IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0521/014/001
Case No: 2050397

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Octapharma Limited

The Zenith Building, **26 Spring Gardens**, **Manchester**, **M2 1AB**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

GAMMANORM, 165 mg/ml solution for injection. Human Normal Immunoglobulin, ampoule.

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **15/10/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

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 (SC/IMIg)

Human normal immunoglobulin 165 mg/ml*
*corresponding to human protein content of which at least 95 % is IgG.

One ampoule of 10 ml contains: 1650 mg * of human normal immunoglobulin.

Distribution of IgG subclasses:

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

IgA max. 82.5 microgram/ml

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear or slightly opalescent and pale yellow to light-brown solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in adults and children in primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency (CVID)
- severe combined immunodeficiency
- IgG subclass deficiencies with recurrent infections

Replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

4.2 Posology and method of administration

Posology

Replacement therapy

The 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 a guidance.

The dosage regimen using the subcutaneous route should achieve a sustained level of 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.

Method of 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 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 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 must be given by a physician or nurse.

Paediatric Patients

Data on children suffering from PID are available. 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.

4.3 Contraindications

Hypersensitivity to any of the components.

Gammanorm must not be given intravenously.

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

4.4 Special warnings and precautions for use

If Gammanorm is accidentally administered into a blood vessel, patients could develop shock.
The recommended infusion rate stated under "4.2 Method of administration" should be adhered to.
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 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 and 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 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 *(see section 4.2, Posology and method of administration);*

- 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, standard medical treatment should be implemented.

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 HIV, HBV and 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.

This medicinal product contains 4.35 mmol (or 100mg) sodium per dose (40 ml). To be taken into consideration by patients on a controlled sodium diet.

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 injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients 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 (reticulocyte count, haptoglobin and Coombs test).

4.6 Pregnancy and lactation

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. 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.

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

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:

Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000,<1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

System Organ Class	**Common**	**Rare**	**Very rare**
Immune system disorders		hypersensitivity	anaphylactic shock
Nervous system disorders			headache, dizziness
Vascular disorders		hypotension	
Gastrointestinal disorders			nausea, vomiting
Musculoskeletal and connective tissue disorders			low back pain, arthralgia
General disorders and administration site conditions	injection site reaction		fever rigors fatigue

For information on viral safety *see section 4.4., Special warnings and precautions for use.*

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 Gammanorm may restore abnormally low immunoglobulin G levels to the normal range.

5.2 Pharmacokinetic properties

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

Data from clinical studies show that trough levels of Gammanorm can be maintained by dosing regimens of 100 mg/kg per 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 reticuloendothelial system.

5.3 Preclinical safety data

There are no relevant data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium chloride
Sodium acetate
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 ($2^{o}C – 8^{o}C$). Keep the ampoule in the outer carton.
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.

6.5 Nature and contents of container

10 ml of solution in an ampoule (Type I glass) – pack size of 1, 10 or 20.

6.6 Special precautions for disposal and other handling

The product 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.

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

7 MARKETING AUTHORISATION HOLDER

Octapharma Limited
The Zenith Building
26 Spring Gardens
Manchester M2 1AB
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 0521/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 2004

Date of last renewal: 15 October 2008

10 DATE OF REVISION OF THE TEXT

February 2009