PRODUCT MONOGRAPH

FLEBOGAMMA® 10%

Immune Globulin Intravenous (Human)

Solution for infusion, 100 mg/mL

Passive immunizing agent

Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration. ATC code: J06BA02

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

Imported and Distributed by:
Grifols Canada Ltd.
5060 Spectrum Way
Suite 405
Mississauga, Ontario
L4W 5N5

Date of Approval:
August 17, 2017

Submission Control No: 194291

Table of Contents

FLEBOGAMMA® 10%

Immune Globulin Intravenous (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Solution for infusion, 100 mg/mL	Sorbitol *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Flebogamma 10% is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold ethanol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment, and Planova nanofiltration using 20 nanometer (nm) filters.
Flebogamma 10% is a purified (at least 97% IgG), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG_1, 27.9% IgG_2, 3.0% IgG_3 and 2.5% IgG_4. Flebogamma 10% contains trace amounts of IgA (typically less than 100 μg/mL) and trace amounts of sodium and IgM.
Flebogamma 10% contains 10 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 2 mg/mL polyethylene glycol. There is no preservative in the formulation. The pH of the solution ranges from 5 to 6 and the osmolality from 240 to 370 mOsm/kg, which is within the normal physiological range.

INDICATIONS AND CLINICAL USE

Flebogamma 10% is indicated for:

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).
- Congenital AIDS with recurrent bacterial infections.

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

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

CONTRAINDICATIONS

• Flebogamma 10% is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.
• Flebogamma 10% is contraindicated in severe IgA-deficient patients (serum IgA <0.05 g/L) with antibodies to IgA and a history of hypersensitivity. *(*see *General* and *Hypersensitivity* subsections in *Warnings and Precautions)*
• Fructose intolerance (see *Hereditary Fructose Intolerance* subsection in *Warnings and Precautions*).
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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

• There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis. Therefore, caution should be exercised when prescribing and administering immunoglobulins. Thrombosis may occur even in the absence of known risk factors. Risk factors for thromboembolic events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilization, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central venous catheters, and cardiovascular risk factors. *(*see *Thromboembolic events* subsection)
• For patients at risk of thrombosis, administer Flebogamma® 10% at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. *(*see *Dosage* and *Administration and Thromboembolic events* subsection)
• Renal dysfunction, acute renal failure, osmotic nephrosis, and death[1] have been related to intravenous immune globulin (IGIV) products. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.
• Administer Flebogamma® 10% at the minimum dose and rate of infusion practicable in patients at risk for renal dysfunction or failure.
• Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. Flebogamma® 10% does not contain sucrose. *(*see *Dosage and Administration and Renal* subsection)

General
Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate given under *Dosage and 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 or 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 carefully monitored and, in particular, patients naive to human normal immunoglobulin, patients switched from an alternative IGIV 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.

The treatment required depends on the nature and severity of the adverse reaction.
In case of shock, standard medical treatment for shock should be implemented.

In all patients, IGIV administration requires:
- adequate hydration prior to the initiation of the infusion of IGIV
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics.

<u>Hypersensitivity</u>
True hypersensitivity reactions are rare. They can occur in patients with anti-IgA antibodies.

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

<u>Transmissible agents</u>
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 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.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Canada Ltd. [1-866-482-5226]. The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

Thromboembolic events
There is clinical evidence of an association between the administration of immunoglobulins and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis.

Since thrombosis may occur in the absence of known risk factors, caution should be exercised in prescribing and administering immunoglobulins. The drug product should be administered at the minimum concentration available and at the minimum rate of infusion practicable. Patients should be adequately hydrated before administration.

Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. Patients at risk of hyperviscosity should be monitored for signs and symptoms of thrombosis and blood viscosity assessed.

Risk factors for thromboembolic adverse events include: obesity, advanced age, hypertension, diabetes mellitus, history of vascular disease or thrombotic episodes, acquired or inherited thrombophilic disorders, prolonged periods of immobilisation, severely hypovolemic patients, diseases which increase blood viscosity, hypercoagulable conditions, use of estrogens, indwelling central vascular catheters, and cardiovascular risk factors.

Hematologic
IGIV products can contain blood group antibodies which may act as haemolysins and induce *in vivo* coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis[2,3]. Haemolytic anaemia can develop subsequent to IGIV therapy due to enhanced red blood cells (RBC) sequestration[4] (see *Drug-Laboratory Interactions*). IGIV recipients should be monitored for clinical signs and symptoms of haemolysis. (See *Monitoring and Laboratory Tests* subsection)

Neurologic
Aseptic meningitis syndrome (AMS) has been reported to occur in association with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae[5,6]. The syndrome usually begins within several hours to 2 days following

IGIV treatment. Cerebrospinal fluid 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) IGIV treatment.

Renal
Cases of acute renal failure have been reported in patients receiving IGIV therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IGIV 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 IGIV 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 IGIV products that do not contain these excipients may be considered. Flebogamma does not contain sucrose, maltose or glucose.

In patients at risk for acute renal failure, IGIV products should be administered at the minimum rate of infusion and dose practicable[7].

Respiratory
Non-cardiogenic pulmonary edema has been reported in patients following IGIV treatment[8]. 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 and anti-HLA antibodies in both the product and patient serum. TRALI may be managed by using oxygen therapy with adequate ventilatory support.

Hereditary Fructose Intolerance
Flebogamma 10% contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). HFI is typically suspected based on dietary history, especially in young children who become symptomatic after breast-feeding. Flebogamma 10% must not be administered to subjects with HFI.

Sexual Function/Reproduction
The effect of Flebogamma 10% on fertility has not been evaluated.

Special Populations

Pregnant Women: The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should be given only if clearly needed.

Nursing Women: Immunoglobulins are excreted into the milk and may contribute to protecting

the neonate from pathogens which have a mucosal portal of entry.

Pediatrics (0 - 2 years of age): The safety and effectiveness of Flebogamma 10% has not been established in pediatric patients below the age of 2 years.

Pediatrics (3 - 17 years of age): Flebogamma 10% was evaluated in 16 pediatric subjects with PID and ITP. The results for these patients appeared to be similar to those for the overall population. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Geriatrics (> 65 years of age): Use caution when administering Flebogamma 10% to patients aged 65 and over who are judged to be at increased risk for developing thrombosis or renal insufficiency. (See *Renal* and *Thromboembolic events* subsections).

Clinical studies did not include sufficient number of subjects over the age of 65 years to determine whether they respond differently from younger patients.

Monitoring and Laboratory Tests
Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma 10% and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.

If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma 10%, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

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

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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Three multicenter clinical trials were performed with Flebogamma 10%, one for replacement therapy in patients with primary immunodeficiency (in both adults and children above 6 years) and two for immunomodulation, in patients with immune thrombocytopenic purpura (ITP) (one in adult patients and another in both adult and children between 3 and 16 years). Forty-six patients were included in the first trial and 37 completed the study. They were followed during 1 year of treatment at a dose of 300-600 mg/kg every 3 to 4 weeks. Eighteen patients were included in the second trial (IG202) and received 0.4 g/kg/day over 5 consecutive days or 1g/kg/day over 2 consecutive days. Patients were followed for three months after first infusion. A total of fifty-eight patients were included in the third study (IG0601) and received 2 intravenous infusions of 1 g/kg/day in 2 consecutive days for a total dose of 2 g/kg. The patients were followed for 1 month. Data from 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.

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 *Dosage and Administration*).

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

Frequencies have been evaluated according to the following convention:

- very common ($\geq$1/10)
- common ($\geq$1/100 to <1/10)
- uncommon ($\geq$1/1,000 to <1/100)
- rare ($\geq$1/10,000 to <1/1,000)

- very rare (<1/10,000)
- not known (cannot be estimated from the available data)

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

Frequency of Adverse Reactions (ADRs) in clinical studies with Flebogamma 10%

MedDRA System Organ Class (SOC)	**Adverse reaction**	**Frequency**
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

MedDRA System Organ Class (SOC)	Adverse reaction	Frequency
	Blood pressure diastolic decreased, blood pressure increased, blood pressure systolic increased, haemoglobin decreased, heart rate increased	Uncommon

Pediatric population

The safety results for 4 pediatric patients (those ≤ 17 years old) included in the PID study and the results for the 12 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 pediatric population did not indicate any pattern of clinically relevant changes.

Abnormal Hematologic and Clinical Chemistry Findings

There were no major and clinically relevant changes in analytical parameters during the clinical studies attributable to Flebogamma 10% indicating a safety concern. In general, the laboratory values for urinalysis, hematology, and serum chemistry were within the respective normal ranges at all time points. There were no changes in viral markers suggesting an infection related to the product.

Post-Market Adverse Drug 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.

Infusion Reactions

In a Post-authorisation Safety Study that included 66 patients, Flebogamma 10% showed a higher rate (18.46%, n=24/130) of infusions associated with potentially related adverse events than Flebogamma 5% (2.22%, n=3/135). However one subject treated with Flebogamma 10% 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. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped (see *Administration* subsection in *Dosage and Administration*).

DRUG INTERACTIONS

Drug-Drug Interactions

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.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Recommended Dose and Dosage Adjustment
The dose and dose regimen is dependent on the indication.

The dose may need to be individualised for each patient dependent on the pharmacokinetic and/or clinical response.

The dose recommendations are summarised in the following table:

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

Immunomodulation:		
Primary immune thrombocytopenia	0.8 - 1 g/kg or	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

Pediatric population

Flebogamma 10% is contraindicated in children aged 0 to 2 years (see *Contraindications*).

The posology in children and adolescents (2 - 18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Administration

For intravenous use.
Flebogamma 10% should be infused intravenously at an initial rate of 0.01 mL/kg/min for the first thirty minutes. If well tolerated, the rate may be gradually increased to a maximum rate of 0.08 mL/kg/min.

It has been reported that the frequency of adverse reactions to IGIV 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 IGIV at a 5% concentration (see *Warnings and Precautions*, *General* subsection).

Monitor patient vital signs throughout the infusion. Slow or stop infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient (see *Warnings and Precautions, General* subsection).

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Replacement therapy: Flebogamma 10% supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Flebogamma 10% also contains a spectrum of antibodies capable of reacting with cells, such as erythrocytes. The role of these antibodies and the mechanism of action of IgG in Flebogamma 10% have not been fully elucidated.

The mechanism of action in indications other than replacement therapy has not been fully elucidated.

Pharmacodynamics

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.

Pharmacokinetics

The production process of Flebogamma 10% is the same than for Flebogamma 5%. The only difference is the final concentration step in which the yield is adjusted to the desired 5% or 10% product strength. Therefore, the PK profile of Flebogamma 5%, as determined in previous clinical trials, is supportive of the PK profile of the 100 mg/ml strength. Nevertheless, relevant PK parameters have been evaluated for Flebogamma 10% in the efficacy and safety study (Study IG304).

A detailed PK analysis of total IgG, IgG subclasses, and antibodies to selected specific antigens was performed for the patients in the PK population.

Nineteen subjects participated in the PK study. Subjects had to have baseline IgG levels <450 mg/dl. Baseline serum IgG levels were defined as those obtained from each subject before initiation of any regular gammaglobulin treatment (intravenous, subcutaneous, intramuscular or plasma).

In the clinical study assessing safety and efficacy in PID, the pharmacokinetics of Flebogamma 10% were assessed for 21 or 28 days after administration in 19 subjects. PK analysis was performed for 10 subjects receiving Flebogamma 10% on a 21-day schedule and for 9 subjects receiving treatment on a 28-day schedule.

The mean dose (range) for those on the 21-day schedule was 476 mg/kg (range: 339-597) and 496 mg/kg (range: 434-588) for those on the 28-day schedule. Blood samples for PK analysis were obtained after Infusion #7 for subjects on a 28-day schedule and after Infusion #9 for subjects on a 21-day schedule. Table 1 summarizes the pharmacokinetic parameters of Flebogamma 10%, measured as serum concentrations of total IgG. The half-life of IgG can vary considerably among patients.

Table 1: Pharmacokinetic Variables of Total IgG in Patients with PID

Variable	**3-Week Dosing Interval (n=10)**		**4-Week Dosing Interval (n=9)**	
	Mean ± SD	**Range**	**Mean ± SD**	**Range**
Cmax (mg/mL)	19.50 ± 2.83	15.10 - 24.40	20.92 ± 3.66	16.80 - 29.20
$AUC_{0 - last}$ (day·mg/mL)	339.51 ± 45.27	241.12 – 380.21	342.37 ± 39.72	276.83 – 408.25
Clearance (mL/day)	115 ± 31	81 – 186	144 ± 47	77 – 237
Half-life (days)[a]	34 ± 10	21 – 58	37 ± 13	24 – 59
Trough IgG level (mg/mL)[b]	9.76 ± 1.65	6.45 – 11.40	8.77 ± 1.26	7.59 – 11.70

a. This half-life is an apparent value derived from a 28 day period of measurement
b. For subjects on the 3-week schedule, average trough levels from Infusion #9 to the end of the study was calculated; for those on a 4-week schedule, the average of the trough levels from Infusion #7 to the end of the study was calculated.

Conclusions for pharmacokinetic study

Overall, the patterns observed in the PK behavior for total IgG levels, IgG subclass levels, and the IgG antibody levels to specified antigens were similar. For total IgG, the estimated half-life is around 34 and 37 days for 21-day infusion schedule and 28-day infusion schedule, respectively.

Moreover, trough total IgG and IgG subclass concentrations were maintained throughout the treatment period with Flebogamma 10%, as evidenced by both the relatively small changes in these parameters observed over the course of the study and the absence of any patients with decreases from screening or first infusion in trough total IgG that were higher than 50%. These trough levels are considered protective for patients with immunodeficiencies, as all the individual values are well above 400 mg/dl, being the mean value much higher than 600 mg/dl.

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% has a half-life of about 34-37 days. This half-life may vary from patient to patient, in particular in primary immunodeficiency.

Special Populations and Conditions

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

No specific studies were performed for the following: Gender, Race, Hepatic Insufficiency, Renal insufficiency.

STORAGE AND STABILITY

The shelf-life for Flebogamma 10% is 2 years not stored above 30 ºC.
Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

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

The solution should be clear or slightly opalescent and colourless or pale yellow. Solutions that are cloudy or have deposits should not be used.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Flebogamma 10% is a ready to use sterile solution of human normal immunoglobulin for intravenous administration.

Flebogamma 10% is supplied in type II glass vials closed with butyl rubber stoppers. The sizes are listed in Table 2.

Table 2 - Available Dosage Forms for Flebogamma 10%

Size	Protein (g)
50 mL	5
100 mL	10
200 mL	20

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Product

Proper name: Flebogamma 10%
Immune Globulin Intravenous (Human)

Product Characteristics

Flebogamma 10% is a sterile 10% solution, intended for intravenous administration, which has as active ingredient human normal immunoglobulin obtained from human plasma following a fractionation process based on the Cohn method.

Plasma used in the manufacture of this product has only been collected in FDA-approved blood establishments. Part of the fractionation can be performed by another licensed manufacturer.

Flebogamma 10% is obtained through a purification procedure which yields an unmodified IgG molecule (containing a fully functional Fc fragment and the corresponding antigen binding domains) with a level of purity close to 100%. Therefore, there is very little content of accompanying proteins that might cause unexpected safety concerns. The profile of residual accompanying proteins is comparable to other marketed products.

Viral Inactivation

A number of precautions are taken to ensure the viral safety of plasma derived products, such as donor and plasma screening. In addition, several manufacturing steps can contribute towards the safety of the final product. The effectiveness of these steps to remove or inactivate viruses from the product is evaluated through virus spiking experiments, using a scaled down version of the manufacturing process.

Plasma used in the manufacture of Flebogamma 10% is obtained from source plasma donors at U.S. centers approved by the U.S. Food and Drug Administration. All plasma donations are, at a minimum, screened and found to be non-reactive/negative or Hepatitis B surface antigen, Hepatitis C antibody, HIV 1/2 antibodies, as well as Hepatitis B, Hepatitis C, and HIV, by NAT testing.

Flebogamma 10% production process includes the following specific virus inactivation/ removal steps:

- Pasteurisation at 60 ºC, 10 hours
- Solvent-Detergent treatment for 6 hours
- Double sequential nanofiltration down to 20 nm Planova filters

Besides these steps, the purification process includes others that can contribute as well to eliminate or inactivate a potentially contaminant theoretical viral load, among them:

- Fraction I precipitation
- Fraction II+III precipitation
- 4% PEG precipitation
- pH 4 treatment during 4 hours at 37 ºC

All the specific virus inactivation/removal steps have been validated with the relevant or model viruses for which a quantifiable viral reduction factor (RF) was expected, based on bibliographical data or Grifols' experience with other plasma products.

The following viruses were selected for the studies which support the evaluation of the virus elimination capacity of the human intravenous immunoglobulin (IGIV3I) production process:

A) Model virus for the Human Immunodeficiency virus (HIV 1/2)

Human Immunodeficiency Virus type 1 (HIV-1)

B) Model virus for Herpesvirus and other dsDNA enveloped viruses (including HBV)

Pseudorabies virus (PRV) and Infectious Bovine Rhinotracheitis virus (IBR)

C) Model virus for Hepatitis C virus (HCV) and West Nile Virus (WNV)

Bovine Viral Diarrhoea virus (BVDV), Sindbis virus (SINDBIS) and

West Nile Virus (WNV).

D) Model virus for the Hepatitis A virus (HAV)

Encephalomyocarditis virus (EMC)

E) Model virus for the B19 virus (VB19)

Porcine Parvovirus (PPV).

F) Additional model viruses used for the nanofiltration step

Simian 40 virus (SV40), Echovirus 11 (Echo11), Bovine enterovirus (BEV).

CLINICAL TRIALS

Study demographics and trial design

Primary Immune Deficiency (PID)

Table 3. Summary of patient demographics for clinical trials in PID

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n =number)	Mean age (Range)	Gender
IG304	To assess the safety, pharmacokinetics, and therapeutic efficacy of Flebogamma 10% Multi-center clinical, open-label.	IGIV3I 10% 300-600 mg/kg/infusion every 3 or 4 weeks for 12 months Intravenous infusion	Enrolled: 46 patients Completed study: 37 patients In detailed PK analysis: 19 patients	36.8 (6 - 65)	30 Male 16 Female

Study IG304

The **clinical study IG304** was designed for approximately 45-50 subjects with PID diseases requiring antibody replacement therapy and who have been receiving IGIV replacement therapy at a steady dose for at least 3 months prior to entry. Subjects participated in the study for 12 months (13 to 17 infusions based on individual dose intervals).

The primary efficacy endpoint was the number of serious bacterial infections per patient per year for the following types of infections: bacterial pneumonia, bacteremia/sepsis, osteomyelitis/septic arthritis, visceral abscesses and bacterial meningitis.

The rate of serious bacterial infections per patient per year was estimated by dividing the total number of serious bacterial infections observed in the study by the total patient years (days on study/365).

Based on the duration of observation in years of the 46 patients in the ITT population, and a total of 1 serious bacterial infection, the estimated infection rate is 0.025 serious bacterial infections/patient/year, with a 98% confidence interval of 0.001-0.133.

Immune Thrombocytopenic Purpura (ITP)

Table 4. Summary of patient demographics for clinical trials in ITP Clinical Trial

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
IG202	Study to evaluate the efficacy and the safety of Flebogamma 10% in patients with immune thrombocytopenic purpura Multicenter, open label, non-controlled trial.	Flebogamma 10% at a dose of 0.4g/kg/day over 5 consecutive days or at 1g/kg/day over a period of 2 consecutive days. Intravenous infusion	18 enrolled	43.7 (20 - 77)	6 Male 12 Female
IG0601	Study to evaluate the efficacy and the safety of Flebogamma 10% in patients with immune thrombocytopenic purpura Multicenter, open label, non-controlled trial.	Flebogamma 10% 1g/kg/day over 2 consecutive days, for a total dose of 2 g/kg. Intravenous infusion	58 enrolled	33.2 (3 - 70)	19 Male 39 Female

Study IG202

The **clinical study IG202** was designed for patients with chronic ITP who presented a platelet count of $\leq 20 \times 10^9$ /l. A total of 20 patients were planned. Each patient received a total dose of 2 g/kg Flebogamma 10%, given intravenously over either 2 days or 5 days in divided doses. All patients were monitored for a 3-month follow-up period after the first infusion.

The primary efficacy variable was the response to therapy, defined as a platelet count $\geq 50 \times 10^9$/l at any time during the study period. The primary efficacy endpoint was measured by the proportion of responders. If a subject received alternative treatments with corticoids or immunosuppressive agents within the 3 months of follow-up, the platelet count measured under intake was not considered for evaluating whether a subject was responder or not.

A total of 18 subjects were enrolled in the study. All 18 subjects completed the study. None discontinued the study early. All who received at least one infusion of the product were included in the ITT population (N=18), which was used for the efficacy and safety analyses. Flebogamma 10% given in 2-day or 5-day regimens, induced treatment response in 13 of the 18 subjects (72.2%) with chronic immune thrombocytopenia (ITP) and was well-tolerated.

The primary efficacy endpoint measured in this study was the response to therapy as defined by a platelet count greater than or equal to 50×10^9/l at any time during the study. In the ITT population (N=18), 13 subjects (72.2%) met the criteria for treatment responders.

Study IG0601

Clinical study IG0601 was designed for a total of 75 male and female subjects, ages 3 to 70 years of age, diagnosed with chronic ITP, to achieve 67 evaluable subjects. Enrollment of pediatric subjects were limited to 25% (not more than 18 subjects) of the total number of subjects (N = 75) needed to be enrolled.

After enrollment, Flebogamma 10% was infused intravenously at a dose of 1 g/kg/day for two consecutive days for a total dose of 2 g/kg.

A total of 58 (46 adults and 12 pediatrics) male and female subjects, ages 3 to 70, diagnosed with chronic ITP, were enrolled in **Study IG0601** and treated (Modified intent-to-treat [mITT] population) with Flebogamma 10%.

The primary efficacy endpoint in this study was the rate of response, defined as the proportion of treated subjects whose platelet counts increased from $\leq 20 \times 10^9$/l to $\geq 50 \times 10^9$/l by Day 8 ± 1 (the day of the first infusion was Day 1). The responder rate was 81% (47/58) in the mITT population. The proportion of adult responders was 76.1% (35/46) and the pediatric responder rate was 100% (12/12) (mITT population).

Guillain Barré syndrome

Information to support the use of Flebogamma 10% in the treatment of cases of Guillain Barré syndrome comes from a systematic review of clinical trials providing moderate quality of evidence (9).

DETAILED PHARMACOLOGY

See *Pharmacokinetics* subsection in *Action and Clinical Pharmacology*.

TOXICOLOGY

The results of the acute toxicity studies show no mortality, neither in mice nor rats, although these studies were performed at dose levels equal or higher than the maximum dose used in humans and the infusion rate was 6 to 30 times higher than the maximum rates recommended for humans. No relevant adverse effects could be confirmed either affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour of treated mice and rats.

In conclusion, the absence of mortality in the toxicological preclinical studies performed with Flebogamma, and the lack of any confirmed relevant adverse sign affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour of the treated mice and rats, supports the safety of Flebogamma for clinical trials in humans.

REFERENCES

1. Cayco AV, Perazella MA, Hayslett JP. Renal insufficiency after intravenous immune globulin therapy: a report of two cases and an analysis of the literature. *J Am Soc Nephrol* 1997; 8:1788-94.
2. Thomas MJ, Misbah SA, Chapel HM, et al. Hemolysis after high-dose intravenous Ig. *Blood* 1993; 15:3789.
3. Reinhart WH, Berchtold PE. Effect of high-dose intravenous immunoglobulin therapy on blood rheology. *Lancet* 1992; 339:662-4.
4. Kessary-Shoham H, Levy Y, Shoenfeld Y, et al. In vivo administration of intravenous immunoglobulin (IVIG) can lead to enhanced erythrocyte sequestration. *J Autoimmune* 1999; 13:129-35.
5. Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. *Ann Intern Med* 1994; 121:259-62.
6. Scribner CL, Kapit RM, Phillips ET, et al. Aseptic meningitis and intravenous immunoglobulin therapy. *Ann Intern Med* 1994; 121:305-6.
7. Tan E, Hajinazarian M, Bay W, et al. Acute renal failure resulting from intravenous immunoglobulin therapy. *Arch Neurol* 1993; 50:137-9.
8. Rizk A, Gorson KC, Kenney L, et al. Transfusion-related acute lung injury after the infusion of IVIG. *Transfusion* 2001; 41:264-8.
9. Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome (review). The Cochrane Library 2012;7: CD002063.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Part III: PATIENT MEDICATION INFORMATION

FLEBOGAMMA® 10%

Immune Globulin Intravenous (Human)

Read this carefully before you start taking **Flebogamma 10%** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Flebogamma 10%**.

Serious Warnings and Precautions

- Immune Globulin Intravenous (Human) products have been reported to be associated with kidney failure. You should talk to your healthcare provider if you have some kind of kidney disease, diabetes, are over 65, seriously dehydrated, have other diseases (called sepsis and paraproteinemia), or are taking drugs that you were told could damage your kidneys.
- Flebogamma 10% and other Immune Globulin Intravenous (Human) products have been reported to be associated with the premature destruction of red blood cells, a condition known as hemolytic anemia. Speak with your healthcare professional if you are taking antibiotics, have received a kidney transplant or blood transfusions, or you have a history of blood disorders.
- Immune Globulin Intravenous (Human) products have been reported to be associated with heart and blood circulation problems such as heart attack, stroke and blood clots (thrombosis). You should talk to your doctor if you have risk factors for these kinds of conditions. Some of these risk factors include obesity, old age, high blood pressure, diabetes, or a history of heart disease. Thrombosis may occur even in the absence of known risk factor.

What is Flebogamma 10% used for?

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

- Patients with Primary Immunodeficiency (PID), an inborn lack of antibodies.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (cancer of the blood where too many white blood cells are produced), in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) and recurrent bacterial infections in myeloma (tumour composed of cells derived from the bone marrow) patients who failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) in patients after a stem cell transplantation (allogeneic haematopoietic stem cell transplantation), when you are given stem cells from another person.
- Children and adolescents with the Acquired Immune Deficiency Syndrome (AIDS), it can be used to prevent troublesome infections.

Treatment of certain autoimmune disorders (immunomodulation) in adults, children and adolescents (2 - 18 years):

- 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.

How does Flebogamma 10% work?
Flebogamma 10% contains human normal immunoglobulin. 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 are the ingredients in Flebogamma 10%?
Medicinal ingredients: Human normal immunoglobulin
Non-medicinal ingredients: Sorbitol and water for injections

Flebogamma 10% comes in the following dosage forms:
Flebogamma 10% is a 100 mg/mL solution for infusion and comes in the following dosage forms: 5 g in 50 mL, 10 g in 100 mL and 20 g in 200 mL pack sizes.

Do not use Flebogamma 10%:
- If you are allergic to human normal immunoglobulin or any of the other ingredients of this medicine.
- 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.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Flebogamma 10%. Talk about any health conditions or problems you may have, including if you:

- have hypo- or agammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) with or without IgA deficiency.
- are having Flebogamma 10% for the first time, or it has been switched from an alternative human normal immunoglobulin (IGIV) 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.

Certain side effects may occur more frequently in case of high rate of infusion.

Effects on blood tests
After receiving Flebogamma 10%, the results of certain blood tests (serological tests) may be interfered for a certain time. If you have a blood test after receiving Flebogamma 10%, 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, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include 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, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Other warnings you should know about:

Children and adolescents
Vital signs (body temperature, blood pressure, heart rate and respiratory rate) should be observed during the infusion of Flebogamma 10%.

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 10% contains sorbitol
Each ml of this medicinal product contains 50 mg of sorbitol. Patients with rare hereditary problems of fructose intolerance (HFI) must not take this medicine.

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Flebogamma 10%:
Effects on vaccines: Flebogamma 10% 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.

How to take Flebogamma 10%:
Flebogamma 10% is given by injection into your veins (intravenous administration).

Usual dose:
The dose that you will be given will depend on your illness and body weight and will be worked out by your doctor.

At the beginning of your infusion you will receive Flebogamma 10% 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).

Overdose:
If you get more Flebogamma 10% 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 kidneys.

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Not applicable

What are possible side effects from using Flebogamma 10%?

These are not all the possible side effects you may feel when taking Flebogamma 10%. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations:

- A sudden fall in blood pressure and, in isolated cases, anaphylactic shock (which symptoms or 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 meningitis (which symptoms or 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 symptoms or 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).
- There have been reports of transfusion-related acute lung injury (TRALI) in patients administered IGIV. Therefore, patients should be monitored for pulmonary adverse reactions.

Other side effects reported in clinical studies with Flebogamma 10%:

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

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

Uncommon (may affect up to 1 in 100 people):
- influenza (flu)
- urinary infection
- red blood cells and white blood cells decreased
- anorexia (lack of appetite)
- dizziness (motion sickness)
- 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)
- tremor (to tremble)
- conjunctivitis (inflammation of the conjuntiva of the eyes)
- maculopathy (illness of the macula, in the retina of the eyes)
- photophobia (excessive sensitivity to light)
- ear pain

- vertigo
- blood pressure increased or decreased
- flushing (to blush)
- haematoma
- thrombosis
- postnasal drip (excessive mucus)
- sinus pain
- wheezing
- abdominal pain (including abdominal pain upper and abdominal pain distension)
- diarrhoea
- flatulence
- vomiting
- acne
- ecchymosis (large skin hematoma)
- erythema (redness of the skin)
- pruritus (itching)
- rash (eruption of the skin)
- arthralgia (joint pain)
- muscle spasms or muscle tightness
- neck pain
- pain in extremities
- chest discomfort/chest pain
- feeling cold
- infusion related reaction and infusion site reaction (including infusion site erythema and infusion site pain)
- fatigue
- feeling jittery (nervousness)
- influenza like illness
- malaise
- oedema peripheral
- haemoglobin decreased
- heart rate increased

Frequency not known (cannot be estimated from available data):
- dyspnoea (difficulty in breathing)

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.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
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.

Keep out of reach and sight of children.

If you want more information about Flebogamma 10%:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.grifols.ca, or by calling 1-800-482-5226.

This leaflet was prepared by:

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

Grifols Canada Ltd. (Importer and Distributor)
5060 Spectrum Way, Suite 405
Mississauga, Ontario
L4W 5N5

Last Revised: