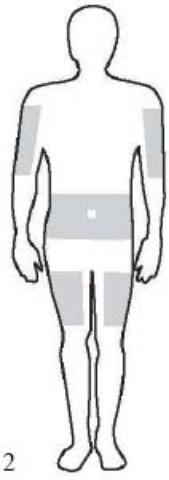


Figure 2



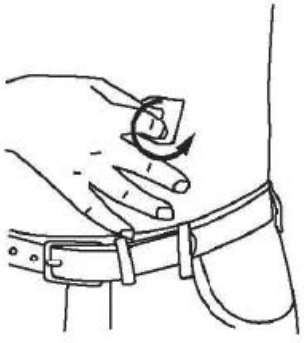


Figure 3

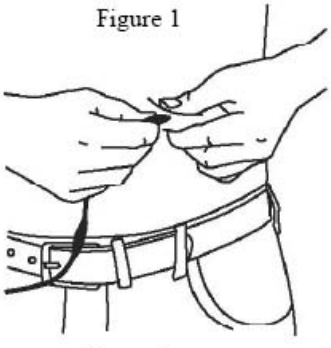


Figure 4

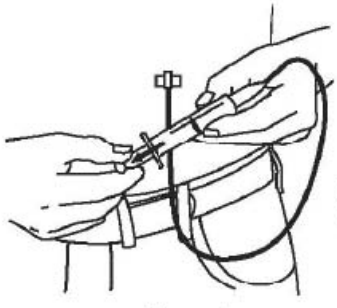


Figure 5

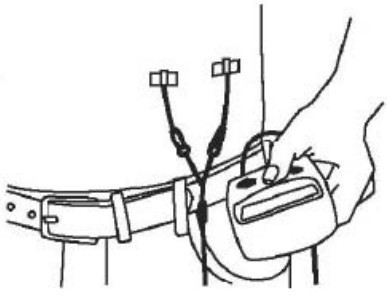


Figure 6

4.3 Contraindications

GAMUNEX® is contraindicated in individuals with known anaphylactic or severe systemic response to human immunoglobulin or any of the excipients of the product. This applies in particular to individuals with severe, selective IgA deficiencies (serum IgA <0.05 g/L) who have known antibodies against IgA (anti-IgA antibody), due to the risk of severe immediate hypersensitivity reactions including anaphylaxis.

4.4 Special warnings and precautions for use

Certain undesirable effects may be related to the rate of infusion. The recommended infusion rate should therefore be followed (see section 4.2 Dose and method of administration). Patients should be carefully observed during the infusion and for at least 20 minutes afterwards.
Certain adverse effects may occur more frequently:

- with a high infusion rate,
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency,
- in patients who are receiving human normal immunoglobulin for the first time or, in rare cases, when the immunoglobulin product is switched or after a prolonged interval without treatment.

Potential complications can often be avoided by ensuring:

- that patients are not hypersensitive to human normal immunoglobulin by initially infusing GAMUNEX® slowly (0.1 mL/kg body weight per hour)
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients receiving human immunoglobulin for the first time and those switched

from a different immunoglobulin or not having received treatment for some time should be monitored for possible undesirable effects during the first infusion and for one hour afterwards.
- the use of glucose solution for dilution prior to infusion should be carefully considered for patients suffering from latent diabetes, diabetes or in patients on a low sugar diet.

If undesirable effects occur, the infusion rate should be reduced or the infusion should be suspended until the symptoms have disappeared. If the symptoms persist even after suspending the infusion, suitable treatment should be instituted. In the event of anaphylactic shock, treatment with the product should be discontinued immediately and current standard medical treatment for shock should be implemented.

Renal effects

Human normal immunoglobulin intravenous products have been reported to be associated with acute renal dysfunction, acute renal failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinaemia, or patients who are overweight or receiving known nephrotoxic drugs. Especially in such patients, IVIg products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. GAMUNEX® does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer. See section 4.2 Dose and method of administration for important information intended to reduce the risk of acute renal failure.

Patients must not be volume depleted prior to the initiation of the infusion of IVIg. Concomitant use of loop diuretics must be avoided. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed prior to the initial infusion of GAMUNEX® and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered. For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing GAMUNEX® at a rate less than 8 mg IG/kg/min (0.08 mL/kg/min).

Increases in creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following infusion with human normal immunoglobulin intravenous products, predominantly with products containing sucrose as stabilizer. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment.

Infection risk

Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the

possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections. All infections, thought by a physician, to possibly have been transmitted by this product should be reported by the physician or other healthcare provider to Pharmaco (N.Z.) Ltd (Phone (09) 377 3336.

The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: human immunodeficiency virus, type I (HIV-1) as the relevant virus for HIV-1 and HIV-2; bovine viral diarrhoea virus (BVDV) as a model for hepatitis C virus (HCV); pseudorabies virus (PRV) as a model for large DNA viruses (e.g. herpes viruses); Reo virus type 3 (Reo) as a model for non-enveloped viruses and for its resistance to physical and chemical inactivation; hepatitis A virus (HAV) as a relevant non-enveloped virus, and porcine parvovirus (PPV) as a model for human parvovirus B19.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV. The measures taken may be of limited value against non-enveloped viruses such as HAV and/or 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.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents. Several of the individual production steps in the GAMUNEX® manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

It is strongly recommended that every time that GAMUNEX® is administered to a patient, the name and batch number of the product are recorded using the supplied tear off labels in order to maintain a link between the patient and the batch of the product.

Anaphylaxis

GAMUNEX® should be administered only intravenously or subcutaneously. On rare occasions, treatment with an immune globulin preparation may cause a precipitous fall in blood pressure and a clinical picture of anaphylaxis, even when the patient is not known to be sensitive to immune globulin preparations. Adrenalin and other appropriate supportive care should be available for the treatment of an acute anaphylactic reaction.

True anaphylactic reactions to GAMUNEX® may occur in recipients with documented prior histories of severe allergic reactions to intramuscular immunoglobulin, but some subjects may tolerate cautiously administered intravenous immunoglobulin without adverse effects. Very rarely an anaphylactoid reaction may occur in subjects with no prior history of severe allergic reactions to either intramuscular or intravenous immunoglobulin.

Aseptic Meningitis Syndrome

An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with human normal immunoglobulin intravenous treatment. The syndrome usually begins within several hours to two days following human normal immunoglobulin intravenous treatment. It is

characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting.

AMS may occur more frequently in association with high dose (2 g/kg) and or rapid infusion of human normal immunoglobulin intravenous treatment. Discontinuation of human normal immunoglobulin intravenous treatment has resulted in remission of AMS within several days without sequelae.

Haemolysis

Human normal immunoglobulin intravenous (IVIg) products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis.

The following risk factors may be related to the development of haemolysis: high doses (such as ≥2 grams/kg, single administration or divided over several days) and non-O blood group. Underlying inflammatory state in an individual patient may increase the risk of haemolysis, but its role is uncertain.

GAMUNEX® may contain low levels of anti-Blood Group A and B antibodies primarily of the IgG4 class. Direct antiglobulin tests (DAT or direct Coombs tests), which are carried out in some centres as a safety check prior to red blood cell transfusions, may become positive temporarily. GAMUNEX® does not contain irregular antibodies to Rhesus antigens or other non-ABO RBC antigens. Haemolytic events were not detected in association with positive DAT findings in clinical trials.

Monitor patients for clinical signs and symptoms of haemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of haemoglobin or haematocrit prior to infusion and within approximately 36 to 96 hours post infusion. If clinical signs and symptoms of haemolysis or a significant drop in haemoglobin or haematocrit have been observed, perform additional confirmatory laboratory testing. If transfusion is indicated for patients who develop haemolysis with clinically compromising anaemia after receiving IVIg, perform adequate cross-matching to avoid exacerbating on-going haemolysis.

Thrombotic events

Thrombotic events have been reported in association with IVIg (See 4.8 Undesirable effects). This association is assumed to be related to a relative increase in blood viscosity through the 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, a history of vascular disease/atherosclerosis or venous or arterial thrombosis, impaired cardiac output, hypercoagulable conditions, prolonged periods of immobilization, use of oestrogens, indwelling central vascular catheters, hyperviscosity, severe hypovolaemia and/or diseases which may increase blood viscosity). The potential risks and benefits of IVIg should be weighed against those of alternative therapies for all patients for whom IVIg administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronaemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Haematoma formation

Do not administer GAMUNEX® subcutaneously in patients with ITP because of the risk of haematoma formation.

Information for patients

Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/oedema, and/or shortness of breath (which may suggest kidney damage) to their physicians.

4.5 Interaction with other medicines and other forms of interaction

Antibodies in GAMUNEX® may interfere with the response to live viral vaccines such as measles, mumps and rubella. Therefore, use of such vaccines should be deferred until approximately 6 months after GAMUNEX® administration.

Avoid simultaneous administration of GAMUNEX® and Heparin through a single lumen delivery device due to GAMUNEX®, Heparin incompatibilities. Flush Heparin Lock (Hep-Lock) through which GAMUNEX® was administered with 5% dextrose in water (D5/W) or 0.9% sodium chloride for injection, and do not flush with Heparin.

Please see 4.2 Dose and method of administration for other drug interactions.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing. Passive transmission of antibodies to erythrocyte antigens e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No studies have been conducted on the effects of GAMUNEX® on fertility.

Use in pregnancy

Animal reproduction studies have not been conducted with GAMUNEX®. It is not known whether GAMUNEX® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. GAMUNEX® should be given to a pregnant woman only if clearly needed.

Use in lactation

The safety of GAMUNEX® for use in human lactation has not been established in controlled clinical trials. Immunoglobulins are excreted into breast milk and GAMUNEX® should only be given with caution to breastfeeding mothers.

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 GAMUNEX®. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

4.8 Undesirable effects

Summary of safety profile

PI: Intravenous

The most common adverse reactions observed at a rate ≥5% in subjects with intravenous treatment in the clinical trials were headache, cough, injection site reaction, nausea, pharyngitis and urticaria.

PI: Subcutaneous

The most common adverse reactions observed at a rate ≥5% of subjects with subcutaneous treatment in the clinical trials were infusion site reactions, headache, fatigue, arthralgia and pyrexia.

ITP

The most common adverse reactions observed at a rate ≥5% in subjects in the clinical trials were headache, vomiting, fever, nausea, back pain and rash.

CIDP

The most common adverse reactions observed at a rate ≥5% in subjects in the clinical trial were headache, fever, chills, hypertension, rash, nausea and asthenia.

For safety with respect to transmissible agents, see 4.4 Special warnings and precautions for use: Infection risk.

Tabulated list of adverse reactions

The following drug related adverse events were compiled from clinical trials with GAMUNEX®.

Intravenous Administration (PI, ITP, CIDP)

MedDRA System Organ Class	MedDRA Term
Incidence of frequency ≥ 1 % and < 10% (common)	
Nervous system disorders	Headache
General disorders and administration site conditions	Pyrexia
Incidence of frequency ≥ 0.1% and < 1% (uncommon)	
Investigations	White blood cell count decreased
Nervous system disorders	Dizziness
*Skin and subcutaneous disorders *Immune system disorders	Urticaria, dermatitis, pruritus, rash
Gastrointestinal disorders	Abdominal pain, diarrhoea, nausea, vomiting
Vascular disorders	Hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Pharyngitis, cough, nasal congestion, wheezing
Musculoskeletal and connective tissue disorders	Arthralgia, back pain, neck pain, shoulder pain
Cardiac disorders	Chest pain
General disorders and administration site conditions	Influenza like illness, malaise, fatigue, chills, asthenia, injection site reaction

*Two System Organ Classes

The following adverse effects have been reported in clinical trials with GAMUNEX® in **rare** frequencies **(≥ 0.01 % and < 0.1%):**
Haemolytic anaemia, dyspnoea, sinusitis, skin exfoliation, anxiety, myalgia, haemoglobin decreased, dyspepsia, contusion, dermatitis, flushing, musculoskeletal stiffness, palmar erythema, aphonia.

Subcutaneous Administration (PI)

Treatment of Primary Immunodeficiency by the subcutaneous route (Study 060001)

Adverse events occurring in study 060001 were divided into 2 types: 1) Local infusion site reactions, and 2) Non-infusion site adverse events. The table below displays those adverse events occurring in ≥ 2% of infusions during the SC phase of the study.

Most Frequent Adverse Experience (≥ 2% of infusions) by Infusion Irrespective of Causality in the SC Phase

Adverse Events (≥2% of infusions) (Number of infusions: 725)	No. of Adverse Events (Rate*)
Local Infusion Site Reactions	427 (0.59)
Mild	389 (0.54)
Moderate	29 (0.04)
Severe	9 (0.01)
Non-infusion Site Adverse Events	
Headache	37 (0.05)
Sinusitis	11 (0.02)

* Rate is calculated by the total number of events divided by the number of infusions received (725)

Drug-related adverse events occurring in ≥5% of subjects are shown below. All local infusion site reactions were *a priori* considered drug-related.

Most Frequent Drug-related Adverse Events (≥5% of subjects) by Subject in the SC Phase

Drug-related Adverse Event (≥5% of subjects)	No. of Subjects n=32 (%)
Local Infusion Site Reactions	24 (75%)
Non-infusion Site Adverse Reactions	
Headache	4 (13%)
Arthralgia	2 (6.3%)
Fatigue	2 (6.3%)
Pyrexia	2 (6.3%)

The table below shows the frequency of drug-related adverse events per infusion that occurred at a rate ≥ 0.01.

Most Frequent Drug-related Adverse Events per Infusion in the SC Phase

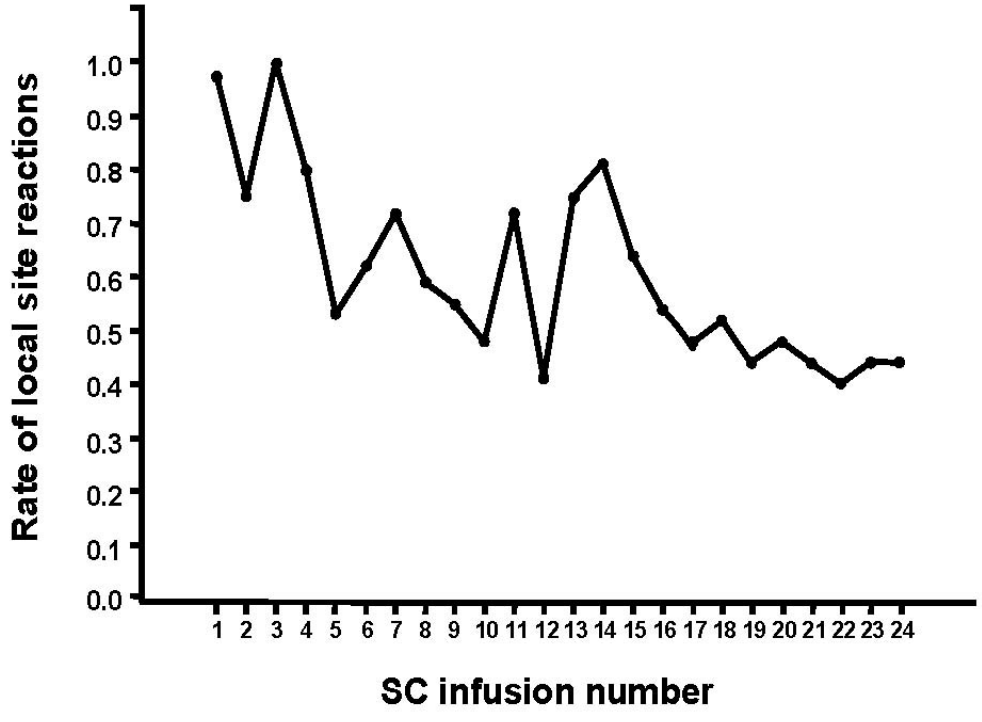
Drug-related Adverse Event (Number of infusions: 725)	No. of Adverse Events (Rate*)
Local Infusion Site Reactions	427 (0.59)
Non-infusion Site Adverse Reactions	
Headache	21 (0.03)
Arthralgia	4 (0.01)
Fatigue	3 (≤0.01)
Hyperhidrosis	2 (≤0.01)
Pyrexia	2 (≤0.01)

* Rate is calculated by the total number of events divided by the number of infusions received (725)

There were no serious bacterial infections in the SC phase of study 060001.

Local infusion site reactions with SC GAMUNEX® consisted primarily of mild to moderate erythema, pain and swelling. No serious local infusion site reactions were observed. The majority of local infusion site reactions resolved within 3 days. The number of subjects experiencing an infusion site reaction and the number of infusion site reactions decreased substantially over time as subjects received continued weekly SC infusions. At the beginning of the SC phase, a rate of approximately 1 infusion site reaction per infusion was reported, whereas at the end of the study this rate was reduced to 0.5 infusion site reactions per infusion, a reduction of 50%. See figure below.

Rate of local infusion site reactions after repeated SC infusions



Post-marketing

The following post-marketing **serious** adverse events have been reported.

MedDRA System Organ Class	MedDRA Term
Incidence of frequency < 0.01% (very rare)	
Infections and infestations	Aseptic meningitis
Immune system disorders	Anaphylactoid reaction

Incidence of frequency < 0.1% (rare)	
Blood and lymphatic system disorders	Haemolytic anaemia

Some cases of haemolytic anaemia, especially in association with pre-existing renal impairment, were severe and required blood component transfusion.

In isolated instances, impairment of renal function with elevation of serum creatinine, to the point of acute renal failure, may occur in the context of administration of immunoglobulins (see 4.4 Special warnings and precautions for use: Renal effects).

Very rarely: Thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses have been reported in association with immunoglobulins in patients at risk (see 4.4 Special warnings and precautions for use: Thrombotic events).

Description of selected adverse reactions

Transfusion-Related Acute Lung Injury (TRALI)

There have been reports of noncardiogenic pulmonary oedema [Transfusion-Related Acute Lung Injury (TRALI) in patients administered IVIg. TRALI is characterized by severe respiratory distress, pulmonary oedema, hypoxaemia, normal left ventricular function, and fever and typically occurs within 1-6 hrs after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IVIg recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

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. In New Zealand report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Overdosage may lead to fluid overload and hyperviscosity particularly in patients at risk including elderly patients and 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

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02

Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of GAMUNEX® is IgG (≥98%) with a sub-class distribution of $IgG_{GAMUNEX®}$, IgG_2, IgG_3 and IgG_4 of approximately 62.8%, 29.7%, 4.8% and 2.7% respectively.

Mechanism of action

PI

GAMUNEX® supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria or their toxins.

ITP

The mechanism of action of high doses of immunoglobulins in the treatment of Idiopathic Thrombocytopaenic Purpura (ITP) has not been fully elucidated. Several lines of evidence suggest that Fc-receptor blockade of phagocytes as well as down regulation of auto-reactive B-cells by anti-idiotypic antibodies provided by IVIg may constitute the main mechanisms of action.

CIDP

The precise mechanism of action in CIDP has not been fully elucidated.

Clinical efficacy and safety

Primary Immunodeficiency (PI)

Efficacy in primary immunodeficiency was assessed in two trials. The first trial was a randomised comparison with Gamimune N, a previous version of the product manufactured using a solvent/detergent method of viral inactivation. Patients received GAMUNEX® IV infusion for 9 months at 100-600mg/kg every 3-4 weeks. Patients were aged 35 years on average and 70% were male. The primary efficacy endpoint was the proportion of patients with at least one of the following validated infections: pneumonia, acute sinusitis and acute exacerbations of chronic sinusitis. Seventy three of the 87 patients were evaluable for efficacy. Thirteen patients (18%) developed at least one validated sino-pulmonary infection, 4 with pneumonia, 4 with acute sinusitis and 5 with exacerbation of chronic sinusitis. Fifty six patients (77%) developed any infection (validated plus clinically-defined non-validated). The annual rate of infection was 0.25 for validated sino-pulmonary infections and 2.88 for any infection. Patients spent 14% of their time on prophylactic antibiotics, 10% on therapeutic antibiotics, 1.1% off school or work, 0.7% on physicians' visits and 0.2% in hospital. The results were comparable with Gamimune N and other similar products.

The mean trough serum IgG concentration was 7.8 g/L. The relationship between trough serum IgG concentration and incidence of validated and any infection is shown in the table below:

Average Serum IgG Levels [g/L] Before Next GAMUNEX® Infusion (at Trough)

Average serum IgG levels [g/L]	Number of subjects with validated infections GAMUNEX®	Number of subjects with any infection (validated plus clinically defined non-validated infections of any organ system) GAMUNEX®
≤7	3/22 (14%)	19/22 (86%)
>7 and ≤9	5/33 (15%)	24/33 (73%)
>9	1/18 (6%)	13/18 (72%)
Cochran-Armitage Trend Test	P=0.46 (NS)	P=0.27 (NS)

NS = Non-significant

The second trial was uncontrolled, in 19 subjects of whom 17 were evaluable. Median age was 14 years, range 6-60, and 82% were male. The dose and dose interval of GAMUNEX® were similar to the previous study. The duration of treatment was 6 months. The average number of infections per patients was 3, range 1-5, and the average number of days off work or school due to infection was 3, range 0-14. Antibiotics were used for an average of 21 days, which was higher than for other similar products. However, the number of subjects was small and the data were not seasonally adjusted.

There were no serious infections or hospitalisations due to infection. The mean trough serum IgG concentration was 7.5 g/L.

Idiopathic Thrombocytopaenic Purpura (ITP)

Efficacy in idiopathic thrombocytopenic purpura was assessed in two trials. In the first trial, 49 patients with platelet counts ≤ 20 x 10^9/L were treated with GAMUNEX® IV infusion 1 g/kg/day for two consecutive days. The mean age of patients was 34 years and 25% were male. Children (age ≤ 18 years) made up 24% of the study population. The primary efficacy variable was platelet response, defined as an increase in platelet count to ≥ 50 x 10^9/L within 7 days of the first dose of GAMUNEX®. Forty three patients (88%) achieved a response. Responses of at least 7 days duration occurred in 33 patients (67%). Sixty eight percent of patients had new bleeding episodes. The results were comparable with other similar products.

In the second study, 18 patients with platelet count ≤ 20 x 10^9 /L were treated with GAMUNEX® IV infusion 1 g/Kg day for two consecutive days. The mean age of patients was 42 years and 39% were male. All were adults. The primary efficacy variable was platelet response, defined differently to the previous trial. It was an increase in platelet count to ≥ 50 x 10^9/L on at least one occasion within 21 days of the first dose of GAMUNEX®. Fifteen patients (83%) responded. The median duration of response was 13 days, range 1-21 days. Fifteen patients (83% had bleeding sites at the start of treatment. Bleeding resolved in all but two patients; however, new bleeding sites developed in three patients (epistaxis x 1, purpura x 2), two of which later resolved. The results were comparable with other similar products.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

The GAMUNEX® CIDP efficacy trial (ICE study), a double-blind, randomised, placebo-controlled study investigated the efficacy and safety of GAMUNEX® in the treatment of CIDP. A total of 117 (adult) CIDP patients were randomised to receive either GAMUNEX® or placebo every three weeks. Loading dose was 2 g/kg; maintenance dose was 1 g/kg (administered intravenously).

Responder rates (determined by improvement in INCAT disability score and maintenance of ≥ 1 improvement over the 24 week efficacy period) were significantly higher in the GAMUNEX® group (54%), compared to the placebo group (21%, p=0.0002). Muscle strength as measured by the MRC score and grip strength, as well as sensation as measured by the ISS score improved significantly more in the GAMUNEX® group compared to placebo.

In view of the limited number of patients ≥ 65 years included in the study, a precise treatment effect could not be determined with regard to the INCAT score; for grip strength, a statistically significant treatment effect was shown in favour of GAMUNEX®.

Of the responders, less than half responded after the loading dose (by week 3), but most responded after the second dose (by week 6). Non-responders were crossed over to the alternative treatment, for again up to a maximum of 24 weeks of therapy.

All responders were re-randomised in an extension phase for another 6 months period of maintenance therapy with either GAMUNEX® or placebo. Of the former responders to GAMUNEX®, the actual relapse rate was significantly higher in the patients randomised to placebo (42%) than in those randomised to GAMUNEX® (13%, p=0.012).

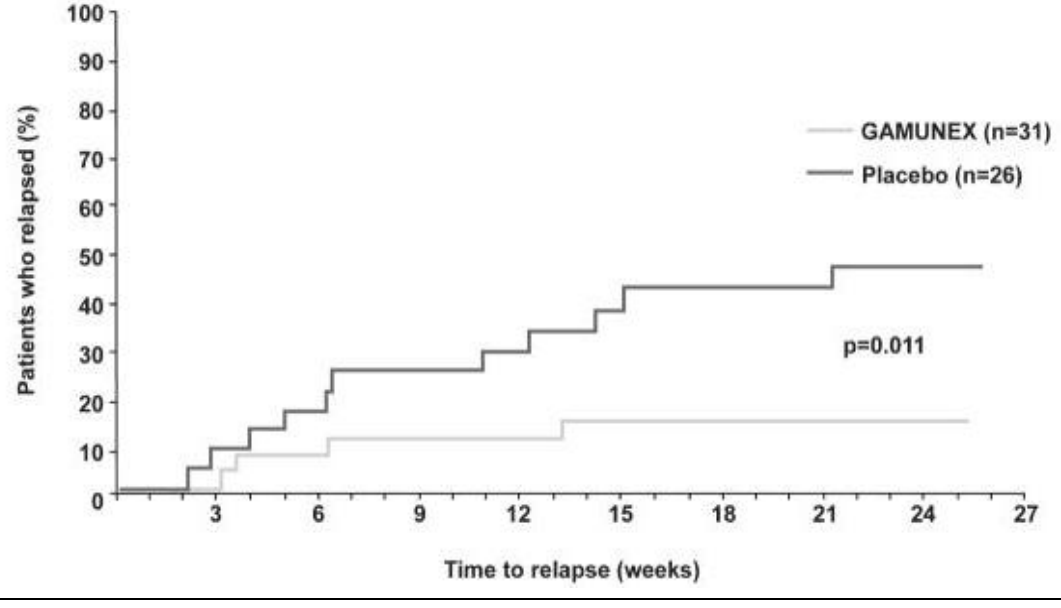
The ICE study has shown short-term and long-term efficacy of GAMUNEX® in the treatment of CIDP.

Primary Endpoint and Other Results of the ICE Study

	GAMUNEX®	Placebo	P value
Responder rate during the efficacy period (primary endpoint)	54%	21%	0.0002
Probability of relapse in the extension period	13%	45%	0.013
Grip strength (kPA)[1] (change from baseline)			
Dominant hand	13.2	1.5	0.0008
Non-dominant hand	13.3	4.3	0.005
Amplitude (mV) in the most severely affected motor nerve (change from baseline) Change excluding Erb's point	0.69 ± 1.86 1.08 ± 2.15	0.47 ± 2.29 0.46 ± 2.03	0.542 0.089
Muscle strength (MRC[a] sum score)[1] (change from baseline)	3.3	0.2	0.001
Sensory function (ISS[b] score)[2] (change from baseline)	-1.2	0.2	0.021

[1] Improvement indicated by positive figure
[2] Improvement indicated by negative figure
[a] MRC: Medical Research Council
[b] ISS: INCAT Sensory Sum Score

Extension Period	Time to Relapse	P-value p= 0.011



Paediatric use

Efficacy and safety data in paediatric patients with CIDP is not available. Efficacy and safety in paediatric patients with PI using the SC route of administration have not been established.

5.2 Pharmacokinetic properties

Intravenous administration

Pharmacokinetic parameters were determined in a trial in 17 patients with primary immunodeficiency stabilized on GAMUNEX® intravenous infusion at a mean dose of 417 mg/kg, range 234-593 mg/kg, and dose interval of 3-4 weeks. The mean age of patients was 36 years and range 19-59. Seventy one percent were male.

Serum IgG concentration was measured following the third infusion of the product. Serum IgG peaked at a median of 2.3 hours after starting the infusion. The concentration-time curve was then biphasic with a distribution phase of about 5 days characterised by a fall in serum IgG concentration to 65-75% of the peak and an elimination phase of median half-life 36 days. Other pharmacokinetic parameters are given in the table below:

Pharmacokinetic Parameters of GAMUNEX®: Intravenous Administration

	Mean ±SD	Median
C_{max} mg/Ml	19.1 ±3.1	19.7
$C_{max\ norm}$ kg/mL	0.047 ±0.007	0.046
T_{max} h	2.7 ±1.0	2.3
$AUC_{(0\text{-}tn)}$ [a] mg*h/mL	6750 ±1350	6950
$AUC_{(0\text{-}tn)\ norm}$ [a] kg*h/mL	16.5 ±1.8	17.0
$T_{½}$ [b] days	35.7 ±8.7	33.1

[a] Partial AUC defined as pre-dose concentration to the last concentration common across both treatment periods in the same patient. The trial was a crossover trial with the other treatment being Gamimune N.

[b] Only 15 patients were valid for determination of $t_{½}$.

Pharmacokinetic parameters were determined in a trial in subjects with primary immunodeficiency stabilized on GAMUNEX® subcutaneous infusion at a dose equivalent to 1.37 times the intravenous dose.

Pharmacokinetic Parameters of GAMUNEX®: Subcutaneous Administration

	N	Mean	Range	%CV
$AUC_{0\text{-}\tau,SC}$ (mg*h/mL)	26	1947	1300-2758	20.4
Adj. $AUC_{0\text{-}\tau,SC}$[a](mg*h/mL)	26	6858	5169-10364	18.1
C_{trough} (mg/mL)	28	11.4	8.1-16.2	20.4

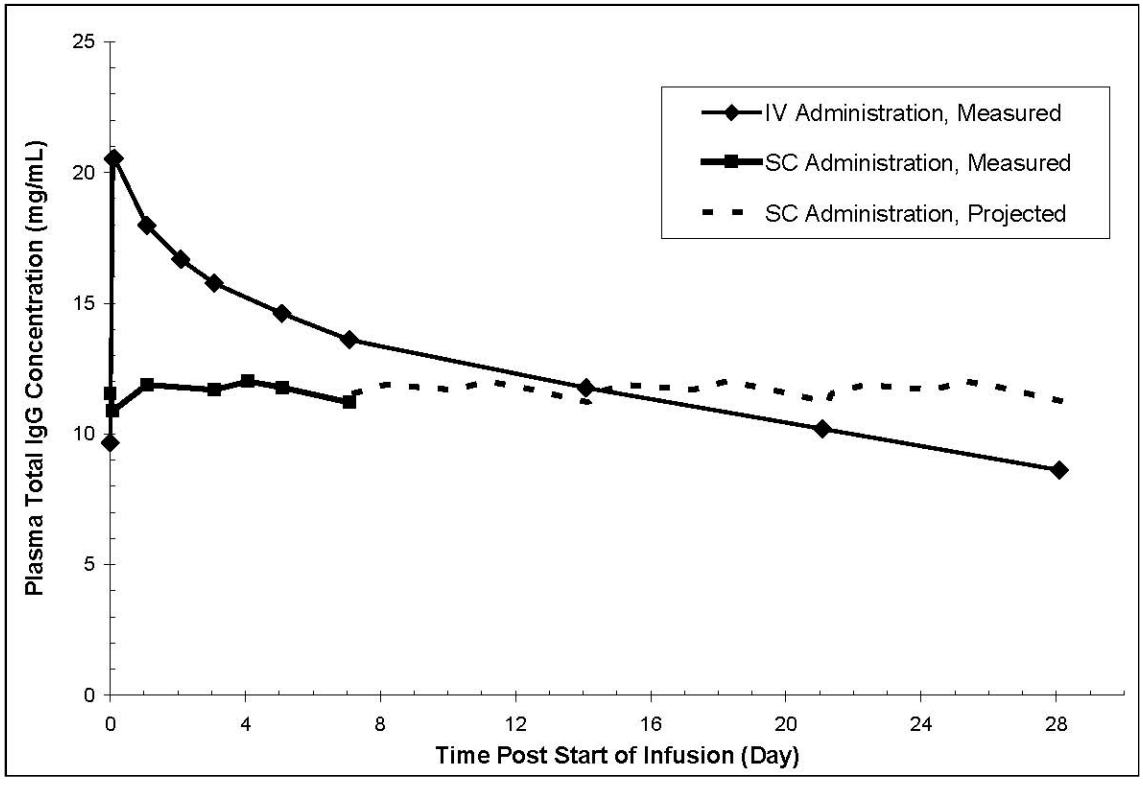
[a] Adj. $AUC_{0\text{-}\tau,SC}$: Adjusted steady-state area under the concentration vs. time curve following SC administration based on IV dosing schedule, calculated as $AUC_{0\text{-}\tau,SC}$ multiplied by 3 or 4 for subjects on every-3-week or every-4-week IV dosing schedule, respectively.

Subcutaneous administration

In a single sequence, crossover trial, the pharmacokinetics, safety, and tolerability of subcutaneously administered GAMUNEX® in subjects with primary immunodeficiency were evaluated. The objectives of the study were to determine a dose of weekly subcutaneously administered GAMUNEX® that produces steady-state AUC of plasma total IgG that is non-inferior to that of the regularly administered IV dose of GAMUNEX®. Subjects were required to have been receiving GAMUNEX® 200-600 mg/kg IV every 3-4 weeks for at least 3 months, at which time they entered the IV phase of

the study. PK profiling around the IV dose occurred and subjects were crossed over to weekly SC infusions. The weekly SC dose was determined by multiplying the total IV dose by 1.37 and dividing the resultant new total dose by 3 or 4 depending on the previous IV interval. A total of 32 and 26 subjects, respectively, had plasma total IgG concentration vs. time profiles for assessment of steady-state PK parameters after IV and SC administration. In contrast to plasma total IgG levels observed with monthly IV GAMUNEX® treatment (rapid peaks followed by a slow decline), the plasma IgG levels in subjects receiving weekly SC GAMUNEX® therapy were relatively stable. See figure below.

Mean Steady-state Plasma Total IgG Concentration vs. Time Curves Following IV Administration or Weekly SC Administration



The primary PK endpoint (AUC of plasma total IgG) following IV and SC administration is summarized in the table below.

Summary of PK Endpoint of AUC

Route of Administration	Statistics	$AUC_{0-\tau,IV}$ (mg*h/mL)	$AUC_{0-\tau,SC}$ (mg*h/mL)	Adj. $AUC_{0-\tau,SC}$[a] (mg*h/mL)
IV (n = 32)	Mean	7640	NA	NA
	%CV	15.9		
	Range	5616-10400		
SC (n = 26)	Mean	NA	1947	6858
	%CV		20.4	18.1
	Range		1300-2758	5169-10364

CV, coefficient of variation; NA, not applicable

[a] Adj. $AUC_{0-\tau,SC}$: Adjusted steady-state area under the concentration vs. time curve following SC administration based on IV dosing schedule, calculated as $AUC_{0-\tau,SC}$ multiplied by 3 or 4 for subjects on every-3-week or every-4-week IV dosing schedule, respectively.

In order to test non-inferiority, the geometric least squares mean (LSM) ratio, SC vs. IV administration, was analyzed using ANOVA. The result showed that the point estimate for the geometric LSM ratio of AUC_{SC} vs. AUC_{IV} was 0.888, with a 90% confidence interval (CI) of 0.861-0.917. The lower bound of the 90% confidence interval is above 0.80 indicating that the SC dose is non-inferior to the IV dose. In addition, the 90% CI is within the limit of 0.80-1.25, a criterion for concluding "bioequivalence" between the two treatments (SC and IV doses).

The mean trough concentration (mean C_{trough}) of plasma total IgG following IV and SC administration are presented in the table below.

Mean Plasma Trough Concentrations of Total IgG (mg/mL) in Plasma

	IV[a] Mean C_{trough}	SC[b] Mean C_{trough}
n	32	28
Mean (mg/mL)	9.58	11.4
%CV	22.3	20.4
Range	6.66-14.0	8.10-16.2

[a] IV mean C_{trough} was calculated as the average C_{trough} (predose concentration) from IV#1 and IV#2.

[b] SC mean C_{trough} was calculated as the average C_{trough} (predose concentration) from SC Weeks #13, #17, #18, #19 and #21.

The IV infusions prior to the SC phase of this study allowed steady-state conditions for the SC phase to be achieved much earlier (by Week 5), due to the loading dose effect of the IV doses.

SC administration was evaluated in three paediatric subjects (age range 13-15) with PI. This number of paediatric subjects was too small for separate evaluation of pharmacokinetics and safety to determine whether they respond differently from adults. Efficacy and safety in pediatric patients using the SC route of administration have not been established.

SC administration should not be used in patients with idiopathic thrombocytopaenic purpura due to risk of haematoma formation.

5.3 Preclinical safety data

Immunoglobulins are normal components of the human body. Because administration of immunoglobulins in animal studies may lead to the formation of antibodies, preclinical safety data are limited. In the acute and sub-acute animal studies that were performed, GAMUNEX® did not show special risks for humans.

Carcinogenicity

No carcinogenicity studies have been conducted on GAMUNEX®.

Genotoxicity

No genotoxicity studies have been conducted on GAMUNEX®.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

GAMUNEX® may be stored for 36 months at 2°C - 8°C (36-46°F), AND may be stored at temperatures not to exceed 25°C (77°F) for up to 6 months anytime during the 36 month shelf life, after which the product must be used immediately or discarded. Refrigerate. Do not freeze. Do not use after the expiration date. Protect from light.

6.5 Nature and contents of container

Solution for intravenous or subcutaneous infusion in Type I or II glass vials with chlorobutyl stoppers.

Pack sizes: 10 mL, 25 mL 50 mL, 100 mL, and 200 mL; hospital packs. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The product should be brought to room or body temperature before use. Visually inspect each vial before use. The solution should be clear to opalescent, and colourless to pale yellow. Solutions that are cloudy or have deposits should not be used. Do not use any solution that has frozen.

Once the container has been opened, the contents should be infused immediately. Subsequent storage, even in a refrigerator, is not permitted on account of possible microbial colonisation.

Discard partially used vials. Any unused product or waste material should be disposed of in accordance with local requirement.

If dilution is necessary prior to infusion, 5% dextrose in water (D5/W) may be used for this purpose. Do not dilute with saline solutions.

Simultaneous administration of GAMUNEX® and heparin through a single lumen delivery device must be avoided.

GAMUNEX® infusion lines can be flushed with 5% dextrose in water (D5/W) or with 0.9% sodium chloride for injection and should not be flushed with heparin.

Heparin Lock through which GAMUNEX® was administered should be flushed with 5% dextrose in water (D5/W) or 0.9% sodium chloride injection and should not be flushed with heparin.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmaco (N.Z.) Ltd
4 Fisher Crescent,
Mt Wellington Auckland 1060,
New Zealand

For Medical/Technical Enquiries
Telephone (09) 377 3336

9. DATE OF FIRST APPROVAL

22 March 2018

10. DATE OF REVISION OF THE TEXT

02 Aug 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Pharmaco contact detail
4.8	Reporting of suspected adverse reactions
4.9	Contacting National Poisons Centre
8	Change in sponsor

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