System Organ Class	Body System Preferred Term	ADR frequency evaluation
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain, abdominal pain upper	Uncommon
Skin and subcutaneous tissue disorders	Urticaria, rash pruritic, dermatitis contact	Uncommon
Musculoskeletal and connective tissue disorder	Back pain, arthralgia, myalgia, muscle cramp	Uncommon
Vascular disorders	Hypotension, hypertension, diastolic hypertension, blood pressure fluctuations	Uncommon
General disorders & administration site conditions	Pyrexia, injection site reaction	Common
	Rigors, asthenia, pain, infusion site inflammation, injection site oedema, injection site pain, injection site pruritus, injection site swelling, migration of implant	Uncommon

For safety with respect to transmissible agents, see section "Special warnings and precautions for use".

Overdose

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

PHARMACOLOGICAL PROPERTIES

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.

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

Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient's circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

Flebogamma® 5% DIF has a half-life of about 30 - 32 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

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

Preclinical safety data

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

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

PHARMACEUTICAL PARTICULARS

List of excipients

D-sorbitol

Water for injections

Incompatibilities

This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line.

Shelf life

2 years.

Special precautions for storage

Do not store above 30 ºC.

Do not freeze.

Nature and contents of container

10 ml solution in a vial (type II glass) with stopper (chloro-butyl-rubber).

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

Pack sizes: 0.5 g/10 ml vial, 2.5 g/50 ml bottle, 5 g/100 ml bottle, 10 g/200 ml bottle and 20 g/400 ml bottle.

Not all pack sizes may be marketed.

Special precautions for disposal and other handling

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

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

Once the container has been opened, the contents should be used immediately. Left-over product must never be kept for later use, nor stored in a refrigerator.

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

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DATE OF REVISION OF THE TEXT

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GRIFOLS

Flebogamma® 5% DIF

Solution for infusion

Human normal immunoglobulin (IVIg)

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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 0.05 mg/ml).

Excipient:

One ml contains 50 mg of D-sorbitol.

For a full list of excipients, see section "List of excipients".

PHARMACEUTICAL FORM

Solution for infusion.

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

CLINICAL PARTICULARS

Therapeutic indications

Flebogamma® 5% DIF is indicated for:

Replacement therapy in:

Primary immunodeficiency syndromes such as:

- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

Immunomodulation

Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.

Guillain Barré syndrome.

Kawasaki disease.

Allogeneic bone marrow transplantation.

Posology and method of administration

Posology

The dose and dosage regimen is dependent on the indication.

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

Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4 - 6 g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 - 0.8 g/kg followed by at least 0.2 g/kg every three weeks.

The dose required to achieve a trough level 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 2 - 4 weeks.

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

Replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections.

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

Idiopathic thrombocytopenic purpura

For the treatment of an acute episode, 0.8 - 1 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs.

Guillain Barré syndrome

0.4 g/kg/day for 3 to 7 days.

Experience in children is limited.

Kawasaki disease

1.6 - 2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose.

Patients should receive concomitant treatment with acetylsalicylic acid.

Allogeneic bone marrow transplantation

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.

For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to 3 months after transplantation.

In case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal.

The dosage recommendations are summarised in the following table:

Indication	Dose	Frequency
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Children with AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks

Indication	Dose	Frequency
Immunomodulation:		
Idiopathic thrombocytopenic purpura	0.8 - 1 g/kg or	on day 1, possibly repeated once within 3 days
	0.4 g/kg/d	for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 3 - 7 days
Kawasaki disease	1.6 - 2 g/kg or	in several doses for 2 - 5 days in association with acetylsalicylic acid
	2 g/kg	in one dose in association with acetylsalicylic acid
Allogeneic bone marrow transplantation:		
- treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day -7 up to 3 months after transplantation
- persistent lack of antibody production	0.5 g/kg	every month until antibody levels return to normal

Method of administration

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

Contraindications

Hypersensitivity to any of the components (see section "Special warnings and precautions for use").

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

Fructose intolerance (see section "Special warnings and precautions for use").

Special warnings and precautions for use

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "Posology and method of administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently

- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency,
- 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.

True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.

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

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly at an initial rate of 0.01 - 0.02 ml/kg/min;
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

There is clinical evidence of an association between IVIg administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and patients with diseases which increase blood viscosity).

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, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, 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 sucrose may be considered.

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

In all patients, IVIg administration requires:

- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

The treatment required depends on the nature and severity of the side effect.

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

Non-cardiogenic pulmonary edema may occur in patients following IGIV treatment. This Transfusion-Related Acute Lung Injury (TRALI) is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours after transfusion.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies in both the product and patient serum.

Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety.

It is strongly recommended that every time Flebogamma® 5% DIF is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Special warnings about excipients: This medicinal product contains 50 mg of sorbitol per ml as excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine. **In babies and young children hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they should not receive sorbitol-containing solutions.** In other patients in case of inadvertent application and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycemia has to be re-established and organ function has to be stabilized by means of intensive care.

Interferences with determination of blood glucose levels are not expected.

Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coomb's test).

Pregnancy and lactation

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.

Effects on ability to drive and use machines

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

Since Flebogamma® 5% DIF might induce dizziness, patients should be cautioned when driving or operating machines.

Undesirable effects

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

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

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

Two multicenter clinical trials were performed, one of them in children and adults with primary immune deficiency and the second one in patients with chronic immune thrombocytopenic purpura in acute phase. Forty-six patients were included in the first trial and 41 completed the study. They were followed during 1 year of treatment at a dose of 300 - 600 mg/kg every 3 to 4 weeks. A total of 20 patients were included in the second study. Patients received a total dose of 400 mg/kg body weight for 5 consecutive days and were followed for 3 months. Therefore, a total of 66 patients have been exposed to Flebogamma® 5% DIF and they have received 806 infusions. Data from both studies indicate a good tolerability of the product as incidence of adverse events was low and most of them were mild to moderate in intensity.

Of the 806 infusions administered in patients enrolled in both studies 10.8% (1-sided 95% CI upper bound = 12.9%) were associated with an adverse event suspected to be related to the product. No patients died, only 6 patients withdrew from the studies but none of them because of potentially related adverse events. Four patients experienced 8 serious adverse events that were considered not related to the study medicinal product. Pyrexia and headache were the most frequently reported adverse events potentially related to the medicinal product in both studies.

The adverse drug reactions reported in the 2 trials by at least the 5% of the patients are summarised and categorised according to the MedDRA system organ class in the table below:

Frequency has been determined using the following criteria:

- 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, undesirable effects are presented in order of decreasing of seriousness.

System Organ Class	Body System Preferred Term	ADR frequency evaluation
Investigations	Coombs test positive, blood pressure systolic decreased, blood pressure systolic increased, body temperature increased	Uncommon
Nervous system disorder	Headache	Common
	Dizziness	Uncommon
Respiratory, thoracic and mediastinal disorder	Bronchitis, cough, wheezing	Uncommon