**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 50 mg/ml 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):
$IgG_1$ 66.6%
$IgG_2$ 28.5%
$IgG_3$ 2.7%
$IgG_4$ 2.2%

Minimum level anti-measles IgG is 4.5 IU/ml.

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.

Excipient 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 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 (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l

*PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (2 - 18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.

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 (in conjunction with acetylsalicylic acid; see 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

## 4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guidance.

*Replacement therapy in primary immunodeficiency syndromes*

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. 3 - 6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) 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 3 - 4 weeks.

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

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

*Replacement therapy in secondary immunodeficiencies (as defined in 4.1)*

The recommended dose is 0.2 - 0.4 g/kg every 3 - 4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase

may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

*Measles pre-/post exposure prophylaxis*

Post-exposure prophylaxis
If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/ml.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis
If a PID/SID patient is at risk of future measles exposure and receives a IVIg maintenance dose of less than 0.53 g/kg every 3 – 4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of >240 mIU/ml of measles antibodies for at least 22 days after infusion.

***Immunomodulation in:***

*Primary immune thrombocytopenia*

There are two alternative treatment schedules:
- 0.8 - 1 g/kg given on day 1; this dose may be repeated once within 3 days.
- 0.4 g/kg given daily for 2 - 5 days. The treatment can be repeated if relapse occurs.

*Guillain Barré syndrome*

0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

*Kawasaki disease*

2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)*

Starting dose: 2 g/kg divided over 2 - 5 consecutive days.
Maintenance doses: 1 g/kg over 1 - 2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

*Multifocal motor neuropathy (MMN)*

Starting dose: 2 g/kg divided over 2 - 5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.
The dose recommendations are summarised in the following table:

| Indication | Dose | Frequency of infusions |
|---|---|---|
| Replacement therapy: | | |
| Primary immunodeficiency syndromes | Starting dose:<br>0.4 - 0.8 g/kg<br><br>Maintenance dose:<br>0.2 - 0.8 g/kg | <br><br><br>every 3 - 4 weeks |
| Secondary immunodeficiencies (as defined in 4.1) | 0.2 - 0.4 g/kg | every 3 - 4 weeks |
| Measles pre/post exposure prophylaxis: | | |
| Post-exposure prophylaxis in susceptible patients | 0.4 g/kg | As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml |
| Post-exposure prophylaxis in PID/SID patients | 0.4 g/kg | In addition to maintenance therapy, given as an extra dose within 6 days of exposure |
| Pre-exposure prophylaxis in PID/SID patients | 0.53 g/kg | If a patient receives a maintenance dose of less than 0.53 g/kg every 3 - 4 weeks, this dose should be increased once to at least 0.53 g/kg |
| Immunomodulation: | | |
| Primary immune thrombocytopenia | 0.8 - 1 g/kg<br><br>or<br><br>0.4 g/kg/d | on day 1, possibly repeated once within 3 days<br><br><br>for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg/d | for 5 days |
| Kawasaki disease | 2 g/kg | in one dose in association with acetylsalicylic acid |
| Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | Starting dose:<br>2 g/kg<br><br>Maintenance dose:<br>1 g/kg | <br>in divided doses over 2 - 5 days<br><br><br>every 3 weeks in divided doses over 1 - 2 days |
| Multifocal motor neuropathy (MMN) | Starting dose:<br>2 g/kg<br><br><br>Maintenance dose:<br>1 g/kg<br><br>or<br><br>2 g/kg | <br>in divided doses over 2 - 5 consecutive days<br><br><br>every 2 - 4 weeks<br><br><br><br>every 4 - 8 weeks in divided doses over 2 - 5 days |

*Paediatric population*

Flebogamma DIF 50 mg/ml 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 must be adjusted to the clinical outcome of the above-mentioned conditions.

*Hepatic impairment*
No evidence is available to require a dose adjustment.

*Renal impairment*
No dose adjustment unless clinically warranted, see section 4.4.

*Elderly*
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration

For intravenous use.
Flebogamma DIF 50 mg/ml should be infused intravenously at an initial rate of 0.01 - 0.02 ml/kg/min for the first thirty minutes. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, 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 (human immunoglobulins) or to any of the excipients (see sections 4.4 and 6.1).

Hereditary 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.

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

## 4.4 Special warnings and precautions for use

**Sorbitol**

**Patients with rare hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.**

**Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.**

**A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.**

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

*Precautions for use*
Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially administering 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 a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the IVIg infusion
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see 4.5)

In case of adverse reaction, either the infusion rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion-related reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.

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
- in patients with an active infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients:
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

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 hypovolaemic 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.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While 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 DIF does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)

AMS has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per $mm^3$, 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

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

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion related acute lung injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1 - 2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration 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 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A and parvovirus B19 viruses.

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 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.

Sodium content

This medicinal product contains less than 7.35 mg sodium per 100 ml, equivalent to 0.37% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Paediatric population
It is recommended to monitor vital signs when administering Flebogamma DIF to paediatric patients.

## 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 medicinal 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.

Loop diuretics
Avoidance of concomitant use of loop diuretics

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. IVIg 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 expected.

Breast-feeding

The safety of this medicinal product for use in breast-feeding mothers has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

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 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 caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion
- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

For safety information 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 (≥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)

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

**Source of the safety database from clinical trials and post-authorisation safety studies in a total of 128 patients exposed to Flebogamma DIF 50 mg/ml (with a total of 1318 infusions)**

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency per patient | Frequency per infusion |
|---|---|---|---|
| Infections and infestations | Nasopharyngitis | Uncommon | Uncommon |
| Immune system disorders | Hypersensitivity | Uncommon | Rare |
| Psychiatric disorders | Abnormal behaviour | Uncommon | Rare |
| Nervous system disorders | Migraine | Uncommon | Rare |
| | Headache | Very Common | Common |
| | Dizziness | Common | Uncommon |
| Cardiac disorders | Tachycardia | Common | Common |
| | Cardiovascular disorder | Uncommon | Rare |
| Vascular disorders | Hypertension | Common | Uncommon |
| | Diastolic hypertension | Common | Uncommon |
| | Systolic hypertension | Uncommon | Uncommon |
| | Hypotension | Common | Common |
| | Diastolic hypotension | Common | Common |
| | Blood pressure fluctuation | Uncommon | Rare |
| | Flushing | Uncommon | Rare |
| Respiratory, thoracic and mediastinal disorders | Bronchitis | Common | Uncommon |
| | Dyspnoea | Uncommon | Rare |
| | Asthma | Uncommon | Rare |
| | Epistaxis | Uncommon | Rare |
| | Productive cough | Uncommon | Uncommon |
| | Cough | Uncommon | Rare |
| | Wheezing | Common | Uncommon |
| | Laryngeal pain | Uncommon | Rare |
| | Nasal discomfort | Uncommon | Rare |
| Gastrointestinal disorders | Diarrhoea | Common | Uncommon |
| | Vomiting | Common | Uncommon |
| | Abdominal pain upper | Common | Uncommon |
| | Abdominal pain | Common | Uncommon |
| | Nausea | Common | Uncommon |
| Skin and subcutaneous tissue disorders | Rash pruritic | Uncommon | Uncommon |
| | Dermatitis contact | Uncommon | Rare |
| | Urticaria | Common | Uncommon |
| | Pruritus | Uncommon | Uncommon |
| | Rash | Uncommon | Rare |
| | Hyperhidrosis | Uncommon | Rare |

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency per patient | Frequency per infusion |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | Arthralgia | Common | Uncommon |
| | Myalgia | Common | Uncommon |
| | Back pain | Common | Uncommon |
| | Neck pain | Uncommon | Rare |
| | Pain in extremity | Uncommon | Rare |
| | Muscle spasms | Uncommon | Rare |
| Renal and urinary disorders | Urinary retention | Uncommon | Rare |
| General disorders and administration site conditions | Pyrexia | Very Common | Common |
| | Chest pain | Uncommon | Rare |
| | Oedema peripheral | Uncommon | Rare |
| | Chills | Common | Uncommon |
| | Rigors | Common | Uncommon |
| | Pain | Common | Uncommon |
| | Asthenia | Uncommon | Rare |
| | Injection site reaction | Common | Uncommon |
| | Infusion site erythema | Uncommon | Rare |
| | Infusion site extravasation | Uncommon | Rare |
| | Injection site pruritus | Uncommon | Rare |
| | Infusion site inflammation | Uncommon | Rare |
| | Injection site swelling | Uncommon | Rare |
| | Injection site oedema | Uncommon | Rare |
| | Infusion site pain | Uncommon | Rare |
| | Injection site pain | Uncommon | Rare |
| Investigations | Blood pressure increased | Uncommon | Rare |
| | Blood pressure systolic increased | Common | Uncommon |
| | Blood pressure systolic decreased | Uncommon | Uncommon |
| | Body temperature increased | Common | Uncommon |
| | Alanine aminotransferase increased | Uncommon | Rare |
| | Coombs test positive | Common | Uncommon |
| Injury, poisoning and procedural complications | Infusion related reaction | Uncommon | Uncommon |

Description of selected adverse reactions

The most reported post-marketing ADRs received since the product was authorised for both concentrations were chest pain, flushing, blood pressure increased and decreased, malaise, dyspnoea, nausea, vomiting, pyrexia, back pain, headache and chills.

Paediatric population

The safety results for 29 paediatric patients (those ≤ 17 years old) included in the PID studies were evaluated. It was observed that the proportion of headache, pyrexia, tachycardia and hypotension in children was higher than in adults. Assessment of vital signs in clinical trials of the paediatric population did not indicate any pattern of clinically relevant changes.

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 the national reporting system listed in Appendix V.

## 4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including infants, elderly patients or patients with cardiac or renal impairment (see section 4.4).

Paediatric population

Information on overdose in children has not been established with Flebogamma 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/µl) although it did not reach normal levels.

Three clinical trials were performed with Flebogamma DIF, two for replacement therapy in patients with primary immunodeficiency (one in both adults and in children above 10 years and another in children between 2 to 16 years) and another for immunomodulation in adult patients with immune thrombocytopenic purpura.

## 5.2 Pharmacokinetic properties

Absorption
Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution
It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination
Flebogamma DIF 50 mg/ml 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.

Measles pre-/post exposure prophylaxis (see references)

No clinical studies have been performed in susceptible patients regarding *Measles pre-/post exposure prophylaxis*.

Flebogamma DIF 50mg/ml meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

- Serum titer at 13.5 days = 270 mIU/ml (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titer of 120 mIU/ml
- Serum titer at 22 days (t1/2) = 180 mIU/ml (dose: 0.4 g/kg)
- Serum titer at 22 days (t1/2) = 238.5 mIU/ml (dose: 0.53 g/kg –pre-exposure prophylaxis)

### 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 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 support the safety of Flebogamma 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, nor with any other IVIg products.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Do not store above 30 ºC.
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 at room temperature (no more than 30 ºC) 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 product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 8. MARKETING AUTHORISATION NUMBER

EU/1/07/404/001-005

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2007

Date of latest renewal: 24 April 2017

## 10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 100 mg/ml solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:
Human normal immunoglobulin ……..100 mg
(purity of at least 97% IgG)

Each vial of 50 ml contains: 5 g of human normal immunoglobulin
Each vial of 100 ml contains: 10 g of human normal immunoglobulin
Each vial of 200 ml contains: 20 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
$IgG_1$ 66.6%
$IgG_2$ 27.9%
$IgG_3$ 3.0%
$IgG_4$ 2.5%

Minimum level anti-measles IgG is 9 IU/ml.

The maximum IgA content is 100 micrograms/ml.

Produced from the plasma of human donors.

Excipient 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 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 (PID) with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l

* PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines

Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (2 - 18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre-/post exposure prophylaxis and active immunisation.

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 (in conjunction with acetylsalicylic acid; see 4.2)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

## 4.2 Posology and method of administration

IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.

Posology

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients.

The following dose regimens are given as a guidance.

*Replacement therapy in primary immunodeficiency syndromes*

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. 3 - 6 months are required after the initiation of therapy for equilibration (steady-state IgG levels) 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 3 - 4 weeks.

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

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

*Replacement therapy in secondary immunodeficiencies (as defined in 4.1)*

The recommended dose is 0.2 - 0.4 g/kg every 3 - 4 weeks.

IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase

may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free.

*Measles pre-/post exposure prophylaxis*

Post-exposure prophylaxis
If a susceptible patient has been exposed to measles, a dose of 0.4 g/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 0.4 g/kg possibly to be repeated once after 2 weeks may be necessary to maintain the serum level > 240 mIU/ml.

If a PID/SID patient has been exposed to measles and regularly receives IVIg infusions, it should be considered to administer an extra dose of IVIg as soon as possible and within 6 days of exposure. A dose of 0.4 g/kg should provide a serum level > 240 mIU/ml of measles antibodies for at least 2 weeks.

Pre-exposure prophylaxis
If a PID/SID patient is at risk of future measles exposure and receives a IVIg maintenance dose of less than 0.53 g/kg every 3 – 4 weeks, this dose should be increased once to 0.53 g/kg. This should provide a serum level of >240 mIU/ml of measles antibodies for at least 22 days after infusion.

***Immunomodulation in:***

*Primary immune thrombocytopenia*

There are two alternative treatment schedules:
- 0.8 - 1 g/kg given on day 1; this dose may be repeated once within 3 days.
- 0.4 g/kg given daily 2 - 5 days. The treatment can be repeated if relapse occurs.

*Guillain Barré syndrome*

0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).

*Kawasaki disease*

2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

*Chronic inflammatory demyelinating polyneuropathy (CIDP)*

Starting dose: 2 g/kg divided over 2 - 5 consecutive days.
Maintenance doses: 1 g/kg over 1 - 2 consecutive days every 3 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.
If the treatment is effective long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.

*Multifocal motor neuropathy (MMN)*

Starting dose: 2 g/kg divided over 2 - 5 consecutive days.
Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
The treatment effect should be evaluated after each cycle; if no treatment effect is seen after 6 months, the treatment should be discontinued.

If the treatment is effective, long-term treatment should be subject to the physician's discretion based upon the patient response and maintenance response. The dosing and intervals may have to be adapted according to the individual course of the disease.
The dose recommendations are summarised in the following table:

| Indication | Dose | Frequency of infusions |
|---|---|---|
| Replacement therapy: | | |
| Primary immunodeficiency syndromes | Starting dose:<br>0.4 - 0.8 g/kg<br><br>Maintenance dose:<br>0.2 - 0.8 g/kg | <br><br><br><br>every 3 - 4 weeks |
| Secondary immunodeficiencies (as defined in 4.1) | 0.2 - 0.4 g/kg | every 3 - 4 weeks |
| Measles pre/post exposure prophylaxis: | | |
| Post-exposure prophylaxis in susceptible patients | 0.4 g/kg | As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml |
| Post-exposure prophylaxis in PID/SID patients | 0.4 g/kg | In addition to maintenance therapy, given as an extra dose within 6 days of exposure |
| Pre-exposure prophylaxis in PID/SID patients | 0.53 g/kg | If a patient receives a maintenance dose of less than 0.53 g/kg every 3 - 4 weeks, this dose should be increased once to at least 0.53 g/kg |
| Immunomodulation: | | |
| Primary immune thrombocytopenia | 0.8 - 1 g/kg<br><br>or<br><br>0.4 g/kg/d | on day 1, possibly repeated once within 3 days<br><br><br>for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg/d | for 5 days |
| Kawasaki disease | 2 g/kg | in one dose in association with acetylsalicylic acid |
| Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | Starting dose:<br>2 g/kg<br><br>Maintenance dose:<br>1 g/kg | <br>in divided doses over 2 - 5 days<br><br><br>every 3 weeks in divided doses over 1 - 2 days |
| Multifocal motor neuropathy (MMN) | Starting dose:<br>2 g/kg<br><br><br>Maintenance dose:<br>1 g/kg<br><br>or<br><br>2 g/kg | <br>in divided doses over 2 - 5 consecutive days<br><br><br><br>every 2 - 4 weeks<br><br><br><br>every 4 - 8 weeks in divided doses over 2 - 5 days |

*Paediatric population*

Flebogamma DIF 100 mg/ml 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 must be adjusted to the clinical outcome of the above-mentioned conditions.

*Hepatic impairment*
No evidence is available to require a dose adjustment.

*Renal impairment*
No dose adjustment unless clinically warranted, see section 4.4.

*Elderly*
No dose adjustment unless clinically warranted, see section 4.4.

Method of administration

For intravenous use.
Flebogamma DIF 100 mg/ml should be infused intravenously at an initial rate of 0.01 ml/kg/min for the first thirty minutes. See section 4.4. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. If well tolerated, advance to 0.02 ml/kg/min for the second 30 minutes. Again, if tolerated, advance to 0.04 ml/kg/min for the third 30 minutes. If the patient tolerates the infusion well, additional increments of 0.02 ml/kg/min may be made at 30-minute intervals up to a maximum of 0.08 ml/kg/min.

It has been reported that the frequency of adverse reactions to IVIg increases with the infusion rate. Infusion rates during the initial infusions should be slow. If there are no adverse reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate. For patients experiencing adverse reactions, it is advisable to reduce the infusion rate in subsequent infusions and limit the maximum rate to 0.04 ml/kg/min or administer IVIg at a 5% concentration (see section 4.4).

## 4.3 Contraindications

Hypersensitivity to the active substance (human immunoglobulins) or to any of the excipients (see sections 4.4 and 6.1).

Hereditary 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.

Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA-containing product can result in anaphylaxis.

## 4.4 Special warnings and precautions for use

**Sorbitol**

**Patients with rare hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.**

**Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.**

**A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.**

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

*Precautions for use*
Potential complications can often be avoided by ensuring that patients:
- are not sensitive to human normal immunoglobulin by initially administering the product slowly (at an initial rate of 0.01 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 a controlled healthcare setting in order to detect potential adverse signs and to ensure that emergency treatment can be administered immediately should problems occur. All other patients should be observed for at least 20 minutes after administration

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the IVIg infusion
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics (see 4.5)

In case of adverse reaction, either infusion the rate must be reduced or the infusion stopped. The treatment required depends on the nature and severity of the adverse reaction.

Infusion-related reaction

Certain adverse reactions (e.g. headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension) 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.

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
- in patients with an active infection or underlying chronic inflammation

Hypersensitivity

Hypersensitivity reactions are rare.

Anaphylaxis can develop in patients:
- with undetectable IgA who have anti-IgA antibodies
- who had tolerated previous treatment with human normal immunoglobulin

In case of shock, standard medical treatment for shock should be implemented.

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 hypovolaemic 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.

Renal parameters should be assessed prior to infusion of IVIg, particularly in patients judged to have a potential increased risk for developing acute renal failure, and again at appropriate intervals. In patients at risk for acute renal failure, IVIg products should be administered at the minimum rate of infusion and dose practicable. In case of renal impairment, IVIg discontinuation should be considered.

While 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 DIF does not contain sucrose, maltose or glucose.

Aseptic meningitis syndrome (AMS)

AMS has been reported to occur in association with IVIg treatment. The syndrome usually begins within several hours to 2 days following IVIg treatment. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per $mm^3$, 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.

Patients exhibiting such signs and symptoms should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis.

Discontinuation of IVIg treatment has resulted in remission of AMS within several days without sequelae.

Haemolytic anaemia

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

Neutropenia/Leukopenia

A transient decrease in neutrophil count and/or episodes of neutropenia, sometimes severe, have been reported after treatment with IVIg. This typically occurs within hours or days after IVIg administration and resolves spontaneously within 7 to 14 days.

Transfusion Related Acute Lung Injury (TRALI)

In patients receiving IVIg, there have been some reports of acute non-cardiogenic pulmonary oedema [Transfusion Related Acute Lung Injury (TRALI)]. TRALI is characterised by severe hypoxia, dyspnoea, tachypnoea, cyanosis, fever and hypotension. Symptoms of TRALI typically develop during or within 6 hours after a transfusion, often within 1 - 2 hours. Therefore, IVIg recipients must be monitored for and IVIg infusion must be immediately stopped in case of pulmonary adverse reactions. TRALI is a potentially life-threatening condition requiring immediate intensive-care-unit management.

Interference with serological testing

After the administration 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 Coomb's 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 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 human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped hepatitis A and parvovirus B19 viruses.

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 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.

Sodium content

This medicinal product contains less than 7.35 mg sodium per 100 ml, equivalent to 0.37% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Post-authorisation Safety Study

A Post-Authorisation Safety Study suggested a higher rate of infusions associated with potentially related adverse events for Flebogamma DIF 100 mg/ml compared to Flebogamma DIF 50 mg/ml (see section 5.1).

Paediatric population
It is recommended to monitor vital signs when administering Flebogamma DIF to paediatric patients.

## 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 medicinal 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.

Loop diuretics
Avoidance of concomitant use of loop diuretics

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. IVIg 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 expected.

Breast-feeding

The safety of this medicinal product for use in breast-feeding mothers has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.

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 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 caused by human normal immunoglobulins (in decreasing frequency) encompass (see also Section 4.4):

- chills, headache, dizziness, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain
- reversible haemolytic reactions; especially in those patients with blood groups A, B, and AB and (rarely) haemolytic anaemia requiring transfusion

- (rarely) a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration
- (rarely) transient cutaneous reactions (including cutaneous lupus erythematosus - frequency unknown)
- (very rarely) thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses
- cases of reversible aseptic meningitis
- cases of increased serum creatinine level and/or occurrence of acute renal failure
- cases of Transfusion Related Acute Lung Injury (TRALI)

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

Tabulated list of adverse reactions
Increase in the frequency of adverse reactions through the clinical trials likely related to the increased infusion rate has been observed (see section 4.2).

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 (≥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)

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

**Source of the safety database from clinical trials and post-authorisation safety studies in a total of 160 patients exposed to Flebogamma DIF 100 mg/ml (with a total of 915 infusions)**

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency per patient | Frequency per infusion |
|---|---|---|---|
| Infections and infestations | Meningitis aseptic | Uncommon | Uncommon |
| | Urinary tract infection | Uncommon | Uncommon |
| | Influenza | Uncommon | Uncommon |
| Blood and lymphatic system disorders | Bicytopenia | Uncommon | Uncommon |
| | Leukopenia | Uncommon | Uncommon |
| Immune system disorders | Hypersensitivity | Common | Uncommon |
| Metabolism and nutrition disorders | Decreased appetite | Uncommon | Uncommon |
| Psychiatric disorders | Insomnia | Uncommon | Uncommon |
| | Restlessness | Uncommon | Uncommon |
| Nervous system disorders | Syncope | Uncommon | Uncommon |
| | Radiculopathy | Uncommon | Uncommon |
| | Headache | Very common | Very common |
| | Tremor | Common | Uncommon |
| | Dizziness | Common | Uncommon |
| Eye disorders | Maculopathy | Uncommon | Uncommon |
| | Vision blurred | Uncommon | Uncommon |
| | Conjunctivitis | Uncommon | Uncommon |
| | Photophobia | Common | Uncommon |

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency per patient | Frequency per infusion |
|---|---|---|---|
| Ear and labyrinth disorders | Vertigo | Common | Uncommon |
| | Ear pain | Uncommon | Uncommon |
| Cardiac disorders | Cyanosis | Uncommon | Uncommon |
| | Tachycardia | Common | Common |
| Vascular disorders | Thrombosis | Uncommon | Uncommon |
| | Lymphoedema | Uncommon | Uncommon |
| | Hypertension | Common | Uncommon |
| | Diastolic hypertension | Common | Uncommon |
| | Systolic hypertension | Uncommon | Uncommon |
| | Hypotension | Common | Common |
| | Haematoma | Uncommon | Uncommon |
| | Flushing | Uncommon | Uncommon |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea | Uncommon | Uncommon |
| | Epistaxis | Uncommon | Uncommon |
| | Sinus pain | Uncommon | Uncommon |
| | Upper-airway cough syndrome | Uncommon | Uncommon |
| | Nasal congestion | Uncommon | Uncommon |
| | Wheezing | Common | Uncommon |
| Gastrointestinal disorders | Diarrhoea | Common | Uncommon |
| | Haematemesis | Uncommon | Uncommon |
| | Vomiting | Common | Common |
| | Abdominal pain upper | Common | Uncommon |
| | Abdominal pain | Common | Uncommon |
| | Abdominal discomfort | Uncommon | Uncommon |
| | Abdominal distension | Uncommon | Uncommon |
| | Nausea | Very common | Common |
| | Flatulence | Common | Uncommon |
| | Dry mouth | Uncommon | Uncommon |
| Skin and subcutaneous tissue disorders | Ecchymosis | Uncommon | Uncommon |
| | Purpura | Uncommon | Uncommon |
| | Pruritus | Common | Uncommon |
| | Rash | Common | Uncommon |
| | Erythema | Uncommon | Uncommon |
| | Palmar erythema | Uncommon | Uncommon |
| | Acne | Uncommon | Uncommon |
| | Hyperhidrosis | Uncommon | Uncommon |
| | Alopecia | Uncommon | Uncommon |
| Musculoskeletal and connective tissue disorders | Arthralgia | Uncommon | Uncommon |
| | Myalgia | Common | Common |
| | Back pain | Common | Common |
| | Neck pain | Common | Uncommon |
| | Pain in extremity | Common | Uncommon |
| | Musculoskeletal discomfort | Uncommon | Uncommon |
| | Limb discomfort | Common | Uncommon |
| | Muscle spasms | Common | Uncommon |
| | Muscle tightness | Common | Uncommon |

| MedDRA System Organ Class (SOC) | Adverse reaction | Frequency per patient | Frequency per infusion |
|---|---|---|---|
| General disorders and administration site conditions | Influenza like illness | Uncommon | Uncommon |
| | Pyrexia | Very common | Common |
| | Chest pain | Common | Uncommon |
| | Chest discomfort | Common | Uncommon |
| | Oedema peripheral | Common | Uncommon |
| | Chills | Common | Common |
| | Rigors | Very common | Common |
| | Malaise | Common | Uncommon |
| | Feeling cold | Common | Uncommon |
| | Fatigue | Common | Uncommon |
| | General physical health deterioration | Uncommon | Uncommon |
| | Pain | Common | Uncommon |
| | Feeling jittery | Uncommon | Uncommon |
| | Infusion site reaction | Common | Uncommon |
| | Infusion site erythema | Uncommon | Uncommon |
| | Infusion site pain | Uncommon | Uncommon |
| Investigations | Haemoglobin decreased | Uncommon | Uncommon |
| | Body temperature increased | Common | Common |
| | Heart rate increased | Common | Uncommon |
| | Blood pressure increased | Common | Uncommon |
| | Blood pressure systolic increased | Common | Uncommon |
| | Heart rate decreased | Uncommon | Uncommon |
| | Blood pressure diastolic decreased | Common | Uncommon |
| | Blood pressure systolic decreased | Uncommon | Uncommon |
| | Reticulocyte count increased | Uncommon | Uncommon |
| Injury, poisoning and procedural complications | Contusion | Common | Uncommon |
| | Infusion related reaction | Uncommon | Uncommon |

Description of selected adverse reactions

The most reported post-marketing ADRs received since the product was authorised for both concentrations were chest pain, flushing, blood pressure increased and decreased, malaise, dyspnoea, nausea, vomiting, pyrexia, back pain, headache and chills.

Paediatric population

The safety results for 4 paediatric patients (those ≤ 17 years old) included in the PID study and the results for the 13 children (aged 3 to 16 years old) included in the ITP study were evaluated. It was observed that the proportion of headache, chills, pyrexia, nausea, vomiting, hypotension, heart rate increase and back pain in children was higher than in adults. Cyanosis was reported in one child but not in adults. Assessment of vital signs in clinical trials of the paediatric population did not indicate any pattern of clinically relevant changes.

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 the national reporting system listed in Appendix V.

## 4.9 Overdose

Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including infants, elderly patients or patients with cardiac or renal impairment (see section 4.4).

Paediatric population

Information on overdose in children has not been established with Flebogamma 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.

Three clinical trials were performed with Flebogamma DIF, one for replacement therapy in patients with primary immunodeficiency (in both adults and in children above 6 years) and two for immunomodulation, in patients with immune thrombocytopenic purpura (one in adult patients and another in both adults and in children between 3 and 16 years).

In a Post-authorisation Safety Study that included 66 patients, Flebogamma DIF 100 mg/ml showed a higher rate (18.46%, n=24/130) of infusions associated with potentially related adverse events than Flebogamma DIF 50 mg/ml (2.22%, n=3/135). However, one subject treated with Flebogamma DIF 100 mg/ml presented mild episodes of headache in all infusions and one more patient had 2 episodes of pyrexia in 2 infusions. It is worth considering that these 2 subjects contributed to the higher frequency of infusions with reactions in this group. There were no other subjects with more than 1 infusion with adverse reactions in both groups.

### 5.2 Pharmacokinetic properties

Absorption
Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration.

Distribution
It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Elimination
Flebogamma DIF 100 mg/ml has a half-life of about 34 - 37 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.

Measles pre-/post exposure prophylaxis (see references)

No clinical studies have been performed in susceptible patients regarding *Measles pre-/post exposure prophylaxis*.

Flebogamma DIF 100 mg/ml meets the minimum measles antibody potency specification threshold of 0.36 x Center for Biologics Evaluation and Research (CBER) Standard. The dosing is based on pharmacokinetic calculations which take body weight, blood volume and half-life of immunoglobulins into consideration. These calculations predict a:

- Serum titer at 13.5 days = 270 mIU/ml (dose: 0.4 g/kg) This provides a safety margin more than double that of the WHO protective titer of 120 mIU/ml
- Serum titer at 22 days (t1/2) = 180 mIU/ml (dose: 0.4 g/kg)
- Serum titer at 22 days (t1/2) = 238.5 mIU/ml (dose: 0.53 g/kg –pre-exposure prophylaxis)

### 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 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 support the safety of Flebogamma 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, nor with any other IVIg products.

### 6.3 Shelf life

2 years.

### 6.4 Special precautions for storage

Do not store above 30 ºC.
Do not freeze.

### 6.5 Nature and contents of container

50 ml, 100 ml or 200 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 at room temperature (no more than 30 ºC) 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 product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/404/006-008

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2007

Date of latest renewal: 24 April 2017

## 10. DATE OF REVISION OF THE TEXT

MM/YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Instituto Grifols, S.A.
Polígono Levante
Can Guasc, 2,
E-08150 Parets del Vallès
Barcelona, Spain

Name and address of the manufacturer responsible for batch release

Instituto Grifols, S.A.
Polígono Levante
Can Guasc, 2
E-08150 Parets del Vallès
Barcelona, Spain

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON** (0.5 g)

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 50 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 50 mg of human normal immunoglobulin (IVIg) of which at least 97% is IgG.

0.5 g / 10 ml

## 3. LIST OF EXCIPIENTS

D-sorbitol, water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/404/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON** (2.5 g, 5 g, 10 g and 20 g)

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 50 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 50 mg of human normal immunoglobulin (IVIg) of which at least 97% is IgG.
The maximum IgA content is 50 micrograms/ml.
2.5 g / 50 ml
5 g / 100 ml
10 g / 200 ml
20 g / 400 ml

## 3. LIST OF EXCIPIENTS

D-sorbitol, water for injections. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use.

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/404/002
EU/1/07/404/003
EU/1/07/404/004
EU/1/07/404/005

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL** (5 g, 10 g and 20 g)

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 50 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 50 mg of human normal immunoglobulin (IVIg) of which at least 97% is IgG.

## 3. LIST OF EXCIPIENTS

D-sorbitol, water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

5 g / 100 ml
10 g / 200 ml
20 g / 400 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use

Read the package leaflet before use.

To hang pull here

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL** (0.5 g and 2.5 g)

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Flebogamma DIF 50 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)
For intravenous use

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 g / 10 ml
2.5 g / 50 ml

## 6. OTHER

To hang pull here

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON** (5 g, 10 g and 20 g)

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 100 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 100 mg of human normal immunoglobulin (IVIg) of which at least 97% is IgG.
The maximum IgA content is 100 micrograms/ml.
5 g / 50 ml
10 g / 100 ml
20 g / 200 ml

## 3. LIST OF EXCIPIENTS

D-sorbitol, water for injections. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 vial

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/404/006
EU/1/07/404/007
EU/1/07/404/008

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL** (5 g)

**1. NAME OF THE MEDICINAL PRODUCT**

Flebogamma DIF 100 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

**3. LIST OF EXCIPIENTS**

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion

5 g / 50 ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

To hang pull here
For intravenous use

Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

**12. MARKETING AUTHORISATION NUMBER(S)**

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

**17. UNIQUE IDENTIFIER – 2D BARCODE**

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL** (10 g and 20 g)

## 1. NAME OF THE MEDICINAL PRODUCT

Flebogamma DIF 100 mg/ml solution for infusion
Human normal immunoglobulin (IVIg)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One ml contains 100 mg of human normal immunoglobulin (IVIg) of which at least 97% is IgG.

## 3. LIST OF EXCIPIENTS

D-sorbitol, water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

10 g / 100 ml
20 g / 200 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

To hang pull here
For intravenous use

Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 30 ºC. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

## 12. MARKETING AUTHORISATION NUMBER(S)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Flebogamma DIF 50 mg/ml solution for infusion**
Human normal immunoglobulin (IVIg)

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Flebogamma DIF is and what it is used for

**What Flebogamma DIF is**

Flebogamma DIF contains human normal immunoglobulin, highly purified protein extracted from human plasma (part of the blood of donors). This medicine belongs to the group of medicines called intravenous immunoglobulins. These are used to treat conditions where the body's defence system against disease is not working properly.

**What Flebogamma DIF is used for**

Treatment of adults, children and adolescents (2 - 18 years) who do not have sufficient antibodies (Flebogamma DIF is used as replacement therapy). There are two groups:

- Patients with Primary Immunodeficiency Syndromes (PID), an inborn lack of antibodies (group 1)

- Patients with Secondary Immunodeficiency Syndromes (SID) with severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l (group 2)

*PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Treatment of susceptible adults, children and adolescents (2 - 18 years) in whom active vaccination against measles is not indicated or not advised.

Treatment of adults, children and adolescents (2 - 18 years) with certain autoimmune disorders (immunomodulation). There are five groups:

- Primary immune thrombocytopenia (ITP), a condition where the number of platelets in the blood stream is greatly reduced. Platelets form an important part of the clotting process and a reduction in their numbers may cause unwanted bleeding and bruising. The product is also used in patients at high risk of bleeding or prior to surgery to correct the platelet count.

- Guillain Barré syndrome, where the immune system damages the nerves and hinders them from working properly.

- Kawasaki disease (in this case in conjunction with acetylsalicylic acid therapy), an illness in children where the blood vessels (arteries) in the body become enlarged.

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a rare and progressive disease causing limb weakness, numbness, pain and fatigue.

- Multifocal motor neuropathy (MMN), a rare disease causing slow progressive asymmetric limb weakness without sensory loss.

## 2. What you need to know before you use Flebogamma DIF

### Do not use Flebogamma DIF

- If you are allergic to human normal immunoglobulin or any of the other ingredients of this medicine (listed in section 6).

- If you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.

- If you have fructose intolerance, a quite rare genetic condition where the enzyme for breaking down fructose is not produced. In babies and young children (aged 0 - 2 years) hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they must not receive this medicine (see special warnings about excipients at the end of this section).

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Flebogamma DIF.

Certain side effects may occur more frequently:
- in case of high rate of infusion.
- if you are having Flebogamma DIF for the first time, or it has been switched from an alternative human normal immunoglobulin (IVIg) product, or it is a long time since your last infusion (e.g. several weeks). You will be watched carefully until an hour after the infusion to detect potential side effects.

Allergic reactions are rare. It may happen particularly if you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.

Patients with pre-existing risk factors

Please tell your doctor if you have any other condition and/or illness, as control is required in patients with pre-existing risk factors for thrombotic events (formation of blood clots inside your blood). In particular, tell your doctor if you have:
- diabetes
- high blood pressure
- history of vascular disease or thrombosis
- overweight
- blood volume decrease
- diseases which increase blood viscosity
- age over 65

Patients with a kidney problem

If you have a renal disease and you are receiving Flebogamma DIF for the first time, you may suffer a problem in your kidneys.

Your doctor will consider your risk factors and take measures such as to decrease the rate of infusion or to stop the treatment.

Effects on blood tests

After receiving Flebogamma DIF, the results of certain blood tests (serological tests) may be interfered for a certain time. If you have a blood test after receiving Flebogamma DIF, please tell the analyst or your doctor that you have been given this medicine.

Special safety warning

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of Flebogamma DIF, the name and batch number of the medicine (stated on the label and carton after Lot) are recorded in order to maintain a record of the batches used.

**Children and adolescents**

Vital signs (body temperature, blood pressure, heart rate and respiratory rate) should be observed during the infusion of Flebogamma DIF.

**Other medicines and Flebogamma DIF**

- Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
- Effects on vaccines: Flebogamma DIF may reduce the effectiveness of certain types of vaccines (live attenuated virus vaccines). In case of rubella, mumps and varicella a period of up to 3 months should elapse after receiving this medicine and before receiving these vaccines. In case of measles, the period is up to 1 year.

- You should avoid the concomitant use of medicines that increase the excretion of water from your body (loop diuretics) during treatment with Flebogamma DIF.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

Patients may experience reactions (for example dizziness or nausea) during treatment, which might affect the ability to drive and use machines.

**Flebogamma DIF contains sorbitol**

**Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.**

**You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.**

**Flebogamma DIF contains sodium**

This medicine contains less than 7.35 mg sodium (main component of cooking/table salt) in 100 ml. This is equivalent to 0.37% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to use Flebogamma DIF

Flebogamma DIF is given by injection into your veins (intravenous administration). It may be self-administered if you have been fully trained by hospital staff or a health care professional. You must make up the infusion in exactly the way you have been shown in order to stop germs getting in. You must never self-administer it alone; a healthcare professional who is experienced in medicine preparation, cannulation, administration and monitoring of adverse reactions must be always present.

The dose that you will be given will depend on your illness and body weight and will be worked out by your doctor (please see section “Instructions for healthcare professionals” given at the end of this leaflet).

At the beginning of your infusion you will receive Flebogamma DIF at a slow rate (0.01 - 0.02 ml/kg/min). Depending on how comfortable you feel, your doctor may then gradually increase the infusion rate (up to 0.1 ml/kg/min).

**Use in children of more than 2 years old**

The dose in children is not considered to be different to that of adults as it will be given depending on the illness and body weight of the children.

**If you use more Flebogamma DIF than you should**

If you get more Flebogamma DIF than you should, your body may take on too much fluid. This could particularly happen when you are a patient at risk, e.g. an elderly patient or a patient having problems with your heart or your kidneys. Tell your doctor immediately.

**If you forget to use Flebogamma DIF**

Tell your doctor or pharmacist immediately and follow his/her instructions.
You must not be given a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations. **Seek medical care with no delay if any of the following side effects happen during or after the infusion:**

- A sudden fall in blood pressure and, in isolated cases, anaphylactic shock (which signs are rash, hypotension, palpitation, wheezing, coughing, sneezing and difficulty breathing among others), even if you have shown no hypersensitivity to previous administration.
- Cases of temporary non-infective meningitis (which signs are headache, fear or intolerance of light, stiff neck).
- Cases of temporary reduction in the number of the red cells in the blood (reversible haemolytic anaemia/haemolysis).
- Cases of transient cutaneous reactions (side effects on your skin).
- Increase in serum creatinine level (a test which measures your kidney function) and/or acute renal failure (which signs are low back pain, fatigue, decrease in the amount of urine).
- Thromboembolic reactions such as myocardial infarction (tight band around the chest with feeling like your heart is beating too fast), stroke (muscle weakness in the face, arm, or leg, trouble speaking or understanding others who are speaking), pulmonary embolism (shortness of breath, chest pain and fatigue), deep vein thromboses (pain and swelling in an extremity).
- Cases of transfusion related acute lung injury (TRALI) that causes hypoxia (lack of oxygen), dyspnoea (difficulty in breathing), tachypnoea (rapid breathing), cyanosis (lack of oxygen in the blood), fever and hypotension.

Other side effects

**Common (may affect up to 1 in 10 infusions)**:
- headache
- fever (body temperature increased)
- tachycardia (acceleration of the heart activity)
- hypotension

**Uncommon (may affect up to 1 in 100 infusions)**:
- bronchitis
- nasopharyngitis
- dizziness (motion sickness)
- hypertension
- blood pressure increased
- wheezing
- productive cough
- abdominal pain (including abdominal pain upper)
- diarrhoea
- vomiting
- nausea
- urticaria
- pruritus (itching)
- rash (eruption of the skin)

- back pain
- myalgia (muscle pain)
- arthralgia (joint pain)
- rigors (cold shivering sensation) or chills
- pain
- injection site reaction
- Coombs test positive
- blood pressure decreased

**Rare (may affect up to 1 in 1000 infusions)**:
- hypersensitivity
- abnormal behaviour
- migraine
- blood pressure fluctuation
- flushing (to blush)
- cough
- asthma
- dyspnoea (difficulty in breathing)
- epistaxis (haemorrhage from the nose)
- nasal discomfort
- laryngeal pain
- dermatitis contact
- hyperhidrosis (excessive sweating)
- rash
- muscle spasms
- neck pain
- pain in extremity
- urinary retention
- asthenia (fatigue)
- chest pain
- infusion site reactions (erythema, extravasation, inflammation, pain)
- injection site reactions (including injection site oedema, pain, pruritus and swelling)
- oedema peripheral
- alanine aminotransferase (hepatic transaminase) increased

**Additional side effects in children and adolescents**

It was observed that the proportion of headache, fever, heart rate increased and low blood pressure in children was higher than in adults.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Flebogamma DIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

Do not store above 30 ºC. Do not freeze.

The solution should be clear or slightly opalescent. Do not use this medicine if you notice that the solution is cloudy or has deposits.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

### What Flebogamma DIF contains

- The active substance is human normal immunoglobulin (IVIg). One ml contains 50 mg of human normal immunoglobulin, of which at least 97% is 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

  The percentage of IgG subclasses is approximately 66.6% $IgG_1$, 28.5% $IgG_2$, 2.7% $IgG_3$ and 2.2% $IgG_4$. It contains trace amounts of IgA (lower than 50 micrograms/ml).

- The other ingredients are sorbitol and water for injections (see section 2 for further information about ingredients).

### What Flebogamma DIF looks like and contents of the pack

Flebogamma DIF is a solution for infusion. The solution is clear or slightly opalescent and colourless or pale yellow.

Flebogamma DIF is supplied as 0.5 g/10 ml, 2.5 g/50 ml, 5 g/100 ml, 10 g/200 ml and 20 g/400 ml vials.
Pack size of 1 vial.
Not all sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in MM/YYYY**

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only (see section 3 for further information):

**Posology and method of administration**

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients. The following dosage regimens are given as a guideline.

The dose recommendations are summarised in the following table:

| Indication | Dose | Frequency of infusions |
|---|---|---|
| Replacement therapy: | | |
| Primary immunodeficiency syndromes | Starting dose:<br>0.4 - 0.8 g/kg<br><br>Maintenance dose:<br>0.2 - 0.8 g/kg | every 3 - 4 weeks |
| Secondary immunodeficiencies | 0.2 - 0.4 g/kg | every 3 - 4 weeks |
| Measles pre/post exposure prophylaxis: | | |
| Post-exposure prophylaxis in susceptible patients | 0.4 g/kg | As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml |
| Post-exposure prophylaxis in PID/SID patients | 0.4 g/kg | In addition to maintenance therapy, given as an extra dose within 6 days of exposure |
| Pre-exposure prophylaxis in PID/SID patients | 0.53 g/kg | If a patient receives a maintenance dose of less than 0.53 g/kg every 3 - 4 weeks, this dose should be increased once to at least 0.53 g/kg |

| | | |
|---|---|---|
| Immunomodulation: | | |
| Primary immune thrombocytopenia | 0.8 - 1 g/kg<br><br>or<br><br>0.4 g/kg/d | on day 1, possibly repeated once within 3 days<br><br><br><br>for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg/d | for 5 days |
| Kawasaki disease | 2 g/kg | in one dose in association with acetylsalicylic acid |
| Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | Starting dose:<br>2 g/kg<br><br>Maintenance dose:<br>1 g/kg | <br>in divided doses over 2 - 5 days<br><br><br>every 3 weeks in divided doses over 1 - 2 days |
| Multifocal motor neuropathy (MMN) | Starting dose:<br>2 g/kg<br><br><br>Maintenance dose:<br>1 g/kg<br><br>or<br><br>2 g/kg | <br>in divided doses over<br>2 - 5 consecutive days<br><br><br>every 2 - 4 weeks<br><br><br><br>every 4 - 8 weeks in divided doses over 2 - 5 days |

Flebogamma 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, the rate of administration may gradually be increased to a maximum of 0.1 ml/kg/min.

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

*Paediatric population*

As the dosage for each indication is given by body weight and adjusted to the clinical outcome of the above-mentioned conditions, the dosage in children is not considered to be different to that of adults.

**Incompatibilities**

Flebogamma DIF should not be mixed with other medicines or intravenous solutions and it should be administered by a separate intravenous line.

**Special precautions**

**Sorbitol**

**Patients with rare hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.**

**Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.**

**A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.**

It is strongly recommended that every time that Flebogamma 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.

**Instructions for handling and disposal**

The product should be brought at room temperature (no more than 30 ºC) before use.

The solution should be clear or slightly opalescent. Do not use Flebogamma DIF if you notice that the solution is cloudy or has deposits.

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

**Package leaflet: Information for the user**

**Flebogamma DIF 100 mg/ml solution for infusion**
Human normal immunoglobulin (IVIg)

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**:


## 1. What Flebogamma DIF is and what it is used for

**What Flebogamma DIF is**

Flebogamma DIF contains human normal immunoglobulin, highly purified protein extracted from human plasma (part of the blood of donors). This medicine belongs to the group of medicines called intravenous immunoglobulins. These are used to treat conditions where the body's defence system against disease is not working properly.

**What Flebogamma DIF is used for**

Treatment of adults, children and adolescents (2 - 18 years) who do not have sufficient antibodies (Flebogamma DIF is used as replacement therapy). There are two groups:

- Patients with Primary Immunodeficiency Syndromes (PID), an inborn lack of antibodies (group 1)

- Patients with Secondary Immunodeficiency Syndromes (SID) with severe or recurrent infections, ineffective antimicrobial treatment and either **proven specific antibody failure (PSAF)*** or serum IgG level of <4 g/l (group 2)

*PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Treatment of susceptible adults, children and adolescents (2 - 18 years) in whom active vaccination against measles is not indicated or not advised.

Treatment of adults, children and adolescents (2 - 18 years) with certain autoimmune disorders (immunomodulation). There are five groups:

- Primary immune thrombocytopenia (ITP), a condition where the number of platelets in the blood stream is greatly reduced. Platelets form an important part of the clotting process and a reduction in their numbers may cause unwanted bleeding and bruising. The product is also used in patients at high risk of bleeding or prior to surgery to correct the platelet count.

- Guillain Barré syndrome, where the immune system damages the nerves and hinders them from working properly.

- Kawasaki disease (in this case in conjunction with acetylsalicylic acid therapy), an illness in children where the blood vessels (arteries) in the body become enlarged.

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a rare and progressive disease causing limb weakness, numbness, pain and fatigue.

- Multifocal motor neuropathy (MMN), a rare disease causing slow progressive asymmetric limb weakness without sensory loss.

## 2. What you need to know before you use Flebogamma DIF

### Do not use Flebogamma DIF

- If you are allergic to human normal immunoglobulin or any of the other ingredients of this medicine (listed in section 6).

- If you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.

- If you have fructose intolerance, a quite rare genetic condition where the enzyme for breaking down fructose is not produced**.** In babies and young children (aged 0 - 2 years) hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they must not receive this medicine (see special warnings about excipients at the end of this section)**.**

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Flebogamma DIF.

Certain side effects may occur more frequently:
- in case of high rate of infusion
- if you are having Flebogamma DIF for the first time, or it has been switched from an alternative human normal immunoglobulin (IVIg) product, or it is a long time since your last infusion (e.g. several weeks). You will be watched carefully until an hour after the infusion to detect potential side effects.

Allergic reactions are rare. It may happen particularly if you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.

Patients with pre-existing risk factors

Please tell your doctor if you have any other condition and/or illness, as control is required in patients with pre-existing risk factors for thrombotic events (formation of blood clots inside your blood). In particular, tell your doctor if you have:
- diabetes
- high blood pressure
- history of vascular disease or thrombosis
- overweight
- blood volume decrease
- diseases which increase blood viscosity
- age over 65

Patients with a kidney problem

If you have a renal disease and you are receiving Flebogamma DIF for the first time, you may suffer a problem in your kidneys.

Your doctor will consider your risk factors and take measures such as to decrease the rate of infusion or to stop the treatment.

Effects on blood tests

After receiving Flebogamma DIF, the results of certain blood tests (serological tests) may be interfered for a certain time. If you have a blood test after receiving Flebogamma DIF, please tell the analyst or your doctor that you have been given this medicine.

Special safety warning

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of Flebogamma DIF, the name and batch number of the medicine (stated on the label and carton after Lot) are recorded in order to maintain a record of the batches used.

**Children and adolescents**

Vital signs (body temperature, blood pressure, heart rate and respiratory rate) should be observed during the infusion of Flebogamma DIF.

**Other medicines and Flebogamma DIF**

- Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
- Effects on vaccines: Flebogamma DIF may reduce the effectiveness of certain types of vaccines (live attenuated virus vaccines). In case of rubella, mumps and varicella a period of up to 3 months should elapse after receiving this medicine and before receiving these vaccines. In case of measles, the period is up to 1 year.

- You should avoid the concomitant use of medicines that increase the excretion of water from your body (loop diuretics) during treatment with Flebogamma DIF.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**

Patients may experience reactions (for example dizziness or nausea) during treatment, which might affect the ability to drive and use machines.

**Flebogamma DIF contains sorbitol**

**Sorbitol is a source of fructose. If you (or your child) have hereditary fructose intolerance (HFI), a rare genetic disorder, you (or your child) must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.**

**You must tell your doctor before receiving this medicine if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.**

**Flebogamma DIF contains sodium**

This medicine contains less than 7.35 mg sodium (main component of cooking/table salt) in 100 ml. This is equivalent to 0.37% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How to use Flebogamma DIF

Flebogamma DIF is given by injection into your veins (intravenous administration). It may be self-administered if you have been fully trained by hospital staff or a health care professional. You must make up the infusion in exactly the way you have been shown in order to stop germs getting in. You must never self-administer it alone; a healthcare professional who is experienced in medicine preparation, cannulation, administration and monitoring of adverse reactions must be always present.

The dose that you will be given will depend on your illness and body weight and will be worked out by your doctor (please see section “Instructions for healthcare professionals” given at the end of this leaflet).

At the beginning of your infusion you will receive Flebogamma DIF at a slow rate (0.01 ml/kg/min). Depending on how comfortable you feel, your doctor may then gradually increase the infusion rate (up to 0.08 ml/kg/min).

**Use in children of more than 2 years old**

The dose in children is not considered to be different to that of adults as it will be given depending on the illness and body weight of the children.

**If you use more Flebogamma DIF than you should**

If you get more Flebogamma DIF than you should, your body may take on too much fluid. This could particularly happen when you are a patient at risk, e.g. an elderly patient or a patient having problems with your heart or your kidneys. Tell your doctor immediately.

**If you forget to use Flebogamma DIF**

Tell your doctor or pharmacist immediately and follow his/her instructions.
You must not be given a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations. **Seek medical care with no delay if any of the following side effects happen during or after the infusion:**

- A sudden fall in blood pressure and, in isolated cases, anaphylactic shock (which signs are rash, hypotension, palpitation, wheezing, coughing, sneezing and difficulty breathing among others), even if you have shown no hypersensitivity to previous administration.
- Cases of temporary non-infective meningitis (which signs are headache, fear or intolerance of light, stiff neck).
- Cases of temporary reduction in the number of the red cells in the blood (reversible haemolytic anaemia/haemolysis).
- Cases of transient cutaneous reactions (side effects on your skin).
- Increase in serum creatinine level (a test which measures your kidney function) and/or acute renal failure (which signs are low back pain, fatigue, decrease in the amount of urine).
- Thromboembolic reactions such as myocardial infarction (tight band around the chest with feeling like your heart is beating too fast), stroke (muscle weakness in the face, arm, or leg, trouble speaking or understanding others who are speaking), pulmonary embolism (shortness of breath, chest pain and fatigue), deep vein thromboses (pain and swelling in an extremity).
- Cases of transfusion related acute lung injury (TRALI) that causes hypoxia (lack of oxygen), dyspnoea (difficulty in breathing), tachypnoea (rapid breathing), cyanosis (lack of oxygen in the blood), fever and hypotension.

Other side effects:

**Very common (may affect more than 1 in 10 infusions)**:
- headache

**Common (may affect up to 1 in 10 infusions)**:
- tachycardia (acceleration of the heart activity)
- hypotension (low blood pressure)
- fever (body temperature increased)
- rigors (cold shivering sensation) or chills
- nausea
- vomiting
- back pain
- myalgia (muscle pain)

**Uncommon (may affect up to 1 in 100 infusions)**:
- hypersensitivity
- influenza (flu)
- dizziness (motion sickness)
- tremor (to tremble)
- photophobia (excessive sensitivity to light)
- vertigo
- hypertension (high blood pressure)
- wheezing

- abdominal pain (including abdominal pain upper)
- diarrhoea
- flatulence
- pruritus
- rash
- limb discomfort
- muscle spasms and muscle tightness
- neck pain
- pain in extremity
- chest discomfort/chest pain
- fatigue
- feeling cold
- malaise
- oedema peripheral
- heart rate increased
- contusion
- urinary infection
- meningitis aseptic (non-infective meningitis)
- red blood cells and white blood cells decreased
- anorexia (lack of appetite)
- insomnia
- radicular syndrome (neck or back pain and other symptoms such as numbness, tingling and weakness in the arms or legs)
- syncope vasovagal (temporary loss of consciousness)
- conjunctivitis (inflammation of the conjuntiva of the eyes)
- maculopathy (illness of the macula, in the retina of the eyes)
- vision blurred
- ear pain
- cyanosis (bluish discoloration of the skin)
- blood pressure increased or decreased
- flushing (to blush)
- haematoma
- thrombosis
- lymphoedema
- dyspnoea (difficulty in breathing)
- epistaxis (haemorrhage from the nose)
- postnasal drip (excessive mucus)
- sinus pain
- upper-airway cough syndrome
- abdominal discomfort and distension
- dry mouth
- haematemesis (vomiting blood)
- acne
- alopecia
- hyperhidrosis (excessive sweating)
- ecchymosis (large skin haematoma)
- erythema (redness of the skin)
- arthralgia (joint pain)
- musculoskeletal discomfort
- infusion related reaction and infusion site reaction (including infusion site erythema and infusion site pain)
- feeling jittery (nervousness)
- influenza like illness
- general physical health deterioration
- haemoglobin decreased
- reticulocyte count increased
- heart rate decreased

**Additional side effects in children and adolescents**

It was observed that the proportion of headache, chills, fever, nausea, vomiting, low blood pressure, heart rate increase and back pain in children was higher than in adults. Cyanosis (lack of oxygen in the blood) was reported in one child but not in adults.

Side effects may be reduced by switching to Flebogamma DIF 50 mg/ml. Please consult your doctor should you have increased side effects.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Flebogamma DIF

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP.

Do not store above 30 ºC. Do not freeze.

The solution should be clear or slightly opalescent. Do not use this medicine if you notice that the solution is cloudy or has deposits.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Flebogamma DIF contains**

- The active substance is human normal immunoglobulin (IVIg). One ml contains 100 mg of human normal immunoglobulin, of which at least 97% is IgG.

  Each vial of 50 ml contains: 5 g of human normal immunoglobulin
  Each vial of 100 ml contains: 10 g of human normal immunoglobulin
  Each vial of 200 ml contains: 20 g of human normal immunoglobulin

  The percentage of IgG subclasses is approximately 66.6% $IgG_1$, 27.9% $IgG_2$, 3.0% $IgG_3$ and 2.5% $IgG_4$. It contains trace amounts of IgA (lower than 100 micrograms/ml).

- The other ingredients are sorbitol and water for injections (see section 2 for further information about ingredients).

**What Flebogamma DIF looks like and contents of the pack**

Flebogamma DIF is a solution for infusion. The solution is clear or slightly opalescent and colourless or pale yellow.

Flebogamma DIF is supplied as 5 g/50 ml, 10 g/100 ml and 20 g/200 ml.
Pack size of 1 vial.
Not all sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Instituto Grifols, S.A.
Can Guasc, 2 - Parets del Vallès
08150 Barcelona - Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in MM/YYYY**

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

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The following information is intended for healthcare professionals only (see section 3 for further information):

**Posology and method of administration**

The dose and dose regimen are dependent on the indication.

The dose may need to be individualised for each patient dependent on the clinical response. Dose based on body weight may require adjustment in underweight or overweight patients. The following dosage regimens are given as a guideline.

The dose recommendations are summarised in the following table:

| Indication | Dose | Frequency of infusions |
|---|---|---|
| Replacement therapy: | | |
| Primary immunodeficiency syndromes | Starting dose:<br>0.4 - 0.8 g/kg<br><br>Maintenance dose:<br>0.2 - 0.8 g/kg | <br><br><br><br>every 3 - 4 weeks |
| Secondary immunodeficiencies | 0.2 - 0.4 g/kg | every 3 - 4 weeks |
| Measles pre/post exposure prophylaxis: | | |
| Post-exposure prophylaxis in susceptible patients | 0.4 g/kg | As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml |
| Post-exposure prophylaxis in PID/SID patients | 0.4 g/kg | In addition to maintenance therapy, given as an extra dose within 6 days of exposure |
| Pre-exposure prophylaxis in PID/SID patients | 0.53 g/kg | If a patient receives a maintenance dose of less than 0.53 g/kg every 3 - 4 weeks, this dose should be increased once to at least 0.53 g/kg |
| Immunomodulation: | | |
| Primary immune thrombocytopenia | 0.8 - 1 g/kg<br><br>or<br><br>0.4 g/kg/d | on day 1, possibly repeated once within 3 days<br><br><br><br>for 2 - 5 days |
| Guillain Barré syndrome | 0.4 g/kg/d | for 5 days |
| Kawasaki disease | 2 g/kg | in one dose in association with acetylsalicylic acid |
| Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) | Starting dose:<br>2 g/kg<br><br>Maintenance dose:<br>1 g/kg | <br>in divided doses over 2 - 5 days<br><br><br><br>every 3 weeks in divided doses over 1 - 2 days |
| Multifocal motor neuropathy (MMN) | Starting dose:<br>2 g/kg<br><br><br>Maintenance dose:<br>1 g/kg<br><br>or<br><br>2 g/kg | <br>in divided doses over 2 - 5 consecutive days<br><br><br><br>every 2 - 4 weeks<br><br><br><br>every 4 - 8 weeks in divided doses over 2 - 5 days |

Flebogamma DIF should be infused intravenously at an initial rate of 0.01 ml/kg/min for the first thirty minutes. If tolerated, advance to 0.02 ml/kg/min for the second 30 minutes. Again, if tolerated,

advance to 0.04 ml/kg/min for the third 30 minutes. If the patient tolerates the infusion well, additional increments of 0.02 ml/kg/min may be made at 30-minute intervals up to a maximum of 0.08 ml/kg/min.

It has been reported that the frequency of adverse reactions to IVIg increases with the infusion rate. Infusion rates during the initial infusions should be slow. If there are no adverse reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate. For patients experiencing adverse reactions, it is advisable to reduce the infusion rate in subsequent infusions and limit the maximum rate to 0.04 ml/kg/min, or administer IVIg at a 5% concentration.

*Paediatric population*

As the dosage for each indication is given by body weight and adjusted to the clinical outcome of the above-mentioned conditions, the dosage in children is not considered to be different to that of adults.

**Incompatibilities**

Flebogamma DIF should not be mixed with other medicines or intravenous solutions and it should be administered by a separate intravenous line.

**Special precautions**

**Sorbitol**

**Patients with rare hereditary fructose intolerance (HFI) must not be given this medicine unless strictly necessary.**

**Babies and young children (below 2 years of age) may not yet be diagnosed with hereditary fructose intolerance (HFI). Medicines (containing sorbitol/fructose) given intravenously may be life-threatening and should be contraindicated in this population unless there is an overwhelming clinical need and no alternatives are available.**

**A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.**

It is strongly recommended that every time that Flebogamma 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.

**Instructions for handling and disposal**

The product should be brought at room temperature (no more than 30 ºC) before use.

The solution should be clear or slightly opalescent. Do not use Flebogamma DIF if you notice that the solution is cloudy or has deposits.

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