Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gammaplex 10%100 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg).

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

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.

Distribution of the IgG subclasses (approx. values):
IgG1 ..... 63%
IgG2 ..... 31%
IgG3 ..... 5%
IgG4 ..... 1%

The maximum IgA content is <20 micrograms/ml.

Produced from the plasma of human donors.

For the 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 (see section 6.6).

The pH of the solution is 4.9 – 5.2, the osmolality is not less than 240 mOsmol/kg and typically 280 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4)
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT)
- Congenital AIDS with recurrent bacterial infections

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

4.2 Posology and method of administration

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

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

In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes
The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. Three to six months are required after the initiation of therapy for equilibration 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 three to four weeks.

The dose required to achieve a trough level of 5-6 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.
Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels.

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections.
The recommended dose is 0.2-0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation
The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia
There are two alternative treatment schedules:
- 0.8-1 g/kg given on day one; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for two to five days The treatment can be repeated if relapse occurs.

Guillain Barré syndrome
0.4 g/kg/day over 5 days.

Kawasaki Disease
1.6-2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Indication	**Dose**	**Frequency of injections**
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	
Congenital AIDS		every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6g/l
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg 0.2 - 0.4 g/kg	

		every 3 - 4 weeks every 3 - 4 weeks to obtain IgG trough level above 5g/l.
Immunomodulation: Primary immune thrombocytopenia Guillain Barré syndrome Kawasaki disease	 0.8 - 1 g/kg or 0.4 g/kg/d 0.4 g /kg/d 1.6 - 2 g/kg or 2 g/kg	 on day 1, possibly repeated once within 3 days for 2 - 5 days for 5 days in divided doses over 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid

Elderly
Do not exceed recommended doses, and administer Gammaplex 10% at the minimum infusion rate practicable.

Renal impairment
In patients judged to be at increased risk of developing renal impairment, Gammaplex 10% should be infused at the minimum rate practicable. Renal function should be assessed before the initial infusion of Gammaplex 10% and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex 10% (see section 4.4).

Hepatic impairment

No dose adjustment is necessary for those with hepatic impairment.

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 adjusted to the clinical outcome of the above mentioned conditions.

Method of administration
For intravenous use.

Human normal immunoglobulin should be infused intravenously at an initial rate of 0.3 ml/kg/hr for 15 minutes. If well tolerated (see section 4.4), the rate of administration may gradually be increased (every 15 minutes as follows: 0.6, 1.2, 2.4, 3.6 ml/kg/hr) to a maximum of 4.8 ml/kg/hr; subsequent infusions can start at 0.6 ml/kg/hr and increased as above.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see also section 4.4).
Hypersensitivity to human immunoglobulins especially in patients with antibodies against IgA.

4.4 Special warnings and precautions for use

Certain severe adverse reactions 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.
Certain adverse reactions may occur more frequently
- in case of high rate of infusion
- 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

Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially injecting the product slowly (0.3 ml/kg/hr).
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve 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 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 of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism
There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infaction, cerebral vascular accident (including stroke), pulmonary embolism and deep vein thromboses which is assumeed 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-exisiting 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 thromophilic disorders, patients with prolonged periods of immobilisation, severely hypovolaemic 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-exisiting renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or aged over 65.

In case 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 these excipients may be considered. Gammaplex 10% does not contain sucrose, glucose or maltose.

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

Transfusion-related acute lung injury (TRALI)
There have been reports of TRALI i.e. noncardiogenic pulmonary oedema, in patients administered IVIg products.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Disontinuation 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 hundred mg/dl.

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

Haemolytic anaemia
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 (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis (see section 4.8).

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 antibodies for example the direct antiglobulin test (DAT, direct Coomb's 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), hepatitis C virus (HCV), and for the non-enveloped hepatitis A and parvovirus B19 viruses.

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 Gammaplex 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.

Hepatic impairment
There are no special warnings or precautions specific for patients with hepatic impairment.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interactions

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 and 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 should have their antibody status checked.

Paediatric population
Interaction studies have not been performed. The reported interactions for adults apply to children.

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 the 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 Gammaplex 10. 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 such as chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins 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 (including cutaneous lupus erythematosus - frequency unknown) have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B and AB. 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: thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

For safety information with respect to transmissible agents, see section 4.4.

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.
Frequency of Adverse Reactions (ADRs) in clinical studies with Gammaplex.

MedDRA System Organ Class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Fluid retention, dehydration	Common
	Decreased appetite, iron deficiency	Uncommon
Psychiatric disorders	Insomnia	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness	Common
	Migraine, hypoesthesia, paraesthesia, lethargy	Uncommon
Ear and labyrinth disorders	Vertigo	Common
	Tinnitus	Uncommon
Cardiac disorders	Palpitations, tachycardia	Common
Vascular disorders	Hypertension, hypotension	Common
	Thrombosis, hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
	Bronchospasm, epistaxis, pharyngolaryngeal pain	Uncommon
Gastrointestinal disorders	Vomiting, nausea, diarrhoea, abdominal pain	Common
	Abdominal distension, constipation, stomatitis	Uncommon
Skin and subcutaneous tissue disorders	Erythema multiforme, urticaria, pruritus	Uncommon
	Cutaneous lupus erythematosus	Unknown
Musculoskeletal, connective tissue disorders	Arthralgia, myalgia, muscle spasms, back pain, neck pain	Common
	Musculoskeletal stiffness, pain in extremity	Uncommon
General disorders and administration site conditions	Pyrexia	Very common
	Chills, chest discomfort /pain, fatigue, asthenia, infusion site reaction, pain	Common
Investigations	Coombs' direct test positive, anaemia/ haemoglobin decreased	Common
	Anti-erythrocyte antibody positive, white blood cell count increased, urinary hemosiderin positive, gastric pH decreased	Uncommon

Description of selected adverse reactions
None of the reported adverse reactions to Gammaplex warrant separate description.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. No clinical trials have been conducted with Gammaplex in children aged 0 - < 2 years.

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, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 1000 donations. 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, but includes immunomodulatory effects.

GMX01
A phase III, multicentre, non-randomised, open-label study in 50 predominantly adult subjects with primary immunodeficiency diseases (PID), where Gammaplex 5% was infused at a dose of 300 to 800 mg/kg every 21 or 28 days, concluded that Gammaplex 5% was well tolerated and efficacious and therefore suitable for the management of subjects with PID. There were no serious acute bacterial infections during the 12 months of treatment, and the most commonly reported adverse reactions were headache (18 patients), nausea (6 patients), pyrexia (6 patients) and fatigue (6 patients).

GMX02
A later phase III, open-label, multicentre clinical study investigating the safety and efficacy of Gammaplex 5% infused at a dose of 1 g/kg/day for two consecutive days in 35 subjects with chronic immune thrombocytopenic purpura (ITP) showed Gammaplex 5% to be an effective treatment, and hence its efficacy in immunomodulation. The most commonly reported adverse reactions were headache (10 patients), vomiting (6 patients) and pyrexia (5 patients).
GMX07
A multicentre Phase III study in PID in two populations: adults and children. The design for the adult cohort (>16 years), a randomised two-period cross-over design, was different from that for children (single arm non-comparative). All subjects had at least five infusions of Gammaplex 10% and all patients aged >16 years had at least five infusions of Gammaplex 5% in addition. Subjects were dosed at either 21- or 28-day intervals; doses at the PK infusions ranged from 254 to 794 mg/kg for Gammaplex 10% and from 269 to 786 mg/kg for Gammaplex 5%. Overall, the proportion of patients with adverse reactions was similar between the two formulations; the most commonly reported adverse reactions for Gammaplex 10% were headache (14.9% of patients), migraine and pyrexia (6.4% of patients for each).

Paediatric population
Study GMX01 above, comprised predominantly of adult subjects with PID and included seven patients aged less than 18 years (9 - 17 years inclusive). There were no reports of serious adverse reactions in any of the paediatric subjects.

Study GMX02 above in ITP included three subjects aged less than 18 years (6 - 17 years inclusive). One of the paediatric subjects (aged six years) experienced a serious adverse reaction (headache, with vomiting and dehydration).

GMX04
A phase III, multicentre, non-randomised, open-label paediatric study in 25 children and adolescent subjects (aged 3-16 years inclusive) with primary immunodeficiency diseases (PID), where Gammaplex 5% was infused at a dose of 300 to 800 mg/kg every 21 or 28 days, concluded that Gammaplex 5% was well tolerated and efficacious in children with PID. There were two serious acute bacterial infections reported during the 12 months of treatment, and the most commonly reported adverse reactions were headache (8 patients), hypotension (4 patients), pyrexia (3 patients) and tachycardia (3 patients).

GMX07
In the analysis, children were categorised as those patients aged <18 years. The proportion of children with adverse reactions for Gammaplex 10% (7/17, 41.2%) was slightly higher than for adults (9/30, 30.0%) but the most commonly reported was headache for both age groups. Pyrexia was reported in 2 children (11.8%). All other adverse reactions in children were not reported by more than one patient.

5.2 Pharmacokinetic properties

Pharmacokinetic/pharmacodynamic relationship(s)
Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed realtively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments. Human normal immunoglobulin has a half-life of about 31.4 days (range 19.7 to 53.8 days) in adults (>18 years). 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 reticuloendothelial system.

Paediatric population

Gammaplex 10% has a half-life in children (aged <18 years) of about 31.0 days (range 17.0 to 50.4 days), similar to that in adults (see above).

5.3 Preclinical safety data

Immunoglobulins are normal constituents of human plasma and therefore toxicity testing in heterologous species is of no relevance. Gammaplex contains highly purified immunoglobulins and has been tested in non-clinical haemodynamic monitoring studies. There is no evidence of effects on blood pressure or heart rate at infusion rates similar to those used clinically. At higher infusion rates or approximately 2- to 7-fold those used clinically, a hypertensive effect was found. No other preclinical studies have been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Polysorbate 80
Water for Injections
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

Gammaplex 10% should be used immediately after opening.

6.4 Special precautions for storage

Do not store above 25^{o}C.

Do not freeze.

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

6.5 Nature and contents of container

50 ml, 100 ml or 200 ml of solution in a Type II glass vial with a halobutyl stopper.

Pack sizes
1 vial (50 ml or 100 ml or 200 ml)

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.

Solutions that are cloudy or have deposits should not be used.

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

7 MARKETING AUTHORISATION HOLDER

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63263 Neu-lsenburg
Amtsgericht Frankfurt
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Germany

8 MARKETING AUTHORISATION NUMBER

PA22765/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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