

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gammagard S/D Human Normal Immunoglobulin for Intravenous Administration Powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient

Human Normal Immunoglobulin (IVIg)

Quantitative Composition

Human Normal Immunoglobulin for Intravenous Administration, Gammagard S/D, may be reconstituted with solvent [Water for Injections] to a 5% (50 mg/mL) solution or a 10% (100 mg/mL) solution of protein of which at least 90% is gamma globulin. Maximum immunoglobulin A (IgA) content: not more than 3 microgram per mL in a 5% solution.

Produced from the plasma of human donors.

Excipients with known effect:

In grams per 100 mL reconstituted product, at 5 %:

Sodium Chloride 0.9

Glucose Monohydrate 1.7

For the full list of excipients, see section 6.1.

IgG Subclasses

Distribution of IgG subclasses:

IgG1 \geq 56.9%

IgG2 \geq 16.0%

IgG3 \geq 3.3%

IgG4 \geq 0.3%

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

p.H. of reconstituted product is 6.4 – 7.2.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy

Primary immunodeficiency syndromes (PID):

- Congenital agammaglobulinaemia and hypogammaglobulinaemia
- Common variable immunodeficiencies
- Severe combined immunodeficiencies
- Wiskott Aldrich syndrome Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections Children with congenital AIDS and recurrent infections **Immunomodulatory effect** Idiopathic thrombocytopenic purpura (ITP) in adults or children at high risk of bleeding or prior to surgery to correct the platelet count. Allogeneic bone marrow transplantation Kawasaki syndrome Guillain-Barré 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 dosage regimen is dependent on the indication.

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

Replacement Therapy in Primary Immunodeficiencies

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5-6 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 body weight (BW) depending on the circumstances (e.g. active infection) followed by at least 0.2 g/kg 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.

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

The recommended dose is 0.2- 0.4 g/kg every three to four weeks.

Idiopathic thrombocytopenic purpura (ITP)

For the treatment of an acute episode, 0.8-1.0 g/kg on day one, repeated on day three if necessary, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs.

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.

Allogeneic Bone Marrow Transplantation:

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant. For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The recommended dose is 0.2-0.4g/kg every three to four weeks. The trough levels should be maintained above 5g/l.

Guillain-Barré syndrome

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

The dosage recommendations are summarized in the following table:

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

| | | |
|--|-------------------------|--|
| <ul style="list-style-type: none"> Treatment of infections and prophylaxis of graft versus host disease | | every week from day -7 up to 3 months after transplantation |
| <ul style="list-style-type: none"> Persistent lack of antibody protection | | every month until antibody levels return to normal |
| Immunomodulation: | | |
| Primary immune thrombocytopenia (Idiopathic thrombocytopenia purpura) | 0.8 – 1.0 g/kg BW or | on day 1, possibly repeated once within 3 days |
| | 0.4 g/kg BW/day | for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg BW/day | for 5 days |
| Kawasaki disease | 1.6 – 2.0 g/kg BW or | in several doses for 2 - 5 days in association with acetylsalicylic acid |
| | 2.0 g/kg BW | in one dose in association with acetylsalicylic acid |

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 abovementioned conditions.

Method of administration:

For intravenous use.

The rate of administration is individualized based on the tolerability of the patient.

It is recommended that antecubital veins be used for Gammagard S/D 10% solutions, if possible. This may reduce the likelihood of the patient experiencing discomfort at the infusion site. Gammagard S/D 5% (50 mg/mL) should be infused intravenously at an initial rate of 0.5 mL/kg BW/hour.

In general, it is recommended that patients beginning treatment with Gammagard S/D or switching from one IVIG brand to another be started at a lowest rate and then increased to the maximal rate if they have tolerated several infusions at intermediate rates of infusion (see section 4.4). If well tolerated, the rate of administration may gradually be increased to a maximum of 4 mL/kg BW/hour. Patients who tolerate Gammagard S/D 5% solutions at 4 mL/kg BW/hour can be infused with the 10% concentration starting at 0.5 mL/kg BW/hour. If no adverse effects occur, the rate can be increased gradually up to a maximum rate of 8 mL/kg BW/hour.

When switching from the 5% solution to the 10% solution, the rate of the 10% solution should be initially reduced to keep the rate of IgG protein administration comparable.

Adverse reactions may occur more frequently in patients especially those with immune deficiency who receive human normal immunoglobulin for the first time, or when they switch from another IVIG brand, or when there has been a long interval since the previous infusion. (see section 4.8).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA. However, Gammagard S/D contains only trace amounts of IgA (not more than 3 microgram IgA per mL in a 5% solution).

Gammagard is contraindicated in patients with a known anaphylactic or severe hypersensitivity response to Gammagard S/D with < 3 microgram/ml IgA in a 5% solution.

4.4 Special warnings and precautions for use

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.

Human Normal Immunoglobulin for Intravenous Administration, Gammagard S/D should only be administered intravenously.

Gammagard S/D is reconstituted to provide a protein solution of 5 g or 10 g per 100 mL of diluent. This fluid volume will result in blood volume expansion with the extent dependent on the dose administered. When administered in high dose over a relatively short period of time, signs and symptomatology of fluid overload may result, especially in susceptible patients such as small children or elderly individuals.

Certain adverse reactions may be related to the rate of infusion. Slowing or stopping the infusion usually allows the symptoms to disappear promptly. The infusion may then be resumed at a rate that does not result in recurrence of the symptoms. (see section 4.8).

The recommended infusion rate given under "4.2 Method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Potential complications can often be avoided by ensuring that patients:

- Are not sensitive to human normal immunoglobulin by initially injecting the product slowly (0.5 mL/kg BW/hour).
- 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 first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.
- Considering that a 5% solution of Gammagard S/D contains 21.7 mg glucose per dose and that the glucose content (max. content of 0.4 g/g of IgG) is taken into account in case of latent diabetes (where transient glycosuria could appear), diabetes, or in patients on a low sugar diet. In all patients, IVIg administration requires:
 - adequate hydration prior to and after the initiation of the infusion of IVIg,
 - monitoring of urine output,
 - monitoring of serum creatinine levels,
 - avoidance of concomitant use of loop diuretics.

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 side effect.

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

Certain adverse reactions may occur more frequently

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

In case of adverse reactions either the rate of administration must be reduced, or the infusion stopped until symptoms disappear.

If severity of reactions persists after discontinuation of the infusion, appropriate treatment is recommended.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies. IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern. These patients should be treated only if their IgA deficiency is associated with an immune deficiency for which therapy with intravenous immune globulin is clearly indicated.

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

Patients with antibodies to IgA or with IgA deficiencies that are a component of an underlying primary immunodeficiency disease for which IVIG treatment is indicated may be at increased risk of anaphylactic reaction. Anaphylaxis has been reported with the use of Gammagard S/D even though it contains low levels of IgA. (see section 4.8). Patients who have had a severe hypersensitivity reaction should only receive Gammagard S/D with utmost caution and in a setting where supporting care is available for treating life-threatening reactions.

Overdosage is possible in overweight and elderly subjects and in those who have impaired renal function (including diabetics at risk for renal failure). In patients with signs of cerebral or cardiac ischemia, the increase in viscosity caused by an immunoglobulin infusion may be a risk in these patient groups, 5-6% solutions should be used and no more than 0.4 g/kg infused daily. Creatinine levels should be measured for 3 days after IVIg Infusion.

Gammagard S/D contains blood group antibodies that may act as haemolysins and induce in vivo coating of red blood cells (RBC) with immune globulin. This may cause a positive direct antiglobulin test [DAT (Coomb's test)]. Delayed haemolytic anaemia can develop subsequent to Gammagard S/D therapy due to enhanced RBC sequestration; acute haemolysis, consistent with intravascular haemolysis, has been reported.

The following risk factors may be related to the development of haemolysis: high doses (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.

Thromboembolism

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular incident (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 a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, known or suspected hyperviscosity, for example dehydration or paraproteins, hypercoagulable disorders, prolonged periods of immobilization, obesity, use of oestrogens, hypertension, diabetes mellitus and a history of vascular disease or indwelling vascular catheter, high dose and rapid infusion, thrombotic episodes, history of thromboembolic event, patients with acquired or inherited thrombophilic disorders, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, Gammagard SD should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure

Severe renal adverse reactions have been reported in patients receiving IVIG treatment, particularly those products containing sucrose (Gammagard S/D does not contain sucrose).

These include acute renal failure, acute tubular necrosis, proximal tubular nephropathy and osmotic nephrosis. 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 years, sepsis, hyperviscosity or paraproteinaemia.

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

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

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Interference with Laboratory Tests

- After infusion 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 for example Hepatitis A, Hepatitis B, measles and varicella. 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 antiglobulin test ([DAT (Coombs test)].
- Administration of Gammagard S/D can lead to false positive readings in assays that depend on detection of beta-D-glucans for diagnosis of fungal infections; this may persist during the weeks following infusion of the product.

Transmissible agents

Gammagard S/D is made from human plasma. 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, such as the Creutzfeldt-Jacob disease (CJD) agent.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C (HCV), and for the non-enveloped hepatitis A (HAV) 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.

Further precautions

Hyperproteinaemia and increased serum viscosity may occur in patients receiving IVIG treatment.

There have been reports of noncardiogenic pulmonary oedema (Transfusion Related Acute Lung Injury, TRALI) in patients administered IVIG.

Sodium content

This medicinal product contains 668 mg sodium per bottle (10 g), equivalent to 34% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

4.5 Interaction with other medicinal products and other forms of interactions

Live Attenuated Virus Vaccines

Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella for a period of at least 6 weeks and up to 3 months following the infusion.

After administration of this 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.

Paediatric population

There are no interaction studies with GAMMAGARD SD in paediatric population.

The listed interactions apply to both adults and children.

4.6 Fertility, pregnancy and lactation

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.

Clinical experience with immunoglobulins suggest that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Maternally administrated IVIG products have been shown to cross the placenta, increasing during the third trimester.

Breast feeding

Immunoglobulins are excreted into the milk.

Fertility

The effects of Gammagard S/D on fertility have not been established.

Physicians should balance the potential risks and only prescribe Gammagard SD if clearly needed.

4.7 Effects on ability to drive and use machines

There is no information on the effects of GAMMAGARD S/D on the ability to drive or operate an automobile or other heavy machinery. The ability to drive and operate machines may be impaired by some adverse reactions associated with GAMMAGARD S/D. 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, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate back pain may occur occasionally.

Rarely human normal immunoglobulins may cause an anaphylactic reaction with a 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 also 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 thrombosis have been observed.

There is clinical evidence of a possible association between IVIg administration and the potential for the development of thrombotic events. The exact cause of this is unknown; therefore, caution should be exercised in the prescribing and infusion of IVIg in patients with a history of and predisposing factors towards cardiovascular disease or thrombotic episodes. Analysis of adverse event reports has indicated that a rapid rate of infusion may be a risk factor for vascular occlusive events.

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Haemolytic anaemia can develop subsequent to IVIG (including GAMMAGARD S/D) therapy. IVIG products can contain blood group antibodies that may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis.

Adverse Reactions from Clinical Trials

Adverse reactions were pooled from a pivotal clinical study of GAMMAGARD S/D and a phase 4 study assessing the acute and mid-term safety of GAMMAGARD S/D.

Frequency has been evaluated using the following criteria: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

| System Organ Class (SOC) | Preferred MedDRA (Version 19.0) Term | Frequency |
|---|---|--|
| INFECTIONS AND INFESTATIONS | Influenza | Uncommon |
| METABOLISM AND NUTRITIONAL DISORDERS | Decreased appetite | Uncommon |
| PSYCHIATRIC DISORDERS | Anxiety Agitation | Uncommon Uncommon |
| NERVOUS SYSTEM DISORDERS | Headache Lethargy | Common Uncommon |
| EYE DISORDERS | Vision blurred | Uncommon |
| CARDIAC DISORDERS | Palpitations | Uncommon |
| VASCULAR DISORDERS | Flushing Blood pressure fluctuation | Common Uncommon |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Dyspnoea Epistaxis | Uncommon Uncommon |
| GASTROINTESTINAL DISORDERS | Vomiting Nausea Diarrhoea Stomatitis Abdominal pain upper Abdominal discomfort | Common Common Uncommon Uncommon Uncommon Uncommon |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Urticaria Pruritus Cold sweat Hyperhidrosis | Uncommon Uncommon Uncommon Uncommon |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Back pain Muscle spasms | Uncommon Uncommon |

| | | |
|--|---|--|
| | Pain in extremity | Uncommon |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Fatigue Chills Pyrexia Chest pain Malaise Pain Chest discomfort Feeling abnormal Feeling cold Feeling hot Influenza like illness Infusion site erythema Infusion site extravasation Infusion site pain | Common Common Common Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon |
| INVESTIGATIONS | Blood pressure increased | Uncommon |

Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported post-marketing. These adverse reactions are listed by System Order Class (SOC), then by Preferred MedDRA (Version 19.0) term in order of severity.

INFECTIONS AND INFESTATIONS: Meningitis aseptic

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Haemolysis, Anaemia, Thrombocytopenia, Lymphadenopathy

IMMUNE SYSTEM DISORDERS: Anaphylactic shock, Anaphylactic/anaphylactoid reaction, Hypersensitivity

PSYCHIATRIC DISORDERS: Restlessness

NERVOUS SYSTEM DISORDERS: Cerebrovascular accident, Transient ischaemic attack, Seizure, Migraine, Dizziness, Paraesthesia, Syncope, Tremor

EYE DISORDERS: Retinal vein thrombosis, Visual impairment, Eye pain, Photophobia

CARDIAC DISORDERS: Myocardial infarction, Cyanosis, Tachycardia, Bradycardia

VASCULAR DISORDERS: Arterial thrombosis, Vena cava thrombosis, Deep vein thrombosis, Thrombophlebitis, Hypotension, Hypertension, Pallor

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Pulmonary embolism, Pulmonary oedema, Hypoxia, Bronchospasm, Wheezing, Hyperventilation, Throat tightness, Cough

GASTROINTESTINAL DISORDERS: Abdominal pain, Dyspepsia

HEPATOBIILIARY DISORDERS: Hepatitis*

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Angioedema, Dermatitis, Erythema, Rash

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: Arthralgia, Myalgia

RENAL AND URINARY DISORDERS: Renal failure

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Infusion site reaction, Asthenia, oedema

INVESTIGATIONS: Coombs direct test positive

*non-infectious hepatitis

Paediatric population

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

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

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

Overdosage may lead to fluid overload and hyperviscosity, particularly in the elderly and 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: J06B A02.

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 prepared from pooled material from not fewer than 1000 donations. It should have 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 immune modulatory effects.

5.2 Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extra-vascular compartments.

Human normal immunoglobulin has a half-life approximately 37.5 ± 15 days. 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.

5.3 Preclinical safety data

Toxicological Properties

Immunoglobulins are normal constituents of the human body.

In animals, single dose toxicity testing is of no relevance and higher doses result in overloading. Repeated dose toxicity testing and embryo-foetal toxicity studies are impractical due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

Since clinical experience provides no hint for tumorigenic or mutagenic effects of immunoglobulins, experimental studies, particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Glucose Monohydrate

Human Albumin (as stabilizer: 1.5 – 3 mg/mL for a 5% solution)

Glycine

Hydrochloric Acid (QS for pH adjustment)

Sodium Hydroxide (QS for pH adjustment)

Solvent:

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

It is recommended that Gammagard S/D be administered separately from other medicinal products that the patient may be receiving.

6.3 Shelf life

Unopened: 2 years.

Once reconstituted: Product should be used within 2 hours of reconstitution with the solvent if kept at a temperature of $\leq 25^{\circ}\text{C}$. When reconstitution has taken place in controlled and validated aseptic conditions the reconstituted product may be stored no longer than 24 hours at 2 to 8°C .

6.4 Special precautions for storage

Unopened pack: Do not store above 25°C .
Do not freeze.

For storage after reconstitution refer to section 6.3.

6.5 Nature and contents of container

Both powder and solvent are supplied in a Type I EP, clear glass bottle, with a rubber stopper, and an aluminium cap with flip-off lid.

Gammagard S/D is available in bottles of 5.0 g and 10.0 g.

Each package of 5.0 g and 10.0 g contains the solvent (96 mL, 192 mL, respectively), a sterile transfer device and a sterile administration set with filter.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When reconstitution is performed aseptically outside of a sterile laminar airflow hood, administration should begin as soon as possible, but not more than 2 hours after reconstitution. When reconstitution is performed aseptically in a sterile laminar airflow hood, the reconstituted product may be stored under constant refrigeration ($2-8^{\circ}\text{C}$), for up to 24 hours. If these conditions are not met, sterility of the reconstituted product cannot be maintained. Partially used vials should be discarded.

Total dissolution should be obtained within 30 minutes. The product should be brought to room or body temperature before use.

Gammagard S/D should be inspected visually for particulate matter and discoloration prior to administration. Before reconstitution, the powder should be white or very faint yellow powder/cake that is substantially free of foreign visible particles. After reconstitution, only clear or slightly opalescent and colourless or pale yellow solutions are to be administered. 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 requirements.

Reconstitution - use aseptic technique:

5.0 g, 10.0 g Sizes

Bring GAMMAGARD S/D and Water for Injections (solvent) to room temperature. This temperature needs to be maintained until dissolution is complete.

A. 5% Solution:

1. Remove bottle caps and clean stoppers with germicidal solution.

2. Remove spike cap from one end of the transfer device.

Do not touch spike.

3a. Place the solvent bottle on a flat surface. Use exposed end of transfer device to spike solvent bottle through centre of the stopper

CAUTION: Failure to insert spike into centre of the stopper may result in dislodging of the stopper.

3b. Ensure that the collar collapses fully into the device by pushing down on the transfer device firmly. While holding onto transfer device, remove remaining spike cover. Do not touch spike.

4. Hold solvent bottle with attached transfer device at an angle to the concentrate bottle to prevent spilling the solvent.

Note: Do not hold solvent bottle upside down, for this can lead to solvent spillage.

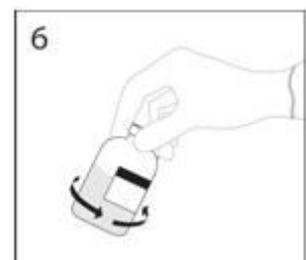
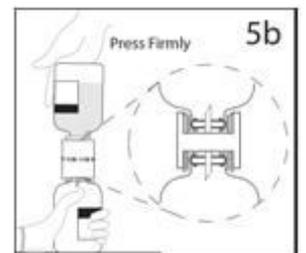
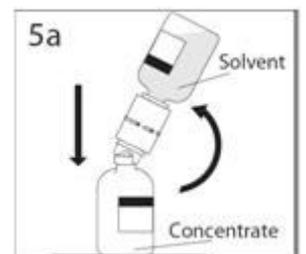
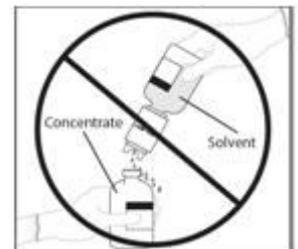
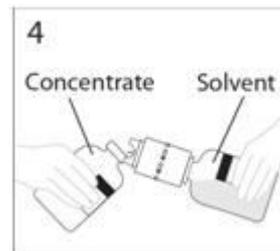
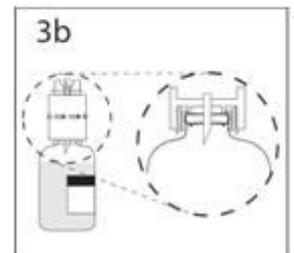
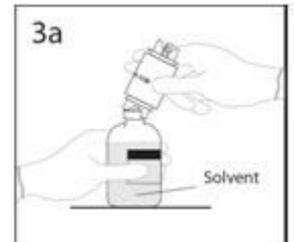
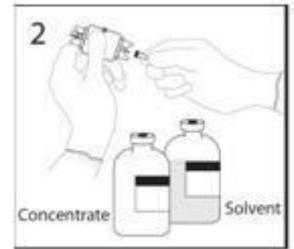
5a. Spike concentrate bottle through the centre of the stopper while quickly inverting the solvent bottle to avoid spilling out solvent.

CAUTION: Failure to insert the spike into the centre of the stopper may result in dislodging of the stopper and loss of vacuum.

5b. Ensure that the collar collapses fully into the device by pushing down on the solvent bottle firmly.

6. After transfer of solvent is complete, remove transfer device and empty solvent bottle. Immediately swirl the concentrate bottle gently to thoroughly mix contents.

CAUTION: Do not shake. Avoid foaming.
Discard transfer device after single use.



B. 10% Solution:

1. Follow step 1 as previously described in A.
2. To prepare a 10% solution, it is necessary to remove half of the volume of solvent. Table 2 indicates the volume of solvent that should be removed from the vial before attaching the transfer device to produce a 10% concentration. Using aseptic technique, withdraw the unnecessary volume of solvent using a sterile hypodermic syringe and needle. Discard the filled syringe and the needle.
3. Using the residual solvent in the solvent bottle, follow steps 2-6 as previously described in A.

| TABLE 2 | | |
|--|--|---------------|
| Required Solvent Volume to be Removed | | |
| Concentration | 5.0 g bottle | 10.0 g bottle |
| 5% | Do not remove any solvent for reconstitution of 5% Solution | |
| 10% | 48mL | 96mL |

Administration - use aseptic technique

5.0 g, 10.0 g Sizes

Follow the direction insert for use, which accompanies the administration set provided in each package. If another administration set is used, ensure that the set contains a similar filter.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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