Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gammanorm, 165 mg/mL, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (SCIg/IMIg)

One mL contains:
Human normal immunoglobulin.....165 mg
(purity of at least 95% IgG)

Each vial of 6 mL contains: 1 g of human normal immunoglobulin.
Each vial of 10 mL contains: 1.65 g of human normal immunoglobulin.
Each vial of 12 mL contains: 2 g of human normal immunoglobulin.
Each vial of 20 mL contains: 3.3 g of human normal immunoglobulin.
Each vial of 24 mL contains: 4 g of human normal immunoglobulin.
Each vial of 48 mL contains: 8 g of human normal immunoglobulin.

Distribution of the IgG subclasses (approx. values):

IgG_1 ..... 59%
IgG_2 ..... 36%
IgG_3 ..... 4.9%
IgG_4.....0.5%

The maximum IgA content is 82.5 micrograms/mL

Produced from the plasma of human donors.

Excipient(s) with known effects:

For vial of 6 ml:
This medicinal product contains less than 1 mmol (23 mg) sodium per vial that is to say essentially 'sodium-free'.

For vials of 10 ml, 12 ml, 20 ml, 24 ml and 48 ml:
This medicinal product contains
25 mg (1.1 mmol) sodium per vial of 10 ml,
30 mg (1.30 mmol) sodium per vial of 12 ml,
50 mg (2.17 mmol) sodium per vial of 20 ml,
60 mg (2.61 mmol) sodium per vial of 24 ml,
120 mg (5.22 mmol) sodium per vial of 48 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
The liquid preparation is clear or slightly opalescent and colourless or pale yellow or light-brown.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Indications for subcutaneous administration (SCIg)

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

- Primary immunodeficiency syndromes such with impaired antibody production (see section 4.4)
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (CLL), in whom prophylactic antibiotics have failed or are contra-indicated.
- Hypogammaglobulinaemia and recurrent bacterial infections in multiple myeloma (MM) patients
- Hypogammaglobulinaemia in patients pre- and post- allogenic haematopoietic stem cell transplantation (HSCT)

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 are dependent on the indication.

Replacement therapy

The medicinal product should be administered via the subcutaneous route.

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

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age. A loading dose of at least 0.2-0.5 g/kg may be required. This may need to be divided over several days, with a maximal daily dose of 0.1 to 0.15 g/kg.

After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals (approximately once per week) to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg. Each single dose may need to be injected at different anatomic sites.

Trough levels should be measured and assessed in conjunction with the incidence of infections. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher trough levels.

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 in replacement therapy indications.

Method of administration

For subcutaneous use.

Subcutaneous infusionfor home treatment should be initiated and monitored by a physician experienced in the guidance of patients for home treatment. The patient must be instructed in the use of a syringe driver, the infusion techniques, the keeping of a treatment diary, recognition of and measures to be taken in case of severe adverse reactions.

For subcutaneous infusions using a pump

Gammanorm may be injected into sites such as abdomen, thigh, upper arm, and lateral hip. It is recommended to use an initial administration speed of 15 mL/hour/site. If well tolerated (see section 4.4), for subsequent infusions, the flow rate may be gradually increased at a rate of 1-2 mL/hour/site to 25 mL per hour per site as tolerated. The maximum flow rate administered, if tolerated, can be 100 mL/hour for all sites combined. More than one infusion device can be used simultaneously. In adults doses over 30 mL may be divided according to patient preference. The maximum volume to be infused per injection site should not exceed 25 mL before the 10th infusion. After the 10th infusion, the maximum volume to be infused per injection site can be gradually increased to 35 mL, if tolerated. The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 mL. There is no limit to the number of infusion sites.

For subcutaneous infusions using a syringe
Gammanorm can be administered using a syringe at a single infusion site.

The proposed maximum infusion rate is set at approximately 1-2 mL/minute.
The weekly dose could be divided into three administrations given every other day. In adults, the maximum volume to be infused per injection site should not exceed 25 mL Gammanorm. In children, the maximum volume to be infused per injection site should not exceed 5-15 mL Gammanorm.

It might be necessary to administer the daily dose on more than one injections site. The maximum flow rate administered, if tolerated, can be 120 mL/hour for all sites combined.

For intramuscular use.
Intramuscular injection must be given by a physician or nurse.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in 6.1 (see section 4.4).

Gammanorm must not be given intravascularly.

It must also not be administered intramuscularly in case of severe thrombocytopenia and in other disorders of haemostasis.

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 administrated product should be clearly recorded.
If Gammanorm is accidentally administered into a blood vessel, patients could develop shock.

The recommended infusion rate stated under section "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 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:

- initially injecting the product slowly (see 4.2);

- ensuring that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative immunoglobulin 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.

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.

Hypersensitivity
True allergic reactions are rare. They can particularly occur in patients with anti-IgA antibodies who should be treated with particular caution. Patients with anti-IgA antibodies, in whom treatment with subcutaneous IgG products remains the only option, should be treated with Gammanorm only under close medical supervision.

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
Arterial and venous thromboembolic events including myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism have been associated with the use of immunoglobulins. Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with preexisting 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 immobilization, severely hypovolaemic patients, patients with diseases which increase blood viscosity).

Patients should be informed about first symptoms of thromboembolic events including shortness of breath, pain and swelling of a limb, focal neurological deficits and chest pain and should be advised to contact their physician immediately upon onset of symptoms.

Aseptic Meningitis Syndrome (AMS)
Aseptic meningitis syndrome has been reported to occur in association with subcutaneous immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following treatment. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae.

Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.

Important information about some of the ingredients of Gammanorm
This medicinal product contains 4.35 mmol (or 100 mg) sodium per dose (40 mL). This should be taken into consideration in patients on a controlled sodium diet.

For vial of 6 ml:
This medicinal product contains less than 1 mmol (23 mg) sodium per vial that is to say essentially 'sodium-free'.

For vials of 10 ml, 12 ml, 20 ml, 24 ml and 48 ml:
This medicinal product contains
25 mg (1.1 mmol) sodium per vial of 10 ml,
30 mg (1.30 mmol) sodium per vial of 12 ml,
50 mg (2.17 mmol) sodium per vial of 20 ml,
60 mg (2.61 mmol) sodium per vial of 24 ml,
120 mg (5.22 mmol) sodium per vial of 48 ml,
equivalent to 1.25%, 1.5%, 2.5%, 3.0% and 6.0%, respectively of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 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 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 a 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 Gammanorm 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.

Gammanorm does not protect against hepatitis A.

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 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 were no specific or additional interactions observed for the paediatric population.

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 Gammanorm should therefore only be given with caution to pregnant women and breast-feeding mothers. Immunoglobulin 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 Gammanorm. 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.

Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash, may frequently occur.

Tabulated list of adverse reactions

The following table shows an overview of adverse reactions observed in clinical studies, post-marketing safety studies, and from other postmarketing sources, categorized according the MedDRA System Organ Class (SOC), Preferred Term Level (PT) and frequency.

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).

For spontaneously reported post-marketing adverse reactions the reporting frequency is categorized as not known.

MeDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
Immune system disorders	hypersensitivity	uncommon
	anaphylactic shock	very rare
Nervous system disorders	meningitis aseptic[#]	not known
	dizziness	common
	tremor	uncommon
	headache	common
Va s c u la r d i s order s	thr o m bo e m bo li c e v en t* [#]	very rare
	pallor	uncommon
	hypotension	rare
Re s p ira tor y , thora c i c an d	bronchospasm	uncommon
m ed ia s ti na l d is order s	dyspnoea	uncommon
	cough	not known
Ga s tro in te s tina l d i s order s	abdominal pain	uncommon
	diarrhoea	uncommon
	nausea	common
	vomiting	common
Sk in an d s ub c u taneou s	urticaria	not known
ti ss u e d is order s	rash	not known
	pruritus	not known
Mu s c u lo s k e le ta l an d	back pain	not known
c onne c ti v e ti ss u e d is order s	myalgia	common
	arthralgia	very rare
Genera l d is order s an d	pyrexia	very rare
ad m in is tra ti o n s i te	chills	very rare
c ond itio n s	fatigue	common
	injection site reaction	very common
	malaise	uncommon
	flushing	not known
	asthenia	uncommon
	feeling hot	uncommon
	feeling cold	uncommon
	influenza-like illness	not known
	face oedema	not known

[#] See also Section 4.4 * MedDRA low level term (LLT)

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

Paediatric population
Frequency, type and severity of adverse reactions in children are 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, 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

Consequences of an overdose are not known.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration, ATC code: J06BA01

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.

Clinical Studies
In the study program 43 subjects with primary immunodeficiency syndromes aged between 22 and 79 years old were treated with Gammanorm. Each subject was treated for two consecutive periods of three months each according to the sequence assigned based on the cross-over design (syringe and then pump, or pump and then syringe) without any intermediate washout period. The total duration of study treatment was therefore 6 months for each subject. The mean dose administered per month was 502.1 mg/kg body weight when given via pump and 475.0 mg/kg body weight when given via syringe. Sustained IgG trough levels with mean concentrations of 9.7 g/L were achieved during the pump treatment sequence and when patients received treatment via syringe, mean IgG concentrations were at 9.4 g/L. Subjects received a mean total of 12.4 Gammanorm infusions per 3-month treatment period during the pump sequence and 34.8 infusions per 3-month treatment period when Gammanorm was administered via syringe.

Paediatric population
No specific studies in the paediatric population were performed with Gammanorm.

5.2 Pharmacokinetic properties

Absorption and distribution
Following subcutaneous administration of Gammanorm, peak serum levels are achieved after 4-6 days.

Data from clinical studies show that trough levels of Gammanorm can be maintained by dosing regimens of 0.1 g/kg per week.

With intramuscular administration, human normal immunoglobulin is bioavailable in the recipient`s circulation after a delay of 2-3 days.

Elimination
IgG and IgG-complexes are broken down in the cells of the reticuloendothelial system.

Paediatric population
No specific studies in the paediatric population were performed with Gammanorm.

5.3 Preclinical safety data

There are no relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium chloride
Sodium acetate
Polysorbate 80
Water for injections.

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
After first opening, the product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect it from light.
Within its shelf-life, the product may be stored below 25°C for up to 1 month, without being refrigerated again during this period, and must be discarded if not used after this.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

6 mL, 10 mL, 12 mL, 20 mL, 24 mL or 48 mL of solution in a vial (Type I glass) with a stopper (bromobutyl rubber) - pack size of 1, 10 or 20.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent and colourless or pale yellow or light brown. 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.

7 MARKETING AUTHORISATION HOLDER

Octapharma (IP) SPRL
Allée de la Recherche 65
1070 Anderlecht
Belgium

8 MARKETING AUTHORISATION NUMBER

PA2219/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st June 2007
Date of last renewal: 15th October 2014

10 DATE OF REVISION OF THE TEXT

October 2020