Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gamunex® 10%, 100 mg/ml, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each vial of 10 ml contains: 1 g of human normal immunoglobulin
Each vial of 50 ml contains: 5 g of human normal immunoglobulin
Each vial of 100 ml contains: 10 g of human normal immunoglobulin
Each vial of 200 ml contains: 20 g of human normal immunoglobulin
Each vial of 400 ml contains: 40 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG1 ..... 62.8%
IgG2 ..... 29.7%
IgG3 ..... 4.8%
IgG4 .....2.7%

Minimum level of anti-measles IgG is 9 IU/ml.

The maximum IgA content is 84 micrograms/ml.

Produced from the plasma of human donors.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
The solution is clear or slightly opalescent and colourless or pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines
Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.
Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.

Immunomodulation in adults, children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain Barré syndrome
- Kawasaki disease (in conjunction with acetylsalicylic acid, see 4.2)

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Immunomodulation in adults aged ≥18 years in:

- Severe acute exacerbations of myasthenia gravis

4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology
The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guidance.

Replacement therapy in primary immunodeficiency syndromes
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/L or within the normal reference range for the population age. 3-6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) to occur. The recommended starting dose is 0.4-0.8 g/kg given once followed by at least 0.2 g/kg given every 3-4 weeks.

The dose required to achieve a trough level of IgG of 6 g/L is of the order of 0.2-0.8 g/kg/month. The dosage interval when steady state has been reached varies from 3-4 weeks.
IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of bacterial infections, it may be necessary to increase the dosage and aim for higher trough levels.

Replacement therapy in secondary immunodeficiencies (as defined in 4.1)
The recommended dose is 0.2-0.4 g/kg every 3-4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

Measles pre-/post exposure prophylaxis
Post-exposure prophylaxis
If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/ml.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis

If a PID/SID patient is at risk of future measles exposure and receives an IVIg maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of > 240 mIU/ml of measles antibodies for at least 22 days after infusion.

Immunomodulation in:
Primary immune thrombocytopenia
There are two alternative treatment schedules:

- 0.8-1 g/kg given on day 1; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for 2-5 days. The treatment can be repeated if relapse occurs.

Guillain Barré syndrome
0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

Kawasaki disease
2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Starting dose: 2 g/kg divided over 2-5 consecutive days

Maintenance doses:
1 g/kg divided over 1-2 consecutive days every 3 weeks.

The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Multifocal motor neuropathy (MMN)
Starting dose: 2 g/kg divided over 2-5 consecutive days.

Maintenance dose: 1 g/kg every 2-4 weeks or 2 g/kg every 4-8 weeks.

The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

Severe acute exacerbations of myasthenia gravis

2 g/kg divided over 2 consecutive days (dose of 1 g/kg per day).

Clinical studies of *Gamunex 10%* did not include sufficient numbers of subjects aged 65 and over to determine a precise treatment effect.

The dosage recommendations are summarised in the following table:

Indication	**Dose**	**Frequency of infusions**
Replacement therapy		
Primary immunodeficiency syndromes	Starting dose:	

	0.4 - 0.8 g/kg Maintenance dose: 0.2 - 0.8 g/kg	 every 3 - 4 weeks
Secondary immunodeficiencies (as defined in 4.1.)	0.2 - 0.4 g/kg	every 3 - 4 weeks
Measles pre/post exposure prophylaxis:		
Post-exposure prophylaxis in susceptible patients	0.4 g/kg	As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml
Post-exposure prophylaxis in PID/SID patients	0.4 g/kg	In addition to maintenance therapy, given as an extra dose within 6 days of exposure
Pre-exposure prophylaxis in PID/SID patients	0.53 g/kg	If a patient receives a maintenance dose of less than 0.53 g/kg every 3–4 weeks, this dose should be increased once to at least 0.53 g/kg
Immunomodulation:		
Primary immune thrombocytopenia	0.8 - 1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 - 5 days
Guillain Barré syndrome	0.4 g /kg/d	for 5 days
Kawasaki disease	2 g/kg	in one dose in association with acetylsalicylic acid
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg	in divided doses over 2-5 days every 3 weeks in divided doses over 1-2 days
Multifocal motor neuropathy (MMN)	Starting dose: 2 g/kg Maintenance dose: 1 g/kg or 2 g/kg	in divided doses over 2-5 consecutive days every 2-4 weeks or every 4-8 weeks in divided doses over 2-5 days
Severe acute exacerbations of myasthenia gravis	2 g/kg	administered over 2 consecutive days (dose of 1 g/kg per day)

Paediatric population
The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and must be adjusted to the clinical outcome of the above-mentioned conditions.

Hepatic impairment
No evidence is available to require a dose adjustment.

Renal impairment
No dose adjustment unless clinically warranted, see section 4.4.

Elderly
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration
For intravenous use.
Human normal immunoglobulin should be infused intravenously at an initial rate of 0.6 – 1.2 ml/kg/hr for 0.5 hr. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, the rate of administration may gradually be increased to a maximum of 4.8 – 8.4 ml/kg/hr.

4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see sections 4.4 and 6.1).

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

4.4 Special warnings and precautions for use

All patients should be closely monitored when high rates of infusion (8.4 ml/kg/hr) are used. In children or patients at risk of renal failure, the maximum infusion rate should not exceed 4.8 ml/kg/hr.

Gamunex 10% must not be mixed with other solutions for infusion (e.g. saline solution) and other medicinal products. If dilution is necessary prior to infusion, 50 mg/ml glucose solution may be used for this purpose. However, in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet use of 50 mg/ml glucose solution should be carefully monitored. Also see warning about acute renal failure below.

Simultaneous administration of *Gamunex* 10% and heparin through a single lumen delivery device must be avoided.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Precautions for use
Potential complications can often be avoided by ensuring that patients:

- are not sensitive to normal human immunoglobulin by initially administering the product slowly (0.6 - 1.2 ml/kg/hr). For patients who are more likely to be sensitive (e.g. switching from another IVIg or previous allergic reaction), an initial infusion rate of 0.1 ml/kg/hr may be considered.
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human 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 a controlled healthcare setting, in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration.

In all patients, IVIg administration requires:

- Adequate hydration prior to the initiation of the IVIg infusion
- Monitoring of urine output
- Monitoring of serum creatinine levels
- Avoidance of concomitant use of loop diuretics (see 4.5).

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion-related reaction
Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) may be related to the rate of infusion. The recommended infusion rate given under section 4.2 must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Adverse reactions may occur more frequently

- in patients who receive human normal 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
- in patients with an active infection or underlying chronic inflammation

Hypersensitivity
Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients

- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

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.

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

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products 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 these excipients may be considered. *Gamunex 10%* does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)
AMS has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per mm3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia
IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced RBC sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis (see section 4.8).

The following risk factors are associated with the development of haemolysis: high doses, whether given as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state. Increased vigilance is

recommended for non-0 blood group patients receiving high doses for non-PID indications. Haemolysis has rarely been reported in patients given replacement therapy for PID.

Isolated cases of haemolysis-related renal dysfunction/renal failure with fatal outcome have occurred.

Neutropenia/Leukopenia
A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)
In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion related acute lung injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1-2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing
After the administration 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 antibodies, for example the direct antiglobulin test (DAT, direct Coombs' test).

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, 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. 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 virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19.

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

It is strongly recommended that every time that *Gamunex 10%* is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Paediatric population
Although limited data is available, it is expected that the same warnings, precautions and risk factors apply to the paediatric population. In post-marketing reports it is observed that IVIg high-dose indications in children, particularly Kawasaki disease, are associated with an increased reporting rate of haemolytic reactions compared to other IVIg indications in children.

Physicians need to strongly consider monitoring haemoglobin levels 24-48 hours after completion of IVIg if haemolysis is suspected. If retreatment is required it is strongly recommended to monitor haemoglobin levels one week after subsequent IVIg dosing if haemolysis is suspected. Families should be instructed to return if their child develops symptoms of haemolysis, such as; pallor, lethargy, dark urine, dyspnoea or palpitations.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per single dose (up to a maximum of 2 g/kg), i.e. essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines, such as measles, rubella, mumps or varicella. After administration of this medicinal product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

Loop diuretics

Avoidance of concomitant use of loop diuretics

Paediatric population

Although specific interaction studies have not been performed in the paediatric population, no differences between adults and children are to be expected.

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. 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 expected.

Breast-feeding

The safety of this medicinal product for use in breast-feeding mothers has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

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

Gamunex 10% has no or negligible influence on the ability to drive and use machines. However, 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

Adverse reactions caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- Chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- Reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus – frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of transfusion related acute lung injury (TRALI).

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to <1/10),

uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Source of the safety data base: clinical trials in a total of 703 patients exposed to *Gamunex 10%* (with a total of 4378 infusions)

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency per patient**	**Frequency per infusion**
Infections and infestations	Pharyngitis	Uncommon	Uncommon
	Sinusitis, Urethritis, Viral upper respiratory tract infection	Uncommon	Rare
Blood and lymphatic system disorders	Haemolytic anaemia, Lymphocytosis	Uncommon	Rare
Immune system disorders	Hypersensitivity	Uncommon	Rare
Psychiatric disorders	Anxiety	Uncommon	Rare
Nervous system disorders	Headache	Very common	Common
	Dizziness	Uncommon	Uncommon
	Aphonia	Uncommon	Rare
Eye disorders	Photophobia	Uncommon	Rare
Vascular disorders	Hypertension	Common	Uncommon
	Hypertensive crisis, Hypotension, Flushing, Hyperaemia	Uncommon	Rare
Respiratory, thoracic and mediastinal disorders	Wheezing, Cough, Nasal congestion,	Uncommon	Uncommon
	Dyspnoea,	Uncommon	Rare
Gastrointestinal disorders	Nausea, Vomiting	Common	Uncommon
	Abdominal pain, Diarrhoea, Dyspepsia	Uncommon	Rare
Skin and subcutaneous tissue disorders	Rash, Pruritus, Urticaria	Common	Uncommon
	Skin exfoliation, Dermatitis, Contact dermatitis, Palmar erythema	Uncommon	Rare
Musculoskeletal and connective tissue disorders	Arthralgia, Back pain	Common	Uncommon
	Myalgia	Uncommon	Uncommon
	Musculoskeletal pain, Musculoskeletal stiffness, Neck pain	Uncommon	Rare
Renal and urinary disorders	Haemoglobinuria	Uncommon	Rare
General disorders and administration site conditions	Pyrexia	Common	Common
	Influenza like illness, Chills, Fatigue	Common	Uncommon

	Asthenia	Uncommon	Uncommon
	Chest pain, Injection site reaction, Malaise	Uncommon	Rare
Investigations	Blood pressure increased, White blood cell count decreased, Haemoglobin decreased, Free haemoglobin present, Red blood cell sedimentation rate increased	Uncommon	Rare
Injury, poisoning and procedural complications	Contusion	Uncommon	Rare

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including infants, elderly patients or patients with cardiac or renal impairment (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02
Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1,000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated.

Gamunex 10% is adjusted to a weakly acidic pH. Since *Gamunex 10%* has a low buffering capacity, it is rapidly neutralised by the blood during the infusion. Even after administration of high doses of *Gamunex 10%*, no change in the pH of the blood was recorded. Osmolality is 258 mOsmol/kg solution and thus approximates to the normal range (285-295 mOsmol/kg).

Clinical trials conducted with *Gamunex 10%* on patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP):
The IVIg-C CIDP efficacy trial (ICE study), a double-blind, randomised, placebo-controlled study investigated the efficacy and safety of *Gamunex 10%* in the treatment of CIDP. A total of 117 CIDP patients were randomised to receive either *Gamunex 10%* or placebo every three weeks. Loading dose was 2 g/kg BW; maintenance dose was 1 g/kg BW.
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 10%* 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 10%* 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 10%*.

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 10%* or placebo. Of the former responders to *Gamunex 10%*, the actual relapse rate was significantly higher in the patients randomised to placebo (42%) than in those randomised to *Gamunex 10%* (13%, p=0.012).

The ICE study has shown short-term and long-term efficacy of *Gamunex 10%* in the treatment of CIDP. The results are summarised in the following table.

Primary endpoint and other results of the ICE study

	Gamunex 10%	Placebo	p
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
Muscle strength (MRC[3] sum score)[1] (change from baseline)	3.3	0.2	0.001
Sensibility (ISS[4] score)[2] (change from baseline)	-1.2	0.2	0.021

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

Clinical trials conducted with *Gamunex 10%* on patients with myasthenia gravis exacerbations:
The study by Zinman et al. (2007) was a randomised, double-blind, placebo-controlled study in 51 patients to evaluate *Gamunex 10%* 2 g/kg given over the course of 2 days in myasthenia gravis (MG) exacerbations. The primary efficacy endpoint was the change from baseline in QMG score on day 14. On day 14, the mean change in QMG score was -2.54 (p = 0.047). A clinically relevant effect on MG exacerbations was only observed in the exploratory subgroup of patients with moderate to severe MG at baseline (QMG score > 10.5), with a mean change of -3.39 (p = 0.010).

Additional support comes from a multicenter, prospective, open-label, non-controlled clinical trial, which also investigated the efficacy and safety of *Gamunex 10%* in the treatment of myasthenia gravis exacerbations. A total of 49 patients were enrolled into the clinical trial to receive a single, total dose of 2 g/kg of *Gamunex 10%* over 2 consecutive days (dose of 1 g/kg per day). There were no MuSK antibody positive patients who participated.
The primary efficacy endpoint was the change in Quantitative Myasthenia Gravis (QMG) score from baseline (day 0) to day 14. The mean changes in QMG score were -6.4 for the Evaluable and -6.7 for the Safety Population. Analysis of the secondary and exploratory efficacy endpoints results (assessed by QMG, MG-ADL, and MG Composite scores) supported the findings on the primary endpoint.

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
Human normal immunoglobulin has a half-life of about 35 days as determined in patients with primary antibody deficiency syndrome and therefore exceeds that of 21 days described in the literature in healthy subjects. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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

Paediatric population
No differences of the pharmacokinetic properties are expected in the paediatric population.

Measles pre-/post exposure prophylaxis
No clinical studies have been performed in susceptible patients regarding *Measles pre-/post exposure prophylaxis*.

Gamunex 10% meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

- Serum titer at 13.5 days = 270 mIU/ml (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titer of 120 mIU/ml
- Serum titer at 22 days (t1/2) = 180 mIU/ml (dose: 0.4 g/kg)
- Serum titer at 22 days (t1/2) = 238.5 mIU/ml (dose: 0.53 g/kg – pre-exposure prophylaxis)

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® 10%* did not show special risks for humans.

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

Store at +2 °C to +8 °C (in a refrigerator). Do not freeze. Keep in outer carton.
The product may be stored in its outer carton for a one-off period of up to 6 months at room temperature (not above 25°C). In that case, the shelf life of the product expires at the end of this 6-month period. The new expiry date must be noted on the outer carton. The new expiry date must be no later than the printed expiry date. Thereafter, it must be used or destroyed. Subsequent refrigeration or freezing is not possible.

6.5 Nature and contents of container

Solution for intravenous infusion in Type I or II glass vials with chlorobutyl stoppers.
Pack sizes:
One vial of 10 ml contains: 1 g of human normal immunoglobulin
One vial of 50 ml contains: 5 g of human normal immunoglobulin
One vial of 100 ml contains: 10 g of human normal immunoglobulin
One vial of 200 ml contains: 20 g of human normal immunoglobulin
One vial of 400 ml contains: 40 g of human normal immunoglobulin
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. The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used. Any unused product or waste material should be disposed of in accordance with local requirement. 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.

If dilution is necessary prior to infusion, 50 mg/ml glucose solution may be used for this purpose. Do not dilute with saline solutions.
Simultaneous administration of Gamunex 10% and heparin through a single lumen delivery device must be avoided.
Gamunex 10% infusion lines can be flushed with 50 mg/ml glucose or with sodium chloride solution (9 mg/ml) and should not be flushed with heparin.

Heparin Lock through which Gamunex 10% was administered should be flushed with 50 mg/ml glucose or sodium chloride solution (9 mg/ml) and should not be flushed with heparin.

7 MARKETING AUTHORISATION HOLDER

Grifols Deutschland GmbH
Colmarer Strasse 22
60528 Frankfurt
Germany

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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