PRODUCT MONOGRAPH

FLEBOGAMMA® 5%

Immune Globulin Intravenous (Human)

Solution for infusion, 50 mg/mL

Passive immunizing agent

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

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FLEBOGAMMA® 5%

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, 50 mg/mL	Sorbitol *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Flebogamma 5% 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 5% is a purified (at least 97% IgG), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG_1, 28.5% IgG_2, 2.7% IgG_3, and 2.2% IgG_4. Flebogamma 5% contains trace amounts of IgA (typically less than 50 µg/mL) and trace amounts of sodium and IgM.
Flebogamma 5% contains 5 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 1 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 5% 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 5% is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.
• Flebogamma 5% 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® 5% 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® 5% 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® 5% 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.

Hypersensitivity
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.

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 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[2-5]. Haemolytic anaemia can develop subsequent to IGIV therapy due to enhanced red blood cells (RBC) sequestration[6] (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[7-10]. 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[11].

Respiratory
Non-cardiogenic pulmonary edema has been reported in patients following IGIV treatment[12]. 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 5% 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 5% must not be administered to subjects with HFI.

Sexual Function/Reproduction
The effect of Flebogamma 5% 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 5% has not been established in pediatric patients below the age of 2 years.

Pediatrics (3 - 17 years of age): Flebogamma 5% was evaluated in 29 pediatric subjects with PID. 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 5% 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 5% 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 5%, 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 5%, two for replacement therapy in patients with primary immunodeficiency (one in both adults and children above 10 years and another in children between 2 to 16 years) and another for immunomodulation in adult patients with immune thrombocytopenic purpura (ITP). 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. 24 pediatric patients were included in the second trial, patients received total dose of 300-800 mg/kg/month IV every 21 or 28 days. The duration of treatment was 12 months. A total of 20 patients were included in the third study (ITP). 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 90 patients have been exposed to Flebogamma 5% and they have received 1,223 infusions. 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

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

Frequencies have been evaluated according to the following convention:

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

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

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

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

Pediatric population

The safety results for 29 pediatric patients (those ≤ 17 years old) included in the PID studies were evaluated. It was observed that the proportion of headache, pyrexia, tachycardia and hypotension in children was higher than in adults. Assessment of vital signs in clinical trials of the 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 5% 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.

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 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 5 days

Pediatric population

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

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 5% supplies a broad spectrum of opsonizing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Flebogamma 5% also contains a spectrum of antibodies capable of reacting with cells such as erythrocytes. The role of these antibodies and the mechanisms of action of IgG in Flebogamma 5% 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

Relevant pharmacokinetic (PK) parameters have been evaluated for Flebogamma 5% in the efficacy and safety study (IG201). At least 15 subjects were needed to participate 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).

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

In the clinical study assessing safety and efficacy in primary immunodeficiency (PID), Flebogamma 5% was administered as an IV infusion (300-600 mg/kg) to subjects every 3 (n = 8) or 4 (n = 12) weeks for 12 months. The pharmacokinetics of total IgG was determined after the 7th infusion for the 3-week dosing interval and after the 5th infusion for the 4-week dosing interval (Table 1 below).

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

Variable	3-Week Dosing Interval (n=8)		4-Week Dosing Interval (n=12)	
	Mean [Range]	SD	Mean [Range]	SD
Cmax (mg/dL)	1,929 [1,300-2,420]	441	2,069 [1,590-2,800]	338
$AUC_{0 - last}$ (day·mg/dL)	31,159 [20,458-40,104]	6,572	32,894 [27,650-41,814]	3,886
Clearance (mL/day)	139 [81-243]	57	109 [59-161]	33
Half-life (days)[a]	30 [19-41]	9	32 [25-39]	5
Trough IgG level (mg/dL)[b]	951.38 [773.17-1,143.15]	132.42	899.89 [776.70-1,137.14]	92.03

a. This half-life is an apparent value derived from a period of measurement of 28 days.
b. For subjects on the 3-week schedule, the average of the trough levels from Infusion 7 to the end of the study was calculated; for those on a 4-week schedule, the average of the trough levels from Infusion 5 to the end of the study was calculated. The means of the subject means are presented in this table.

There were 3 adolescent (up to 16 years of age) subjects who underwent pharmacokinetic testing, all of whom were on the 3-week infusion schedule. There were no clinically relevant differences among the adults and adolescents that were tested.

Conclusions for pharmacokinetic study

Overall, the patterns observed in the PK behaviour 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 31 days for both infusion schedules.

Moreover, trough total IgG and IgG subclass concentrations were maintained throughout the treatment period with Flebogamma 5%, 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.

To sum up, the results obtained with Flebogamma 5% show a pharmacokinetic profile similar to Flebogamma (a Grifols IGIV in clinical use since 1992) and other IVIG products. In addition, IgG trough levels are comparable to those after previous treatments and well above the minimum considered protective.

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% has a half-life of about 30-32 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 5% 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 5% is a ready to use sterile solution of human normal immunoglobulin for intravenous administration.

Flebogamma 5% 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 5%

Size	Protein (g)
10 mL	0.5
50 mL	2.5
100 mL	5
200 mL	10
400 mL	20

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Product

Proper name: Flebogamma 5%
Immune Globulin Intravenous (Human)

Product Characteristics

Flebogamma 5% is a sterile 5% 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 5% 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 5% 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 5% 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
IG201	Study to evaluate Safety, Efficacy, and Pharmacokinetics of Flebogamma 5% for Replacement Therapy in Primary Immunodeficiency Diseases (PID) Multicenter clinical, open-label.	IGIV3I 5% 300-600 mg/kg every 21 or 28 days Intravenous infusion	Enrolled: 46 patients Completed study: 41 patients In detailed PK analysis: 20 patients	38.9 (15 - 75)	29 Male 17 Female
IG0705	Clinical Study to Evaluate the Efficacy and Safety of Flebogamma 5% for Replacement Therapy in Pediatric Subjects with Primary Immunodeficiency Diseases (PIDD)	IGIV3I 5% 262-625 mg/kg every 3-4 weeks Intravenous infusion	Enrolled: 24 patients Completed study: 19 patients	9.0 (2-16)	19 Male 5 Female

Study IG201

The **clinical study IG201** 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.

To estimate the infection rate and develop the appropriate 1-sided 99% upper confidence bound, a generalized linear model for Poisson regression was used. Infection rates for individuals were calculated by dividing the number of events for that individual by the total amount of follow-up time.

Since the subjects in the clinical study were assigned to two different treatment intervals (3-week vs. 4-week infusion schedules), the dosage had to be adjusted to ensure that the subjects received approximately the same dosage on an annualized basis. Therefore, subjects in the 3-week schedule received 75% of the monthly (4-week) dosage per infusion. This resulted in a mean annualized dosage of 451 mg per kg per month for subjects in the 3-week schedule (n=13, range 288-588 mg per kg per month) and 448 mg per kg per month for subjects in the 4-week schedule (n=33, range 298-591 mg per kg per month).

During the study period, the annual rate of acute serious bacterial infection, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.021 (with an upper 1-sided 98% confidence interval of 0.112). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported.

Study IG0705

The **clinical study IG0705** was designed for 25 paediatric subjects to determine if the efficacy, safety and pharmacokinetics of this product differ in any way from characteristics demonstrated in the previous pivotal trial of this product (IG201).

The primary objective of this study was to determine if Flebogamma 5% was efficacious in children and adolescents with respect to FDA minimal requirements (no more than 1 serious bacterial infection per subject per year).

The annual rate of acute serious bacterial infections, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per subject per year, was 0.051 (with an upper 1-sided 99% confidence limit of 0.53). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported.

Immune Thrombocytopenic Purpura (ITP)

Table 6. 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 5% in patients diagnosed with immune thrombocytopenic purpura Multicenter, open label, non-controlled trial.	IGIV3I 5% at a dose of 0.4g/kg/day for 5 consecutive days. Intravenous infusion	20 patients	47 (18 - 85)	7 Male 13 Female

Study IG202

The **clinical study IG202** was designed for including 20 patients with chronic ITP who presented a platelet count below 20 x 10^9 /l. Subjects participated in the study for 3 months after first infusion with Flebogamma 5%.

The primary efficacy variable was the response to therapy, defined as a platelet count to $\geq$ 50 x 10^9/l at any time during the study period. If a patient 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 patient was responder or not.

Twenty patients were enrolled in the **study IG202** and received at least 1 infusion of Flebogamma 5%. Nineteen patients (95%) completed the study, and 1 patient (5%) was withdrawn from the study because she did not present an immune idiopathic thrombocytopenic purpura, disclosed after the initiation of treatment with Flebogamma 5%. The patients received a total of 97 infusions.

Efficacy analyses were performed on both intention-to-treat and per-protocol populations (ITT and PP, respectively). The ITT population includes all patients who were enrolled into the study and received at least 1 infusion of Flebogamma 5% (20 patients). The PP population includes patients who were enrolled into the study and received five infusions of the study drug (19 patients).

From the 20 patients in the ITT population a total 14 patients (70%) were responders to the treatment with Flebogamma 5%. The remaining 6 patients (30%) were classified as non-responders. In the PP population a total of 74% of patients were responders to the study drug.

Guillain Barré syndrome

Information to support the use of Flebogamma 5% in the treatment of cases of Guillain Barré syndrome comes from a systematic review of clinical trials providing moderate quality of evidence (13).

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.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Part III: PATIENT MEDICATION INFORMATION

FLEBOGAMMA® 5%
Immune Globulin Intravenous (Human)

Read this carefully before you start taking **Flebogamma 5%** 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 5%**.

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 5% 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 5% 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 5% work?
Flebogamma 5% 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 5%?
Medicinal ingredients: Human normal immunoglobulin
Non-medicinal ingredients: Sorbitol and water for injections

Flebogamma 5% comes in the following dosage forms:
Flebogamma 5% is a 50 mg/mL solution for infusion and comes in the following dosage forms: 0.5 g in 10 mL, 2.5 g in 50 mL, 5 g in 100 mL, 10 g in 200 mL and 20 g in 400 mL pack sizes.

Do not use Flebogamma 5%:
- 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 5%. 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.
- you are having Flebogamma 5% 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 5%, the results of certain blood tests (serological tests) may be interfered for a certain time. If you have a blood test after receiving Flebogamma 5%, 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 5%.

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 5% 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 5%:
Effects on vaccines: Flebogamma 5% 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 5%:
Flebogamma 5% 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 5% at a slow rate (0.01-0.02 ml/kg/min). Depending on how comfortable you feel, your doctor may then gradually increase the infusion rate (up to 0.1 ml/kg/min).

Overdose:
If you get more Flebogamma 5% 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 5%?

These are not all the possible side effects you may feel when taking Flebogamma 5%. 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 5%:

Common (may affect up to 1 in 10 people):
- headache
- injection site reaction
- fever (body temperature increased)

Uncommon (may affect up to 1 in 100 people):
- Coombs test positive
- dizziness (motion sickness)
- blood pressure increased or decreased
- bronchitis
- cough
- wheezing
- abdominal pain (including abdominal pain upper)
- diarrhoea
- vomiting
- nausea
- urticaria
- pruritus (itching)
- rash (eruption of the skin)
- dermatitis contact
- back pain
- myalgia

- arthralgia (joint pain)
- muscle cramp
- rigors (cold shivering sensation) or chills
- asthenia
- pain
- infusion site inflammation
- injection site reaction (including injection site oedema, pruritus, swelling and pain)
- migration of an implant

Frequency not known (cannot be estimated from available data):
- chest pain
- flushing (to blush)
- malaise
- dyspnoea (difficulty in breathing)

Additional side effects in children and adolescents

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

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 5%:

- 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.

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