

1. NAME OF THE MEDICINAL PRODUCT

Flebogamma 5% DIF solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:

Human normal immunoglobulin 50 mg
(purity of at least 97% of IgG)

Each vial of 10 ml contains: 0.5 g of human normal immunoglobulin

Each vial of 50 ml contains: 2.5 g of human normal immunoglobulin

Each vial of 100 ml contains: 5 g of human normal immunoglobulin

Each vial of 200 ml contains: 10 g of human normal immunoglobulin

Each vial of 400 ml contains: 20 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):

IgG₁ 66.6%

IgG₂ 28.5%

IgG₃ 2.7%

IgG₄ 2.2%

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effect:

One ml contains 50 mg of D-sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear or slightly opalescent and colourless or pale yellow.

Flebogamma 5% DIF is isotonic, with an osmolality from 240 to 370 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Replacement therapy in adults, children and adolescents (2-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production (see section 4.4).
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogenic haematopoietic stem cell transplantation (HSCT).
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, children and adolescents (2-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease.

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 is dependent on the indication.

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

Replacement therapy in primary immunodeficiency syndromes

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 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 given once, followed by at least 0.2 g/kg given every three to four weeks.

The dose required to achieve a trough level of 5-6 g/l is of the order of 0.2 - 0.8 g/kg/month. The dose interval when steady state has been reached varies from 3 - 4 weeks.

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

Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections

The recommended dose is 0.2 - 0.4 g/kg every three to four weeks.

Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation

The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5 g/l.

Primary immune thrombocytopenia

There are two alternative treatment schedules:

- 0.8-1 g/kg given on day one; this dose may be repeated once within 3 days
- 0.4 g/kg given daily for two to five days.

The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day over 5 days.

Kawasaki disease

1.6 - 2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

The dose recommendations are summarised in the following table:

| Indication | Dose | Frequency of injections |
|--|---|--|
| Replacement therapy in primary immunodeficiency | - starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg | every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l |
| Replacement therapy in secondary immunodeficiency | 0.2 - 0.4 g/kg | every 3 - 4 weeks to obtain IgG trough level of at least 5 - 6 g/l |
| Congenital AIDS | 0.2 - 0.4 g/kg | every 3 - 4 weeks |
| Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation | 0.2 - 0.4 g/kg | every 3 - 4 weeks to obtain IgG trough level above 5 g/l |

| | | |
|---------------------------------|----------------------------------|---|
| Immunomodulation: | | |
| Primary immune thrombocytopenia | 0.8 - 1 g/kg or 0.4 g/kg/d | on day 1, possibly repeated once within 3 days for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg/d | for 5 days |
| Kawasaki disease | 1.6 - 2 g/kg or 2 g/kg | in divided doses over 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid |

Paediatric population

Flebogamma 5% DIF is contraindicated in children aged 0 to 2 years (see section 4.3).

The posology in children and adolescents (2-18 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 of the above-mentioned conditions.

Method of administration

For intravenous use.

Flebogamma 5% DIF should be infused intravenously at an initial rate of 0.01 - 0.02 ml/kg/min for the first thirty minutes. If well tolerated (see section 4.4), the rate of administration may gradually be increased to a maximum of 0.1 ml/kg/min.

4.3 Contraindications

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

Hypersensitivity to human immunoglobulins, especially in patients with antibodies against IgA.

Fructose intolerance (see section 4.4).

In babies and young children (aged 0-2 years) hereditary fructose intolerance (HFI) may not yet be diagnosed and may be fatal, thus, they must not receive this medicinal product.

4.4 Special warnings and precautions for use

Sorbitol

Each ml of this medicinal product contains 50 mg of sorbitol. Patients with rare hereditary problems of fructose intolerance must not take this medicine.

In persons more than 2 years old with HFI, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal

disorders, apathy, height and weight retardation). Therefore a detailed history with regard to HFI symptoms has to be taken of each patient prior to receiving Flebogamma 5% DIF. In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

Interferences with determination of blood glucose levels are not expected.

Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under section 4.2 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 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 ensuring that patients:

- are not sensitive to human normal immunoglobulin by initially injecting the product slowly (at an initial rate of 0.01-0.02 ml/kg/min)
- 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.

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.

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.

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern.

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

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, cerebral vascular accident (including 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 should 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, and patients with diseases which increase blood viscosity).

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

Acute renal failure

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, hypovolaemia, 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 containing various excipients such as sucrose, glucose and maltose, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain these excipients may be considered. Flebogamma 5% DIF does not contain sucrose, maltose or glucose.

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

Aseptic meningitis syndrome (AMS)

Aseptic meningitis syndrome has been reported to occur in association with IVIg treatment. Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm³, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dl. AMS may occur more frequently in association with high-dose (2 g/kg) IVIg treatment.

Haemolytic anaemia

IVIg products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IVIg therapy due to enhanced red blood cells (RBC) sequestration. IVIg recipients should be monitored for clinical signs and symptoms of haemolysis. (See section 4.8.)

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

Flebogamma 5% DIF is made from human plasma. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

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 viral safety.

It is strongly recommended that every time that Flebogamma 5% DIF 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.

Paediatric population

It is expected that the same interactions than those mentioned for the adults may be presented by 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 therefore should only be given with caution to pregnant women and breast-feeding mothers. IVIg products have been shown to cross the placenta, increasingly after 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, such as dizziness, associated with Flebogamma 5% DIF. 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.

Cases of reversible aseptic meningitis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin. Reversible haemolytic reactions have been observed in patients, especially those with blood groups A, B, and AB. Rarely, haemolytic anaemia requiring transfusion may develop after high dose IVIg treatment (see also Section 4.4).

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

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses.

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

Tabulated list of adverse reactions

The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention:

- very common ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ to $< 1/1,000$)
- very rare ($< 1/10,000$)
- not known (cannot be estimated from the available data)

Within each frequency grouping, adverse reactions are presented in order of decreasing of seriousness.

Frequency of Adverse Reactions (ADRs) in clinical studies with Flebogamma 5% DIF

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency |
|--|--|------------------|
| Nervous system disorders | Headache | Common |
| | Dizziness | Uncommon |
| Vascular disorders | Hypotension, hypertension, diastolic hypertension, blood pressure fluctuations | Uncommon |
| Respiratory, thoracic and mediastinal disorders | Bronchitis, cough, wheezing | Uncommon |
| Gastrointestinal disorders | Diarrhoea, nausea, vomiting, abdominal pain, abdominal pain upper | Uncommon |
| Skin and subcutaneous tissue disorders | Urticaria, rash pruritic, dermatitis contact | Uncommon |
| Musculoskeletal and connective tissue disorders | Back pain, arthralgia, myalgia, muscle cramp | Uncommon |
| General disorders and administration site conditions | Pyrexia, injection site reaction | Common |
| | Rigors, asthenia, pain, infusion site inflammation, injection site oedema, injection site pain, injection site pruritus, injection site swelling, migration of implant | Uncommon |
| Investigations | Coombs test positive, blood pressure systolic decreased, blood pressure systolic increased, body temperature increased | Uncommon |

Paediatric population

The safety results for 3 paediatric patients (those ≤ 16 years old) included in the PID study appeared to be generally similar to those for the overall patient population.

4.9 Overdose

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

Paediatric population

Information on overdose in children has not been established with Flebogamma 5% DIF. However, as in adult population, overdose may lead to fluid overload and hyperviscosity as with any other intravenous immunoglobulins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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 donors. 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. A significant increase in median platelet levels was achieved in a clinical trial in chronic ITP patients (64,000/ μ l) although it did not reach normal levels.

Two clinical trials were performed with Flebogamma 5% DIF, one for replacement therapy in patients with primary immunodeficiency (both in adults and in children above 10 years) and another for immunomodulation in adults patients with immune thrombocytopenic purpura.

5.2 Pharmacokinetic properties

Human normal immunoglobulin 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 3-5 days equilibrium is reached between the intra- and extravascular compartments.

Flebogamma 5% DIF has a half-life of about 30-32 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.

Paediatric population

No differences of the pharmacokinetic properties are expected in the paediatric population.

5.3 Preclinical safety data

Single dose toxicity studies were carried out in rats and mice. The absence of mortality in the non-clinical studies performed with Flebogamma 5% DIF with doses up to 2500 mg/kg, and the lack of any confirmed relevant adverse sign affecting respiratory, circulatory and central nervous system, of the treated animals supports the safety of Flebogamma 5% DIF.

Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-sorbitol
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

2 years.

6.4 Special precautions for storage

Do not store above 30 °C.
Do not freeze.

6.5 Nature and contents of container

10 ml, 50 ml, 100 ml, 200 ml or 400 ml solution in a vial (type II glass) with stopper (chloro-butyl-rubber).

Pack size: 1 vial

Not all pack sizes may be marketed.

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 and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

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

7. MARKETING AUTHORISATION HOLDER

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Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

8. MARKETING AUTHORISATION NUMBER(S)

Flebogamma 5% DIF 0.5g/10 ml, Reg. number: 7136
Flebogamma 5% DIF 2.5 g/50 ml, Reg. number: 7137
Flebogamma 5% DIF 5 g/100 ml, Reg. number: 7138
Flebogamma 5% DIF 10 g/200 ml, Reg. number: 7139
Flebogamma 5% DIF 20 g/400 ml, Reg. number: 7140

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 September 2015

10. DATE OF REVISION OF THE TEXT 09/2015