- 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 of seriousness.

System Organ Class	Body System Preferred Term	ADR frequency evaluation
Infections and infestations	Influenza, urinary tract infection	Uncommon
Blood and lymphatic system disorders	Bicytopenia, leukopenia	Uncommon
Metabolism and nutrition disorders	Anorexia	Uncommon
Nervous system disorders	Headache	Very common
	Dizziness, radicular syndrome, syncope vasovagal, tremor	Uncommon
Eye disorders	Conjunctivitis, maculopathy, photophobia	Uncommon
Ear and labyrinth disorders	Ear pain, vertigo	Uncommon
Cardiac disorders	Tachycardia	Common
Vascular disorders	Hypotension	Common
	Diastolyc hypertension, flushing, hematoma, hypertension, systolic hypertension, thrombosis	Uncommon
Respiratory, thoracic and mediastinal disorders	Postnasal drip, sinus pain, wheezing	Uncommon
Gastrointestinal disorders	Nausea	Common
	Abdominal distension, abdominal pain, abdominal pain upper, diarrhoea, flatulence, vomiting	Uncommon
Skin and subcutaneous tissue disorders	Acne, ecchymosis, erythema, pruritus, rash	Uncommon
Musculoskeletal and connective tissue disorders	Back pain, myalgia	Common
	Arthralgia, muscle spasms, muscle tightness, neck pain, pain in extremity	Uncommon
General disorders and administration site conditions	Pain, pyrexia, rigors	Common
	Chest discomfort, chest pain, chills, fatigue, feeling cold, feeling jittery, influenza like illness, infusion related reaction, infusion site erythema, infusion site pain, infusion site reaction, malaise, peripheral oedema	Uncommon
Investigations	Body temperature increased	Common
	Blood pressure diastolic decreased, blood pressure increased, blood pressure systolic increased, haemoglobin decreased, heart rate increased	Uncommon

Paediatric population

The safety results for 3 paediatric patients (those ≤ 16 years old) included in the PID study and the results for the 9 children (aged 3 to 15) included in the ITP study appeared to be generally similar to those for the overall patient population.

Overdose

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

Paediatric population

Information on overdose in children has not been established with Flebogamma® 10% DIF. However, as in adult population, overdose may lead to fluid overload and hyperviscosity as with any other intravenous immunoglobulins.

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.

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® 10% DIF 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.

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® 10% DIF with doses up to 2,500 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® 10% 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

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

Pack sizes: 5 g/50 ml bottle, 10 g/100 ml bottle and 20 g/200 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® 10% DIF

Solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

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

One vial of 50 ml contains: 5 g of human normal immunoglobulin
One vial of 100 ml contains: 10 g of human normal immunoglobulin
One 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%

The maximum IgA content is 100 micrograms/ml.

Produced from the plasma of human donors.

Excipients with known effect:
One ml contains 50 mg of D-Sorbitol.
For the full list of excipients, see section "List of excipients".

PHARMACEUTICAL FORM

Solution for infusion
The solution is clear or slightly opalescent and colourless or pale yellow.
Flebogamma® 10% DIF is isotonic, with an osmolality from 240 to 370 mOsm/kg.

CLINICAL PARTICULARS

Therapeutic indications

Replacement therapy in adults, children and adolescents (2-18 years) in:
- Primary immunodeficiency syndromes with impaired antibody production.
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia in patients after allogenic haematopoietic stem cell transplantation (HSCT).

Replacement therapy in children and adolescents (2-18 years) in:
- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, children and adolescents (2-18 years) in:
- Idiopathic Thrombocytopenic Purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome.
- Kawasaki disease.

Posology and method of administration

Posology

The dose and posology is dependent on the indication.

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

Replacement therapy in primary immunodeficiency syndromes

The dose 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/month given in divided doses every three to four 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 dose interval when steady state has been reached varies from 3 - 4 weeks.

Trough levels should be measured and assessed in conjuction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels (> 6 - 9 g/l).

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

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

Hypogammaglobulinaemia in patients after allogenic haematopoietic stem cell transplantation

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

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 5 days.

Kawasaki disease

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

The dose recommendations are summarised in the following table:

Indication	Dose	Frequency
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg	
	- thereafter: 0.2 - 0.8 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 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 and adolescents with AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg	every 3 - 4 weeks
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 5 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 aci
Paediatric population	See above	See above

Paediatric population

The safety and efficacy of Flebogamma® 10% DIF in children and adolescents aged 3 to 16 years have been established in 3 primary immunodeficient patients and in 9 patients with immune thrombocytopenic purpura.

The safety and efficacy of Flebogamma® 10% DIF in children aged 0 to 2 years have not been established in clinical trials.

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

Method of administration

Flebogamma® 10% 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 (see section "Special warnings and precautions for use").

Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section "Special warnings and precautions for use").

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

Hereditary fructose intolerance (see section "Special warnings and precautions for use"). **In babies and young children hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they should not receive this medicinal product.**

Special warnings and precautions for use

Sorbitol

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

In case of inadvertent application and suspicion of hereditary fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

Interferences with determination of blood glucose levels are not expected.

Infusion rate

Certain severe adverse reactions to the medicinal product may be related to the rate of infusion. The recommended infusion rate given under section "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.

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 ml/kg/min;
- are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

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

The treatment required depends on the nature and severity of the adverse reactions.

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

In all patients, IVIg administration requires:

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

Hypersensitivity

True hypersensitivity reactions are rare. They can occur in 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.

Thromboembolism

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).

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, 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 an excipient 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. Flebogamma® 10% DIF does not contain sucrose.

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

Haemolytic anaemia

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

Transfusion-Related Acute Lung Injury (TRALI)

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.

Interference with serological testing

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

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (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 HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

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

It is strongly recommended that every time that Flebogamma® 10% 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.

Paediatric population

It is expected that similar adverse reactions than those mentioned for the adults may be presented by the paediatric population.

Interaction with other medicinal products and other forms of interaction

Live attenuated virus vaccines

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

Paediatric population

It is expected that the same interactions than those mentioned for the adults may be presented by the paediatric population.

Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

Clinical experience with immunoglobulins suggests that no harmful effects on fertility are to be expected.

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® 10% DIF. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines.

Undesirable effects

Summary of the safety profile

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.

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

Tabulated summary 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 "Posology and method of administration").

The adverse reactions categorised according to the MedDRA system organ class reported in any patient in the 3 trials are summarised in the table below. Frequency of each adverse reaction has been determined using the following criteria:

- very common (≥ 1/10)
- common (≥ 1/100 to < 1/10)