

DATA SHEET

GAMMANORM

NAME OF DRUG

GAMMANORM, Human Normal Immunoglobulin (SC/IM)g, 165 mg/mL, Solution for Injection or Infusion

One ampoule or vial of 10 mL GAMMANORM contains 1650 mg human normal immunoglobulin.

One vial of 20 mL GAMMANORM contains 3300 mg human normal immunoglobulin.

DESCRIPTION

GAMMANORM contains human normal immunoglobulin G (IgG) $\geq 95\%$, with a broad spectrum of antibodies against infectious agents. The Immunoglobulin A (IgA) content is ≤ 82.5 micrograms/mL. It is composed of the following distribution of IgG subclasses:

IgG ₁	ca. 59%
IgG ₂	ca. 36%
IgG ₃	ca. 4.9%
IgG ₄	ca. 0.5%

GAMMANORM contains all the IgG antibodies which are present in the normal population. It is prepared from pooled material from more than 1000 donors.

Quantitative composition

1 mL of solution contains:

Protein, of which at least 95% is	
Human Normal Immunoglobulin G	165 mg
Glycine	20 mg
Sodium chloride and sodium acetate	
corresponding to sodium	2.5 mg
Water for Injections	1 mL
IgA	≤ 82.5 micrograms

PHARMACOLOGY

Pharmacodynamic properties

ATC code: J06B A01

Human normal immunoglobulin contains the IgG antibodies present in the normal population, with a broad spectrum of antibodies against infectious agents. GAMMANORM has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of GAMMANORM may restore abnormally low IgG levels to the normal range.

Pharmacokinetic properties

With subcutaneous administration of human normal immunoglobulin, peak levels are achieved in the recipient's circulation after approximately 4-6 days.

No formal pharmacokinetic studies have been completed with GAMMANORM, thus all studies reported are based on the GAMMANORM predecessor product.

In a clinical study the kinetics of IgG and IgG subclasses were studied in 23 patients with Common Variable Immunodeficiency (CVID) who received human normal immunoglobulin subcutaneously (SC) at a dose of 100 mg/kg/week for a period of 18 months. Seventeen of these patients had been treated previously by the IM or IV routes. Out of these 17 patients, 11 were treated with weekly infusions (100 mg/kg/week) (Group I), while in 6 (Group II) the treatment was carried out as daily infusions (100 mg/kg/day) for 5 consecutive days during the first week (100 mg/kg/day) of treatment and then as weekly infusions thereafter (100 mg/kg/week). The remaining 6 patients had never been treated with any form of gammaglobulin (Group III); these patients received weekly SC infusions (100 mg/kg/week).

The following results were achieved for this study:

	Group I (n=11)	Group II (n=6)	Group III (n=6)
Weight (kg)	66 ± 11	67 ± 9	68 ± 19
Serum volume (L)	2.4 ± 0.2	2.4 ± 0.2	2.4 ± 0.5
Dose per infusion (mL)	40 ± 7	49 ± 10	41 ± 12
Serum IgG concentrations (g/L)			
At time of diagnosis	1.3 ± 1.2	2.3 ± 1.3	2.2 ± 1.4
Before SC treatment	4.8 ± 3.4	6.7 ± 2.8	2.2 ± 1.4
After 6 months of treatment	8.2 ± 1.6	11.5 ± 3.7	8.2 ± 1.8
After 12 months of treatment	9.7 ± 1.9	11.1 ± 4.0	9.9 ± 0.6
After 18 months of treatment	10.2 ± 1.5	11.2 ± 4.2	9.5 ± 1.1

Stable steady state levels of IgG were obtained after one week in the subgroup of patients who received daily infusions for 5 days (Group II).

These data show that trough levels can be maintained with dosing regimens of 100mg/kg once a week.

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

IgG and IgG-complexes are broken down in the cells of the reticulo-endothelial system.

CLINICAL TRIALS

No formal clinical studies have been completed with GAMMANORM, thus all studies reported are based on the GAMMANORM predecessor product.

Studies in Patients with Primary Hypogammaglobulinaemia

Twenty-five (25) adult patients with unspecified primary hypogammaglobulinaemia were treated with human normal immunoglobulin (100 mg/kg/week, 34 to 40 mL/h) for between 10 and 46 months. Patients were aged between 18 and 73 years (mean: 43 years); 10 men and 15 women took part in the study. After 6 months of SC therapy, the serum IgG concentrations

were similar to those obtained after IV infusion and the median value was within the normal range.

In a second study, performed at multiple centres, 165 patients with primary immunodeficiency were followed during SC IgG replacement therapy for between 5 months and over 9 years (median treatment time was 3 years). The 69 women and 96 men enrolled in the study were aged between 13 and 76 years (mean: 43 years). The study population included patients with CVID (n=101), X-linked agammaglobulinaemia (XLA, n=7) and IgG subclass deficiencies with (n=5) or without (n=52) concurrent IgA deficiency. The mean doses at the 4 participating centres were between 220 and 465 mg/kg/month, administered once weekly in most patients.

In the study population with CVID or XLA a significant correlation was found between the monthly immunoglobulin doses given and the serum IgG levels reached after 6 months on SC therapy.

Study in Patients with Secondary Hypogammaglobulinaemia

Seventeen (17) patients with secondary immunodeficiency were treated subcutaneously with normal human immunoglobulin (50 mg/kg/week). After 6 months of therapy mean serum IgG levels increased from 3.1 g/L to 5.5 g/L. Higher doses could be used to achieve IgG levels within the normal range.

The time spent in hospital due to infections decreased from 272 days to 112 days in 11 of the 17 patients. The therapy was associated with a significant reduction in the number of hospital admissions due to infection and in the number of courses of antibiotic treatment compared with before treatment.

Study in Children with Hypogammaglobulinaemia

Eight (8) children with immunodeficiency were treated subcutaneously with normal human immunoglobulin for an average of 3 years (range 1.5 to 6 years).

In total, approximately 1100 infusions were given. The patients received immunoglobulin doses ranging from 58 mg/kg/week to 149 mg/kg/week (mean 97 mg/kg/week) and achieved serum levels of IgG of between 5.2 g/L and 9.6 g/L. Diagnosis, age, dose and serum IgG levels in children treated with SC immunoglobulin transfusions at home are given in the table below.

Diagnosis	Patient number	Age at start of therapy	Dose (mg/kg/week)	Serum IgG level (g/L)
XLA	1	2	87	6.8
	2	8	77	8.0
	3	2.5	92	6.6
CVID	4	7.5	58	7.3
SCID	5	7.5	149	5.2
HIM	6	3.5	80	5.9
	7	2.5	126	6.9
	8	4	104	9.6

Abbreviations: XLA=X-linked agammaglobulinaemia; CVID=common variable immunodeficiency; SCID=severe combined immunodeficiency; HIM=hyper-immunoglobulin M syndrome

INDICATIONS

- Replacement therapy in adults and children with primary immunodeficiency syndromes such as:
 - congenital agammaglobulinaemia and hypogammaglobulinaemia
 - common variable immunodeficiency
 - severe combined immunodeficiencies
 - IgG subclass deficiencies with recurrent infections
- Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

CONTRAINDICATIONS

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA. GAMMANORM is contraindicated in any patient who has a history of allergic reaction to any human immunoglobulin preparation or hypersensitivity to any constituent of the product.

GAMMANORM must not be administered intramuscularly in cases of severe thrombocytopenia and in other disorders of haemostasis.

PRECAUTIONS

GAMMANORM is made from human plasma. Products made from human plasma may contain infectious agents that can cause disease, such as viruses and theoretically Creutzfeldt-Jacob Disease (CJD) agents.

Standard measures to prevent infections resulting from the use of plasma-derived products include:

- i. selection of donors;
- ii. screening of individual donations and plasma pools for specific markers of infection; and
- iii. the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

The viral inactivation/removal steps for GAMMANORM include solvent-detergent treatment and ethanol precipitation step.

Despite this, when plasma-derived products 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.

The measures taken may be of limited value against non-enveloped viruses such as HAV and parvovirus B19. Parvovirus B19 may cause serious reactions in pregnant women who are sero-negative (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. in haemolytic anaemia); however, 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.

Vaccination for patients in receipt of medicinal products made from human plasma should be considered where appropriate.

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.

GAMMANORM must not be administered intravenously. If GAMMANORM is accidentally administered into a blood vessel, patients could develop shock. In case of shock, the current medical standards for shock treatment should be observed.

For intramuscular administration, care should be taken to draw back the plunger of the syringe before injection to ensure that the needle is not in a blood vessel.

The recommended infusion rate should be adhered to (see **DOSAGE AND ADMINISTRATION**). Patients should be closely monitored and carefully observed for any adverse events throughout the infusion period and for at least 20 minutes after the infusion.

Certain adverse drug 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 treatment has been stopped for more than eight weeks.

True hypersensitivity reactions are rare. They can particularly occur in the very rare cases of IgA deficiency with anti-IgA antibodies. These patients should be treated with caution.

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

Potential complications can often be avoided by ensuring that:

- i. patients are not sensitive to human normal immunoglobulin by first injecting the product slowly (see **DOSAGE AND ADMINISTRATION**);
- ii. patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naïve to human normal immunoglobulin, patients switched from an alternative 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.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, the current medical standards for shock treatment should be observed.

Use in Pregnancy

The safety of GAMMANORM for use in human pregnancy has not been established. 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.

Use in lactation

The safety of immunoglobulin G for use during lactation has not been established.

Genotoxicity

No studies have been conducted.

Carcinogenicity

No studies have been conducted.

Interactions with other medicines

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

After administration of this product, an interval of three months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to one year. Therefore patients receiving measles vaccine should have their antibody status checked.

Effects on laboratory tests

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 or D may interfere with some serological tests (e.g. reticulocyte count, haptoglobin and Coombs Test).

Effects on ability to drive and use machines

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

ADVERSE REACTIONS

Adverse reactions for GAMMANORM are rare. In case of severe reactions, the infusion should be stopped and an appropriate treatment should be initiated.

The following adverse reactions have been observed for GAMMANORM:

System Organ Class	Common (>1% and <10%)	Rare (>0.01% and <0.1%)	Very rare (<0.01%)
Immune system disorders	-	hypersensitivity	anaphylactic shock
Nervous system disorders	-	-	Headache Dizziness
Vascular disorders	-	hypotension	-
Gastrointestinal disorders	-	-	Nausea Vomiting
Musculoskeletal and connective tissue disorders	-	-	Back pain Arthralgia
General disorders and administration site conditions	injection site reaction	-	Pyrexia Rigors

			Fatigue
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When large doses are given, it is advisable to administer them in divided doses at different sites.

For information on viral safety, see **PRECAUTIONS**.

DOSAGE AND ADMINISTRATION

Replacement Therapy

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

The dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as guidance.

The dosage regimen should achieve a sustained level of immunoglobulin G (IgG). A loading dose of at least 0.2-0.5 g/kg may be required. After steady state IgG levels have been attained, maintenance doses are administered at repeated intervals to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg.

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

For intramuscular administration see below.

Administration:

GAMMANORM should be administered via the subcutaneous or intramuscular route. In exceptional cases, where subcutaneous administration may not be applicable, low doses of GAMMANORM can be administered via the intramuscular route.

Subcutaneous infusion for home treatment

Home treatment should be initiated by a physician experienced in the guidance of patients for home treatment. The patient will be instructed in the use of a syringe driver, infusion techniques, the keeping of a treatment diary and measures to be taken in the case of severe adverse events.

Subcutaneous infusion with pump

A common dose is 0.6 mL (100 mg) GAMMANORM per kg bodyweight once a week, which may be administered at several infusion sites. Initial infusion rate: 10 mL/hour/pump. The infusion rate may be gradually increased by 1 mL/hour/pump every three to four weeks. The maximum dose administered has been 40 mL/hour using two pumps simultaneously.

When large doses are given, it is advisable to administer them in divided doses at different sites.

Intramuscular injection

Intramuscular injection must be given by a physician or nurse.

Paediatric Patients

In children suffering from PID, as with adults, trough levels should be measured in order to adjust the dose and dosage interval. After steady state IgG levels have been attained, maintenance doses of about 80 to 100 mg/kg/week are usually administered to reach a cumulative monthly dose of the order of 0.4-0.8 g/kg. If home treatment is considered, advice from a physician experienced in the guidance of patients for home treatment should be sought. The patient's parents should be instructed in the use of the application device, infusion techniques, the keeping of a treatment diary and measures to be taken in case of severe adverse events.

Instructions for Use, Handling and Disposal

GAMMANORM should be brought to room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

The product does not contain an antimicrobial agent. It must, therefore be used immediately after opening the ampoule or vial. Product is for single use in one patient only. Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

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

OVERDOSAGE

Consequences of an overdose are unknown.

PRESENTATION

Each ampoule or vial contains 165 mg/mL GAMMANORM, solution for injection or infusion. GAMMANORM comes in the following pack sizes:

- 10 mL of solution in a 10 mL ampoule (type I glass) – pack sizes of 1, 10 or 20 ampoules
- 10 mL of solution in a 20 mL vial (type I glass) – pack sizes of 1, 10 or 20 vials
- 20 mL of solution in a 20 mL vial (type I glass) – pack sizes of 1, 10 or 20 vials

STORAGE CONDITIONS

Shelf life is 3 years.

Store at 2°C to 8°C (Refrigerate. Do not freeze).

Protect from light.

Do not use after expiry date.

The packaged product may be stored below 25°C for a single period of one month. In this case the product expires at the end of the 1-month period. The product may not be returned to

refrigerated storage after storage below 25°C. The date of removal from refrigeration and the new expiry date must be noted on the outer carton.

Medicine Classification

Prescription Medicine

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