Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gammabulin S/D 160 mg/ml Solution for injection, 5 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Normal Immunoglobulin (SC/IMIg).
1 ml solution contains:
human protein 160 mg
(of which at least 90 % are immunoglobulin)

Distribution of IgG subclasses:

IgG1	45-75 %
IgG2	20-45 %
IgG3	3-10 %
IgG4	2-8 %

Maximum IgA content: 4.8 mg/ml.
1 vial of 5 ml contains 800 mg human protein (of which at least 90 % are immunoglobulin).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
The product is a clear or slightly opalescent, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Replacement therapy in patients with primary or secondary immunodeficiency.

- Congenital agammagloculinaemia and hypogammaglobulinaemia.
- Common variable immunodeficiency.
- Severe combined immunodeficiency.
- IgG subclass deficiencies with or without concomitant IgA deficiency.
- Specific antibody deficiencies.

Replacement therapy in secondary immunodeficiency disorders such as hypogammaglobulinaemia or low levels if IgG due to low grade B-cell tumours.

4.2 Posology and method of administration

Replacement therapy: human normal immunoglobulin i.m. may prevent serious infection in patients with immunoglobulin deficiency. The dosage should be adjusted to maintain an approximate level of 2g/I of circulating IgG.

The usual posology consists of 0.66 ml/kg body weight (100 mg/kg) given every 3 to 4 weeks, with a double dose given at onset of therapy.

4.2.1 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.
All recommendations and doses given below refer to the 16% solution and are expressed in ml.

Antibody deficiency syndrome in dys-, hypo- and agammaglobulinaemia:
By intramuscular administration of Gammabulin S/D antibody concentrate the frequency and severity of recurring bacterial infections can be reduced. For treatment of immunoglobulin deficiency, it is necessary to achieve and maintain an immunoglobulin level of approximately 200 mg per 100 ml serum.

Initial dosage: 1.8ml per kg bodyweight, e.g. in three single administrations of 0.6 ml/kg bodyweight each at intervals of 24 hours.

Maintenance dose: 0.6ml per kg bodyweight monthly.

The dosage regimen using the subcutaneous route should achieve a sustained trough level of IgG (measured before the next infusion). Depending on the severity and number of infections, loading via the subcutaneous or intravenous route may be required.

After steady state of IgG levels have been attained, the recommended maintenance dose is in the order of at least 0.1 g/kg/week (0.625 ml/kg/week) or 0.2 g/kg (1.25 ml/kg) at intervals of 14 days or 0.4 – 0.6 g/kg/month (2.5 – 3.75 ml/kg/month).

If a steady state of IgG serum level has not been reached prior to subcutaneous treatment, a loading dose of daily subcutaneous infusion (0.1 g/kg) (0.625 ml/kg/week) for approx. 5 days will suffice to achieve a steady state, after which weekly doses can be applied.

In cases of antibody deficiency syndromes, the therapeutic aim is to reach and maintain a serum IgG level of at least 4-6 g/l.

In exceptional cases, where subcutaneous administrations not applicable, the product can be administered intramuscularly.

4.2.2 Method of administration

<u>Subcutaneous</u>
Gammabulin S/D should be administered via subcutaneous infusion.

Subcutaneous infusion for home treatment should be initiated after thorough training by a physician experienced in the guidance of patients for home treatment. In order to obtain steady state Immunoglobulin G serum levels the treatment can then be continued by the patient or guardian. Once the patient is familiar with the method and no unacceptable side effects were observed during the training phase the treatment can be continued by the patient or the guardian in order to reach the steady state of the serum level.

It is recommended to use a battery operated syringe driver for the infusion with an initial administration speed of 10 ml/h/pump.

The infusion speed can be enhanced by 1 ml/h/pump every subsequent infusion. The recommended maximum speed is 20 ml/h/pump. More than one pump can be used simultaneously. The infusion site should be changed every 5-15 ml.

<u>Intramuscular</u>
Intramuscular injection should be given by a physician or nurse.

If large doses are to be administered, it is advisable to split the dose and administer it to various regions. As a general rule, no more than 5 ml in adults and 3 ml in children should be injected in the same anatomical area and no more than 25 ml per day should be administered. Larger doses have been administered safely.

4.3 Contraindications

Hypersensitivity to any of the components.
Injections must not be given intravenously. Gammabulin S/D must not be administered intramuscularly to patients suffering from severe thrombocytopenia or any disorder of haemostasis.

4.4 Special warnings and precautions for use

4.4.1 Precautions

When Gammabulin S/D is administered into a blood vessel, patients could react with shock symptoms. Therefore, it must be ensured that Gammabulin is not administered into a blood vessel.

Precautions should be taken to avoid any sciatic nerve injury, when administering intramuscular injections.

The recommended infusion rate given under *"4.2.2 Method of Administration"* must be closely followed. Patients must be carefully observed for any symptoms throughout the infusion period.

Patients in self-home treatment and the guardian must be trained to be able to detect the early signs of hypotensive reactions that occur very seldom. If severe anaphylactoid reactions occur, the use of an adrenalin pen may prevent further development of anaphylactic reaction. In any case, the patient or guardian should contact a doctor immediately.

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 anaphylactic reactions are rare. They can occur in the seldom cases of IgA deficiency with anti-IgA antibodies. For the treatment of patients with IgA deficiency and anti-IgA antibodies appropriate precautions must be taken as a risk of intolerance, though lower than with the intravenous administration of immunoglobulin, cannot be ruled out.

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.

- that patients are carefully observed 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 observed during the first infusion and for the first hour after the first infusion should be observed 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 systemic reactions like high pulse rate, nausea and cold sweats requires immediate discontinuation of the injection. In case of shock, the current medical standards for shock treatment are to be observed.

In patients at risk, the product should be administered at the minimum infusion-rate practicable.

No specific clinical studies for the treatment of children were conducted with this product. However, data from the literature show that also children will benefit from subcutaneous treatment.

4.4.2 Special Warnings

Gammabulin 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 markets infection and the inclusion/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 reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulin 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 Gammabulin 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

4.5.1 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.

4.5.2 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 (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 therefore should only be given with caution to pregnant women or breast-feeding mothers. However, clinical experience with immunoglobulin suggests that no harmful effects on the course of pregnancy, on the foetus and the neonate are to be expected.

Continued treatment of the pregnant woman is important to ensure that the neonate is born with appropriate passive immunity.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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. However, compared to the intravenous route, very few adverse systemic reactions have occurred with the subcutaneous administration.

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure

and moderate low back pain may occur occasionally.

Occasionally, local pain, soreness, induration, redness, swelling or tenderness may occur at the injection/infusion site. To a large extent, these can be prevented by splitting larger doses into several smaller doses and by injecting/infusing these smaller doses at different injection/infusion sites.

In rare cases itching, bruising, rush, erythema, fever, nausea, vomiting, hypotension, dizziness, and tachycardia have been observed.

In very rare cases anaphylactic/anaphylactoid reactions, such as dyspnea, chest tightness, flushing of the face and skin, feeling of heat, and urticaria, may occur.

For information on viral safety, see “4.4.2 Special Warnings”.

4.9 Overdose

No undesirable effects specifically resulting from overdose are known.

5 PHARMACOLOGICAL PROPERTIES

Gammabulin S/D is a liquid immunoglobulin concentrate for subcutaneous or intramuscular administration, which is manufactured from pooled human plasma.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration. ATC-code: JO6BA01.

Human normal immunoglobulin contains mainly IgG (Immunoglobulin G) 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 material from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma.

Adequate doses of this medicinal product may restore abnormally low IgG levels to the normal range.

5.2 Pharmacokinetic properties

For subcutaneous administration peak levels of human normal immunoglobulin are achieved in the recipient’s circulation after a median delay of about 4 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

For intramuscular administration peak levels of human normal immunoglobulin are achieved in the recipient’s circulation after a delay of about 2-3 days.

5.3 Preclinical safety data

Single dose toxicity testing studies demonstrate that the doses several times higher than the maximum recommended human dose had no toxic effects on laboratory animals. Repeated dose toxicity testing in animals is impracticable due to interference with developing antibodies to heterologous protein.

Since human proteins have not been seen to cause tumourigenic or mutagenic effects, experimental studies particularly in heterologous species, are not considered necessary.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycine
Sodium Chloride
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products and is to be administered as a separate injection/infusion.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8ºC).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

The nature of the product is supplied in vials made of glass hydrolytic class Type I that are closed with bromobutyl rubber stopper.
Gammabulin S/D is available in packages containing either:
1 vial with 5 ml solution for injection/infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

The liquid preparation is clear and pale yellow to light brown; during storage it may show formation of slight turbidity or a small amount of particulate matter. Do not use solution that are more than just slight turbid.

Entered vials must not be reused.

After opening of the vial the product must be used immediately.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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