

## SUMMARY OF PRODUCT CHARACTERISTICS

This prescribing information is intended for international use only. Please always consult your full country-specific prescribing information as licenses and licensing conditions may vary from country to country.

### 1. NAME OF THE MEDICINAL PRODUCT

GAMMAGARD S/D 0.5 g / 2.5 g / 5.0 g / 10.0 g Powder and solvent for solution for infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

GAMMAGARD S/D is presented as powder and solvent for solution for infusion containing (0.5 g, 2.5 g, 5.0 g, 10.0 g) human normal immunoglobulin (IVIg) per vial. GAMMAGARD S/D may be reconstituted with Sterilized 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 human normal immunoglobulin G (IgG).

Distribution of IgG subclasses:

IgG<sub>1</sub> ≥ 56.9%

IgG<sub>2</sub> ≥ 16.0%

IgG<sub>3</sub> ≥ 3.3%

IgG<sub>4</sub> ≥ 0.3%

Maximum immunoglobulin A (IgA) content: not more than 3 microgram per mL.

Excipients: Human Albumin, Glycine, Sodium Chloride, Glucose Monohydrate

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Powder and solvent for solution for intravenous infusion

GAMMAGARD S/D is a lyophilized, white or very faint yellow powder / cake, substantially free of foreign visible particles.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Replacement Therapy in:

Primary Immunodeficiency Syndromes (PID) such as:

- congenital agammaglobulinemia and hypogammaglobulinemia
- common variable immunodeficiency
- severe combined immunodeficiencies
- Wiskott Aldrich Syndrome

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

< Premature children with low birth weight. > \*)

- \*) For a national SPC the choice of text indicated between < > depends on whether the item is approved in that country or not.

#### Immunomodulation

- Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome
- Kawasaki disease

#### Allogeneic Bone Marrow Transplantation

### **4.2 Posology and method of administration**

The dose and regimen are dependent on the indication.

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

#### Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4-6 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) followed by at least 0.2 g/kg BW every three weeks.

The dose required to achieve a trough level of 6 g/L is of the order of 0.2-0.8 g/kg BW/month. The dosage interval when steady state has been reached varies from 2-4 weeks.

Trough levels should be measured in order to adjust the dose and dosage interval.

#### Replacement therapy in myeloma or chronic lymphocytic leukaemia (CLL) with severe secondary hypogammaglobulinemia and recurrent infections; replacement therapy in children with congenital AIDS and recurrent infections

The recommended dose is 0.2-0.4 g/kg BW every three to four weeks to obtain IgG trough level of at least 4-6 g/L.

#### < Premature children with low birth weight >

< For prophylaxis of late onset infection in premature children with low birth weight neonates aged less than 7 days receive 0.5 g/kg BW and the same dosage one week later, followed by a total of 5 infusions every 14 days, or until discharge from the hospital. >

#### Idiopathic Thrombocytopenic Purpura (ITP)

For the treatment of an acute episode, 0.8-1g/kg BW on day one, which may be repeated once within 3 days, or 0.4 g/kg BW daily for two to five days. The treatment can be repeated if a relapse occurs.

#### Guillain Barré Syndrome:

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

#### Kawasaki Disease:

1.6-2.0 g/kg BW should be administered in divided doses over two to five days or 2.0 g/kg BW 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 starting dose is normally 0.5 g/kg BW/week, starting seven days before transplantation and for up to 3 months after transplantation.

In case of persistent lack of antibody production, dosage of 0.5 g/kg BW/month is recommended until antibody level returns to normal.

The dosage recommendations are summarized in the following table:

<b>Indication</b>	<b>Dose</b>	<b>Frequency of Injections</b>
Replacement therapy in primary immunodeficiency	starting dose: 0.4 – 0.8 g/kg BW thereafter: 0.2 – 0.8 g/kg BW	every 2 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L
Replacement therapy in secondary immunodeficiency	0.2 – 0.4 g/kg BW	every 3 – 4 weeks to obtain IgG trough level of at least 4 – 6 g/L
Children with AIDS	0.2– 0.4 g/kg BW	every 3 - 4 weeks
< Premature children with low birth weight (neonates aged less than 7 days) >	< 0.5 g/kg BW >	< two injections one week apart, followed by a total of 5 infusions every 14 days or until discharge from hospital >
Immunomodulation:		
Idiopathic thrombocytopenic purpura	0.8 – 1 g/kg BW or 0.4 g/kg BW/day	on day 1, possibly repeated once within 3 days for 2 – 5 days
Guillain Barré syndrome	0.4 g/kg BW/day	for 5 consecutive days
Kawasaki disease	1.6 – 2 g/kg BW or 2 g/kg BW	in several doses for 2 – 5 days in association with acetylsalicylic acid  in one dose in association with acetylsalicylic acid
Allogeneic bone marrow transplantation:		
- Treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg BW	every week from day –7 up to 3 months after transplantation
- Persistent lack of antibody production	0.5 g/kg BW	every month until antibody levels return to normal

GAMMAGARD S/D 5% (50 mg/mL) should be infused intravenously at an initial rate of 0.5 mL/kg BW/hour. 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.

### 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency when the patient has antibodies against IgA. However GAMMAGARD S/D contains only trace amounts of IgA (not more than 3 microgram per mL).

#### **4.4 Special warnings and precautions for use**

Certain severe adverse drug reactions may be related to the rate of infusion. 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.

Certain adverse reactions may occur more frequently

- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinemia with or without IgA deficiency;
- 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.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.

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.

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (0.5 to 1 mL/kg BW/hour);
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or, when there has been a long interval since the previous infusion, should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration;
- 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.

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, 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 shall 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 hypovolemic patients, patients with diseases which increase blood viscosity.

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, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age 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, 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.

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

In 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.

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.

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.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses 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 GAMMAGARD S/D 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.

#### **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 and varicella. 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.

##### Interference with serological testing

After infusion of immunoglobulin the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D may interfere with some serological tests for red cell allo-antibodies (e.g. Coombs test), reticulocyte count and haptoglobin.

#### **4.6 Pregnancy and lactation**

The safety of GAMMAGARD S/D 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 suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

#### **4.7 Effects on ability to drive and use machines**

No effects on ability to drive and use machines have been observed.

#### **4.8 Undesirable effects**

With human normal immunoglobulin for intravenous administration, adverse reactions such as chills, headache, 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, isolated cases of reversible haemolytic anaemia / haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and / or acute renal failure have been observed.

Thromboembolic events 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.

With GAMMAGARD S/D, the adverse reactions reported in the listing hereafter are based on reports from post-marketing experience:

Nervous system disorders: headache, dizziness, paraesthesia and dysaesthesia, tremor, convulsions, aseptic meningitis, central nervous system haemorrhages and cerebrovascular accidents.

Eye disorders: photophobia, visual disturbance, eye pain, retinal vein thrombosis.

Psychiatric disorders: anxiety, agitation, restlessness.

Blood and lymphatic system disorders: direct positive Coombs test, haemolysis, anaemia, thrombocytopenia, lymphadenopathy.

Immune system disorders: hypersensitivity, anaphylactic or anaphylactoid reaction, anaphylactic shock.

Cardiac disorders: palpitations, tachycardia, cyanosis, myocardial infarction.

Vascular disorders: flushing, hypertension, pallor, hypotension, thrombophlebitis, deep vein thrombosis.

Respiratory, thoracic and mediastinal disorders: cough, throat tightness, hypoxia, hyperventilation, dyspnoea, wheezing, bronchospasm, pulmonary embolism.

Gastrointestinal disorders: nausea, vomiting, dyspepsia, abdominal pain, diarrhoea.

Skin and subcutaneous tissue disorders: erythema, pruritus, rash, urticaria, dermatitis, hyperhidrosis, angioedema.

Musculoskeletal and connective tissue disorders: arthralgia, myalgia, back pain, muscle spasms.

Renal and urinary disorders: renal failure.

General disorders and administration site conditions: chills, pyrexia, asthenia, fatigue, chest pain, oedema, influenza like illness, injection and infusion site reactions.

For safety with respect to transmissible agents see section 4.4.

#### **4.9 Overdose**

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

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

GAMMAGARD S/D contains mainly functionally intact immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents.

GAMMAGARD S/D 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.

### **5.2 Pharmacokinetic properties**

GAMMAGARD S/D 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 to 5 days equilibrium is reached between the intra- and extravascular compartments.

The half-life of GAMMAGARD S/D is about  $37.7 \pm 15$  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**

The safety of GAMMAGARD S/D has been demonstrated in several preclinical studies. Preclinical data reveal no special risks for humans based on conventional studies of safety pharmacology and genotoxicity.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Powder:

Human Albumin (0.06 g/g IgG)  
Glycine  
Sodium Chloride  
Glucose Monohydrate

#### Solvent:

Sterilized Water for Injections

### **6.2 Incompatibilities**

GAMMAGARD S/D 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**

2 years

Chemical and physical in-use stability of reconstituted GAMMAGARD S/D has been demonstrated for 2 hours at room temperature. From a microbiological point of view the product should be used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, when reconstitution has taken place in controlled and validated aseptic conditions.

### **6.4 Special precautions for storage**

Do not store above +25°C.  
Do not freeze, the solvent vial might break.  
Keep vial in the outer carton in order to protect from light.  
Do not use after the expiry date.  
Keep out of the reach and sight of children.

For storage conditions of the reconstituted medicinal product, see section 6.3.

### **6.5 Nature and contents of container**

All powder and solvent presentations come in Type I glass vials. Powder and solvent vials are closed with bromobutyl rubber, siliconised stoppers.

GAMMAGARD S/D is available in pack sizes of 0.5 g, 2.5 g, 5.0 g and 10.0 g.

Each package of 0.5 g contains the solvent (10 mL), a sterile double-ended needle, a sterile filter needle, a 10 mL sterile plastic syringe and a sterile mini-infusion set.

Each package of 2.5 g, 5.0 g and 10.0 g contains the solvent (50 mL, 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°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.

Reconstituted material should be a clear to slightly opalescent and colourless to pale yellow solution. Do not use solutions that are cloudy or have deposits. Reconstituted products should be inspected visually for particulate matter and discolouration prior to administration.

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

### **Reconstitution - use aseptic technique:**

#### **0.5 g Size**

#### A. 5% Solution:

1. Bring GAMMAGARD S/D and Sterilized Water for Injections (solvent) to room temperature. This temperature needs to be maintained until dissolution is complete.
2. Remove caps from concentrate and solvent vials to expose central portion of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective cover from one end of the double-ended needle and insert exposed end through solvent stopper at its centre.
5. Remove protective cover from other end of the double-ended needle. Invert solvent vial over upright concentrate vial, then rapidly insert free end **perpendicularly** through the concentrate vial stopper at its **centre**.
6. The vacuum in the concentrate vial will draw in the solvent. When solvent transfer is complete, remove empty solvent vial and double ended needle from concentrate vial. Discard double-ended needle after single use.
7. Thoroughly wet the dried material by tilting or inverting and gently rotating the bottle. **Do not shake. Avoid foaming.**
8. Repeat gentle rotation as long as undissolved product is observed.

#### B. 10% Solution:

Follow steps 1-3 as previously described in A.

4. Reconstitute the concentrate with the appropriate volume of solvent using a sterile hypodermic needle and syringe. The volume of solvent required for a 10% solution is 5 mL for 0.5 g size. Using aseptic technique, draw required volume into a sterile hypodermic needle and syringe. The solvent is then injected into the concentrate vial.
5. Discard any unused solvent after single use.
6. Thoroughly wet the dried material by tilting or inverting and gently rotating the bottle. **Do not shake. Avoid foaming.**
7. Repeat gentle rotation as long as undissolved product is observed.

### 2.5 g, 5.0 g, 10.0 g Sizes

#### A. 5% Solution:

1. Bring GAMMAGARD S/D and Sterilized Water for Injections (solvent) to room temperature. This temperature needs to be maintained until dissolution is complete.
2. Remove caps from concentrate and solvent vials to expose central portion of rubber stoppers.
3. Cleanse stoppers with germicidal solution.
4. Remove protective cover from the spike of transfer device.
5. Place the solvent vial on a flat surface and, while holding the vial to prevent slipping, insert the spike of the transfer device **perpendicularly through the centre** of the vial stopper.
6. Press down firmly so that the transfer device fits snugly against the solvent vial. **Caution: Failure to use centre of stopper may result in dislodging the stopper.**
7. Remove protective cover from other end of the transfer device. Hold solvent vial to prevent slipping.
8. Hold concentrate vial firmly and at an angle of approximately 45 degrees. Invert the solvent vial with the transfer device at an angle complementary to the concentrate vial (approximately 45 degrees) and firmly insert the transfer device into the concentrate vial through the centre of the rubber stopper. **Note: Invert the solvent vial with attached transfer device rapidly into the concentrate vial in order to avoid loss of solvent.** **Caution: Failure to use centre of stopper may result in dislodging the stopper and loss of vacuum.**
9. The solvent will flow into the concentrate vial quickly. When solvent transfer is complete, remove empty solvent vial and transfer device from concentrate vial. Discard transfer device after single use.
10. Thoroughly wet the dried material by tilting or inverting and gently rotating the vial. **Do not shake. Avoid foaming.**
11. Repeat gentle rotation as long as undissolved product is observed.

**B. 10% Solution:**

Follow steps 1-3 as previously described in A.

4. Reconstitute the concentrate with the appropriate volume of solvent using a sterile hypodermic needle and syringe. The volume of solvent required for a 10% solution is 25 mL for the 2.5 g size, 48 mL for the 5.0 g size and 96 mL for the 10.0 g size. Using aseptic technique, draw required volume into a sterile hypodermic needle and syringe. Discard the filled syringe.
5. Using the residual solvent in the solvent vial, follow steps 4-11 as previously described in A.

**Administration - use aseptic technique**

**0.5 g Size**

1. Attach the filter needle to an empty plastic syringe.
2. Draw back the plunger to admit air into the syringe.
3. Place the reconstituted GAMMAGARD S/D vial on a flat surface and, while holding the bottle firmly to prevent slipping, insert the needle perpendicularly through the centre of the vial stopper.
4. Inject air into vial and then withdraw the reconstituted material into the syringe.
5. Remove syringe and inject solution intravenously through the mini-infusion set.

**2.5 g, 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**

<country-specific>

**8. MARKETING AUTHORISATION NUMBER(S)**

<country-specific>

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<country-specific>

**10. DATE OF REVISION OF THE TEXT**

<country-specific>