

GRIFOLS

Immune Globulin Intravenous (Human)
Flebogamma® 5% DIF
 5% Liquid Preparation

Initial U.S. Approval: 2006

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Flebogamma® 5% DIF safely and effectively. See full prescribing information for Flebogamma® 5% DIF.

WARNING: ACUTE RENAL DYSFUNCTION AND FAILURE

See full prescribing information for complete boxed warning.

- Immune globulin intravenous (IGIV) products, particularly those with sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.
- For patients pre-disposed to renal dysfunction or failure, administer Flebogamma® 5% DIF at the minimum concentration available and the minimum infusion rate practicable.
- Flebogamma® 5% DIF does not contain sucrose.

INDICATIONS AND USAGE

Flebogamma® 5% DIF is a human immune globulin G (IgG) indicated for treatment of primary (inherited) humoral immunodeficiency disorders. (1)

DOSAGE AND ADMINISTRATION

Intravenous Use Only

- Treatment of Primary Immunodeficiency (2.2)

	Dose	Initial Infusion Rate	Maintenance Dose rate (if tolerated)
PI	300-600 mg/kg every 3 - 4 weeks	0.01 mL/kg/minute (0.5 mg/kg/min)	Increase to 0.10 mL/kg/minute (5 mg/kg/min)

- For patients at risk of renal dysfunction or thrombotic events, administer Flebogamma® 5% DIF at the minimum infusion rate practicable. [5.2, 5.4]
- Ensure that patients with pre-existing renal insufficiency are not volume-depleted and discontinue Flebogamma® 5% DIF if renal function deteriorates. [5.2]

DOSAGE FORMS AND STRENGTHS

Flebogamma® 5% DIF is supplied in 0.5, 2.5, 5, 10 and 20 g single use bottles. [3]

	0.5 g	10 mL
	2.5 g	50 mL
	5 g	100 mL
	10 g	200 mL
	20 g	400 mL

CONTRAINDICATIONS

- Anaphylactic or severe systemic reactions to human immunoglobulin.
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity.

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have Epinephrine immediately available to treat any acute severe hypersensitivity reactions. [5.1]
- Monitor renal function, including blood urea nitrogen, serum creatinine and urine output in patients at risk of developing acute renal failure. [5.2]
- Hyperproteinemia, with resultant changes in serum osmolality and electrolyte imbalances may occur in patients receiving IGIV therapy. [5.3]
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events and consider baseline assessment of blood viscosity for those at risk of hyperviscosity. [5.4]
- Aseptic Meningitis Syndrome (AMS) has been reported with IGIV treatments, especially with high doses or rapid infusion. [5.5]
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia. [5.6]
- Monitor patients for pulmonary adverse reactions (TRALI). [5.7]
- Flebogamma® 5% DIF is made from human plasma may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent. [5.8]
- Transitory rise of various passively transferred antibodies in patient blood may yield positive serological testing results. [5.9]
- Patients receiving Flebogamma® 5% DIF for first time or being restarted on product after treatment hiatus of more than 8 weeks may be at higher risk for development fever, chills, nausea, and vomiting. [5.10]

ADVERSE REACTIONS

The most common temporally related adverse reactions with an incidence \geq 5% include: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema. [6]

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines and confound results of serological testing [7].

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed. [8.1]
- Geriatric: In patients over age 65 or in any patients at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Flebogamma® 5% DIF at the minimum infusion rate practicable. [8.5]

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Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF

5% Liquid Preparation

FULL PRESCRIBING INFORMATION

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death (1). 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. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Flebogamma® 5% DIF does not contain sucrose. (See *Dosage and Administration* [2.3] and *Warnings and Precautions* [5.2] for important information intended to reduce the risk of acute renal failure.)

1 INDICATIONS AND USAGE

Flebogamma® 5% DIF is an immune globulin intravenous (Human) 5% preparation that is indicated for the treatment of primary immune deficiency, such as common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

2 DOSAGE AND ADMINISTRATION

Intravenous Use Only

2.1 Preparation and Handling

- Flebogamma® 5% DIF should be inspected visually for particulate matter and color prior to administration. If particles are detected the vial shall not be used. Do not use if turbid.
- If large doses are to be administered, several vials of Flebogamma® 5% DIF may be pooled into an empty sterile IV solution container by using aseptic technique.
- Dilution with IV fluids is not recommended. Injection of other medications into intravenous tubing being used for Flebogamma® 5% DIF is not recommended.
- Specific drug interactions and incompatibilities have not been studied.
- Flebogamma® 5% DIF should be infused through a separate intravenous line. Do not add any medications or IV fluids to the Flebogamma® 5% DIF infusion container. Do not mix IGIV products of different formulations or from different manufacturers.
- According to international recommendations for infusion equipment for medical use, an in-line filter with a pore size of 15 to 20 microns is recommended for the infusion. Antibacterial filters (0.2 micron) may also be used, although they may slow infusions.
- Discard unused contents and administration devices after use.

2.2 Treatment of Primary Humoral Immunodeficiency (PI)

As there are significant differences in the half-life of IgG among patients with primary immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response.

The usual dose of Flebogamma® 5% DIF for patients with PI is 300 to 600 mg/kg body weight (6.0 to 12.0 mL/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.

2.3 Administration

The recommended initial infusion rate of Flebogamma® 5% DIF is 0.01 mL/kg body weight/minute (0.5 mg/kg/minute). If the infusion is well-tolerated, during the first 30 minutes, the rate may be gradually increased to a maximum of 0.10 mL/kg/minute (5 mg/kg/minute).

For patients judged to be at risk for developing renal dysfunction or thromboembolic events, Flebogamma® 5% DIF should be administered at the minimum infusion rate practicable. (See *Warnings and Precautions* [5.2, 5.4])

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. Any vial that has been entered should be used promptly. Partially used vials should be discarded and not saved for future use because the solution contains no preservative. Do not use if turbid. Solution that has been frozen should not be used.

3 DOSAGE FORMS AND STRENGTHS

- 0.5 g protein in 10 mL solution
- 2.5 g protein in 50 mL solution
- 5 g protein in 100 mL solution
- 10 g protein in 200 mL solution
- 20 g protein in 400 mL solution

4 CONTRAINDICATIONS

- Anaphylactic or severe reactions to human immune globulin.
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity. (See *Warnings and Precautions* [5.1])

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Flebogamma® 5% DIF infusion immediately and institute appropriate treatment. Have Epinephrine immediately available for treatment of acute severe hypersensitivity reactions.

Flebogamma® 5% DIF contains trace amounts of IgA (less than 50 µg/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Flebogamma® 5% DIF is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction.

Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented.

5.2 Renal Failure

Assure that patients are not volume depleted prior to the initiation of the infusion of Flebogamma® 5% DIF. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure (1). Assess renal function, including measurement of BUN/serum creatinine, before the initial infusion of Flebogamma® 5% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinue use of the product.

For patients judged to be at risk for developing renal dysfunction, including 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% DIF at the minimum rate of infusion practicable (2). (See *Boxed Warning*) (See *Dosing and Administration* [2.3])

5.3 Hyperproteinemia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma® 5% DIF. It is clinically critical to distinguishing true hyponatremia from a pseudohyponatremia that is caused by a decreased calculated serum osmolality or elevated osmolar gap because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a higher risk of thrombotic events.

5.4 Thromboembolic Events

Thrombotic events may occur during or following IGIV treatment (11 - 13). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, or known/suspected hyperviscosity. 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. For patients judged to be at risk of developing thrombotic events, administer Flebogamma® 5% DIF at the minimum rate of infusion practicable.

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae (3 - 6). AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic milliliter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Provide a thorough neurological examination to patients exhibiting such symptoms and signs, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently following high-dose (e.g., > 1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Patients with a history of migraine may be more susceptible. (See *Patient Counseling Information* [17])

5.6 Hemolysis

Flebogamma® 5% DIF may contain blood group antibodies which may act as hemolysins and induce *in vivo* coating of red blood cells (RBC) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis (7 - 9). Hemolytic anemia may develop subsequent to Flebogamma® 5% DIF therapy due to enhanced RBC sequestration (10).

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after Flebogamma® 5% DIF infusion, perform appropriate confirmatory laboratory testing. (See *Patient Counseling Information* [17])

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema may occur in patients following IGIV treatment (14). This Transfusion-Related Acute Lung Injury (TRALI) is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours after transfusion.

Monitor patients for pulmonary adverse reactions. (See *Patient Counseling Information* [17]) If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies in both the product and patient serum.

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

5.8 Infectious Disease Transmission

Flebogamma® 5% DIF is made from human plasma. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk of transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma® 5% DIF. (See *Patient Counseling Information* [17])

5.9 Laboratory Tests

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma® 5% DIF and at appropriate intervals thereafter.

Consider 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.

5.10 Special Care Precautions

All patients, but especially individuals receiving Flebogamma® 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of inflammatory reactions characterized by fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding information in the *Dosage and Administration* [2.3] section may reduce the risk of these types of events.

6 ADVERSE REACTIONS

The most common temporally related adverse reactions (\geq 5%) occurring during or within 72 hours of the end of an infusion observed for PI were: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema (see Table 1). The adverse reactions often begin within 60 minutes of the start of the infusion.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse events were reported in a study of 46 individuals with primary humoral immunodeficiency diseases receiving infusions every 3 to 4 weeks of 300 to 600 mg/kg body weight. Forty-three (94%) subjects experienced at least 1 adverse event irrespective of the relationship with the product, and these subjects reported a total of 595 adverse events. None of the 46 subjects who participated in this study discontinued the study prematurely due to an adverse event considered related to the study drug. One subject had treatment-emergent bronchiectasis, mild, ongoing, after infusion #10; and one subject had recurrent moderate leucopenia after the 7th and 12th infusions.

Adverse events that occurred with an incidence of \geq 5% on a per subject basis are summarized in Table 1.

Table 1. Adverse Events Occurring with an Incidence of \geq 5% Irrespective of Causality

Adverse Event	Subjects (%) [N = 46]	Infusions* (%) [N = 709]
Sinusitis	20 (44)	5 (0.7)
Pyrexia	17 (37)	15 (2)
Headache	16 (35)	26 (4)
Upper respiratory tract infection	15 (33)	6 (0.8)
Combined bronchitis [1]	14 (30)	9 (1)
Cough or Productive cough	10 (22)	3 (0.4)
Diarrhoea	9 (20)	7 (1)
Pharyngitis	8 (17)	3 (0.4)
Asthma	8 (17)	0 (0)
Infusion site reaction [2]	7 (15)	13 (2)
Nasal congestion	7 (15)	0 (0)
Arthralgia	7 (15)	1 (0.1)
Nausea	6 (13)	3 (0.4)
Postnasal drip	6 (13)	2 (0.3)
Dizziness	6 (13)	1 (0.1)
Joint problems [3]	5 (11)	0 (0)
Rigors	5 (11)	6 (0.8)
Conjunctivitis	5 (11)	2 (0.3)
Nasopharyngitis	5 (11)	2 (0.3)
Rhinorrhoea	5 (11)	3 (0.4)
Back pain	4 (9)	5 (0.7)
Dyspnoea	4 (9)	1 (0.1)
Abdominal pain	4 (9)	1 (0.1)
Gastroenteritis	4 (9)	0 (0)
Dermatitis contact	4 (9)	2 (0.3)
Urticaria	4 (9)	3 (0.4)
Anemia	4 (9)	1 (0.1)
Erythema	4 (9)	4 (0.6)
Myalgia	3 (7)	2 (0.3)
Pain	3 (7)	5 (0.7)
Fatigue	3 (7)	1 (0.1)
Wheezing	3 (7)	1 (0.1)
Dyspepsia	3 (7)	0 (0)
Toothache	3 (7)	1 (0.1)
Sinus congestion	3 (7)	1 (0.1)
Muscle strain	3 (7)	1 (0.1)
Thermal burn	3 (7)	1 (0.1)
Abrasion	3 (7)	0 (0)
Eczema	3 (7)	1 (0.1)
Rash papular	3 (7)	1 (0.1)

* Number of infusions for which AE onset occurred during an infusion or within 72 hours post-infusion.

- Includes reported preferred terms of Bronchiectasis NOS, Bronchitis NOS, and Bronchitis acute NOS.
- Corresponds to preferred term of Injection site reaction NOS. If combined to include Infusion site inflammation, Injection site edema, Injection site pain, Injection site pruritis, Injection site reaction NOS, and Injection site swelling, there are 9 (20) subjects and 17 (2) infusions.
- Includes reported preferred terms of Bursitis, Chondromalacia patellae, Epicondylitis, Joint sprain, Joint swelling, Tenosynovitis, and Trigger finger.

The total number of AEs (regardless of attribution) reported whose onset were within 72 hours after the end of an infusion of Flebogamma® 5% DIF was 216. There were a total of 709 infusions, resulting in a rate of 0.305 (upper bound 95% CI = 41.2%) temporally associated AEs per infusion. There were 144 infusions (20.1%, 1-sided 95% upper bound CI = 24.4%) associated with 1 or more AEs that began within 72 hours after the completion of an infusion.

A summary of infusions with mild, moderate, and severe treatment-related adverse events is in Table 2.

Table 2. Summary of Infusions with Mild, Moderate, and Severe Treatment-Related Adverse Events

Severity of AE	No. Infusions with AE	Adjusted %*	Confidence Interval†
Mild	58	7.9	10.4
Moderate	25	3.6	4.9
Severe	1	0.1	0.3

* Adjusted % = average of the % of infusions with a treatment-related adverse event for each individual subject.

† The 95% upper bound for the adjusted % of infusions for which at least 1 treatment-related adverse event was reported was derived by using the t-statistic.

The number and percent of subjects with treatment-emergent rises in AST or ALT are in Table 3.

Table 3. Number (%) of Subjects with Treatment-Emergent Rises in AST or ALT (N = 46)

Laboratory Test	Assessment Criteria	n	%
AST	Above 3x the ULN*	3	6.5
ALT	Above 3x the ULN	1	2.2

* ULN = upper limit of normal.

None of these subjects had a concomitant treatment-emergent rise in total bilirubin.

6.2 Post-marketing Experience

The following adverse reactions have been identified during the post-approval use of IGIV products, including Flebogamma® 5% DIF [see *References* (15)]. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to exposure to the product.

System	Adverse Reaction
Respiratory	Apnea, Acute Respiratory Distress Syndrome (ARDS), Transfusion-Related Acute Lung Injury (TRALI), cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
Cardiovascular	Cardiac arrest, thromboembolism, vascular collapse, hypotension
Neurological	Coma, loss of consciousness, seizures, tremor
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiforme, bullous dermatitis
Hematologic	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
Musculoskeletal	Back pain
Gastrointestinal	Hepatic dysfunction, abdominal pain
General/Body as a Whole	Pyrexia, rigors

7 DRUG INTERACTIONS

Immunoglobulin administration may transiently impair the efficacy of live viral vaccines, such as measles, mumps, and rubella. The immunizing physician should be informed of recent therapy with Flebogamma® 5% DIF so that appropriate measures may be taken. (See *Patient Counseling Information* (17))

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been performed with Flebogamma® 5% DIF. It is also not known whether Flebogamma® 5% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma® 5% DIF should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.

8.4 Pediatric Use

Efficacy and safety in pediatric patients have not been established.

8.5 Geriatric Use

Subjects over 65 are at increased risk of renal failure with IGIV treatment. (See *Boxed Warnings and Precautions* (5.2)). For these subjects, and for any other subjects at risk of renal failure, the infusion rate of Flebogamma® 5% DIF should be limited to < 0.06 mL/kg/min (3 mg/kg/minute). Clinical studies of Flebogamma® 5% DIF did not include sufficient numbers of subjects over the age of 65, and therefore, the information available on these subjects is limited.

In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Flebogamma® 5% DIF at the minimum infusion rate practicable.

11 DESCRIPTION

Immune Globulin Intravenous (Human), Flebogamma® 5% DIF (dual inactivation plus nanofiltration) (IGIV) is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid, preparation of highly 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 down to 20 nm filters. Flebogamma® 5% DIF is a highly purified (≥ 97% IgG), unmodified, human IgG that contains the antibody specificities found in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG₁ is 66.6%, IgG₂, 28.5%, IgG₃, 2.7%, and IgG₄, 2.2%. Flebogamma® 5% DIF contains trace amounts of IgA (typically < 50 µg/mL) and IgM.

In the final formulation, Flebogamma® 5% DIF contains 5 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 3 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/L, which is within the normal physiological range. The Fc and Fab functionality is maintained in Flebogamma® 5% DIF. All Source Plasma used in the manufacture of Flebogamma® 5% DIF was collected only at FDA approved plasmapheresis centers in the United States and tested by FDA-licensed serological tests and found to be non-reactive (negative) for Hepatitis B Surface Antigen (HBsAg), antibodies to Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) and negative on Nucleic Acid Test (NAT) for HCV and HIV. Additionally, NAT testing for the presence of HCV and HIV in the manufacturing plasma pool is also performed and found to be negative.

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. Virus elimination experiments have been performed on 7 steps of the production process.

Flebogamma® 5% DIF production process includes the following specific virus inactivation/removal steps:

- Pasteurization at 60 °C, 10 hours
 - Solvent-Detergent treatment for 6 hours
 - Nanofiltration down to 20 nm Planova filters
- Grifols has developed a pasteurization method (heat treatment at 60 °C, 10 hours) using sorbitol as a stabilizer, which avoids denaturation of proteins and preserves antibody activity. Pasteurization achieves significant inactivation of both enveloped and non-enveloped viruses.
- Solvent detergent treatment inactivates lipid coated potential viral contaminants such as HIV, HBV and HCV by destroying the lipid coat and the associated virus binding sites. By using this method, infection of the target cells and in-vivo virus replication is prevented.
- Planova nanofiltration down to 20 nm pore size filter is included in the production process. This procedure eliminates potential viruses by a specific size exclusion mechanism. This has been shown to be effective in removing by more than 4 log₁₀ the virus of the smallest size assayed (porcine Parvovirus) by the smallest pore size nanofilter (20 nm).

The following purification processes can eliminate or inactivate a theoretical viral load as well:

- Fraction I precipitation
- Fraction II+III precipitation
- 4% PEG precipitation
- pH 4 treatment for 4 hours at 37 °C

The viral reduction data (in log₁₀) from these experiments are summarized in Table 4.

Table 4. Flebogamma® 5% DIF: viral reduction capacity of combined steps (log₁₀)

Target virus	HIV-1, HIV-2 (env. RNA)		HBV, Herpesvirus (env. DNA)		HCV (env. RNA)		WNV (env. RNA)	HAV (non-env. RNA)	Virus B19 (non-env. DNA)
	PRV	IBR	BVDV	SINDBIS	WNV	EMC	PPV		
Fraction I precipitation	< 1.00*	nd	nd	nd	nd	2.78	nd	< 1.00*	
Ethanol incubation (Fraction II+III)	1.48	nd	nd	nd	nd	< 1.00*	nd	nd	
PEG precipitation	≥ 6.10	≥ 5.92	nd	≥ 5.78	nd	nd	≥ 6.41	6.35	
Acid pH treatment	2.47	≥ 5.32	nd	< 1.00*	nd	nd	1.36	na	
Pasteurization	≥ 5.64	≥ 4.96	≥ 6.33	≥ 4.69	≥ 6.49	≥ 5.42	≥ 5.56	4.08	
Solvent Detergent	≥ 4.61	≥ 6.95	nd	≥ 6.14	nd	≥ 5.59	na	na	
Nanofiltration 20 nm	a	a	a	a	a	a	a	4.61	
Overall Reduction Capacity	≥ 20.30	≥ 23.15	≥ 6.33	≥ 16.61	≥ 6.49	≥ 13.79	≥ 13.33	15.04	

* When the RF is < 1 log₁₀, it is not taken into account for the calculation of the overall reduction capacity. ≥: No residual infectivity detected / nd: not done / na: non-applicable, since the virus is theoretically resistant to this treatment.

a) During the nanofiltration validation, 9 different viruses (HIV, PRV, BVDV, WNV, EMC, SV40, BEV, Echo 11 and PPV) were evaluated. Eight of these viruses were inactivated by the process conditions and/or removed by prefiltration. Only PPV, the virus of smallest size, was affected neither by the filtration conditions nor by the prefiltration and it was able to be assayed with the nanofilters.

Abbreviations: HIV: Human Immunodeficiency Virus, PRV: Pseudorabies Virus, IBR: Infectious Bovine Rhinotracheitis Virus, BVDV: Bovine Viral Diarrhea Virus, SINDBIS: Sindbis Virus, WNV: West Nile Virus, EMC: Encephalomyocarditis Virus, PPV: Porcine Parvovirus.

Additionally, the manufacturing process was investigated for its capacity to decrease infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.

Several of the individual production steps in Flebogamma® 5% DIF manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include: 4% Polyethylene glycol precipitation (≥ 6.19 log₁₀) and Planova nanofiltration down to 20 nm (≥ 5.45 log₁₀). These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Flebogamma® 5% DIF supplies a broad spectrum of opsonic and neutralizing IgG antibodies against bacteria, viral, parasitic, and mycoplasma agents and their toxins. The mechanism of action in PI has not been fully elucidated.

12.2 Pharmacodynamics

Immunoglobulins are fractionated blood products made from pooled human plasma. Immunoglobulins are endogenous proteins produced by B lymphocyte cells. The main component of Flebogamma® 5% DIF is IgG (≥ 97%) and a sub-class distribution of IgG₁, IgG₂, IgG₃, and IgG₄ of approximately 66.6%, 28.5%, 2.7% and 2.2%, respectively.

12.3 Pharmacokinetics

In the clinical study assessing safety and efficacy in primary immunodeficiency disease (PI), Flebogamma® 5% DIF was administered as an IV infusion (300 to 600 mg/kg) to subjects with PI 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 5).

Table 5. Pharmacokinetic Variables of Total IgG in Patients with PID

Variable	3-Week Dosing Interval (n = 8)		4-Week Dosing Interval (n = 12)	
	Mean	SD	Mean	SD
C _{max} (mg/dL)	1,929	441	2,069	338
	[1,300-2,420]*		[1,590-2,800]	
AUC _{0-24h} (day·mg/dL)	31,159	6,572	32,894	3,886
	[20,458-40,104]		[27,650-41,814]	
Clearance (mL/day)	139	57	109	33
	[81-243]		[59-161]	
Half-life (days) ^b	30	9	32	5
	[19-41]		[25-39]	
Trough IgG level (mg/dL) ^c	951.38	132.42	899.89	92.03
	[773.17-1,143.15]		[776.70-1,137.14]	

a. The numbers in brackets are the minimum and maximum values.

b. This half-life is an apparent value derived from a period of measurement of 28 days.

c. 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 (≤ 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of Flebogamma® 5% DIF or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

Acute toxicity studies were performed in mice and rats at doses up to 2.5 g/kg body weight with infusion rates 6 to 30 times higher than the maximum rates recommended for humans. Although the NOAEL was not determined, no relevant adverse effects could be confirmed affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity, and behavior of the treated mice and rats. Five out of the 25 rats treated with the highest dose at approximately 8 times the maximum infusion rate recommended for humans, showed a transient "reddish urine" sign which was not confirmed as a relevant toxicity causing phenomenon after renal macro and microscopical analysis. This phenomenon was associated to hemolysis when serum was analyzed, suggesting a possible relation to cross reactivity of rodent red cells with human antibodies. No "reddish urine" was detected in any mouse, a much smaller animal where the rate of infusion was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any renal alteration either.

14 CLINICAL STUDIES

A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy, safety and pharmacokinetics of Flebogamma® 5% DIF in adult and pediatric subjects with PI. A total of 46 patients aged 15-75 years (63% male, 37% female) were enrolled, and were treated with Flebogamma® 5% DIF at a dose of 300-600 mg/kg per infusion every 3 or 4 weeks for 12-months. During the study period, the annual rate of acute serious bacterial infection, the key efficacy variable, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses and bacterial meningitis per subject per year, was 0.021 (with an upper 1-sided 98% confidence interval of 0.001 to 0.112). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported (Table 6).

Table 6. Summary of Bacterial Infections (Intention-to-Treat Population, N = 46)

Infections	Patients (N=46) N (%)	Episodes	Estimates (1)	98% CI (2)
Bacterial pneumonia	1 (2.2)	1		
Bacteremia or sepsis	0 (0.0)	0		
Osteomyelitis/septic arthritis	0 (0.0)	0		
Bacterial meningitis	0 (0.0)	0		
Total patients	1 (2.2)	1	0.021	(0.001-0.112)

[1] Estimate = Total episodes/Total patient years.

[2] The confidence interval is obtained by using a generalized linear model procedure for Poisson distribution.

The number of days of work/school missed, the number of hospitalizations and the number of days of each hospitalization, the number of visits to physicians or emergency rooms, the number of other infections documented by positive radiographic findings and fever, and the number of days of therapeutic and prophylactic oral/parenteral antibiotic use was also monitored. These additional efficacy variables were annualized by using the subject-years exposure data only of those subjects experiencing the endpoints, not the entire study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days/subject/year. (The calculation uses all subjects, including those who had no infections, see Table 7).

Table 7. Summary of Secondary Efficacy Variables

Variable	Subjects		Mean number of events, days or visits/subject/year (1)
	N	%	
Work/school days missed	23	50.0	12.95
Days of normal activities missed	18	39.1	7.28
Days in hospital	4	8.7	0.77
Visits to physician/ER	29	63.0	4.31
Number of other documented infectious episodes	33	71.7	1.96
Days of therapeutic oral antibiotic use	35	76.1	55.52
Days of therapeutic parenteral antibiotic use	2	4.3	0.14
Days of other therapeutic antibiotic use	16	34.8	44.30
Days of prophylactic oral antibiotic use	19	41.3	81.08
Days of prophylactic parenteral antibiotic use	1	2.3	0.02
Days of other prophylactic antibiotic use	0	0.0	0.00

[1] Days of work/school missed per patient year are derived as total days of work/school missed divided by total days in study multiplied by 365. If data are missing for a period (e.g., between Infusion 2 and Infusion 3), then number of days in this period is not counted in the denominator. All other endpoints are derived similarly.

The dosing statistics for this study are in Table 8.

Table 8. Statistical Summary of the Mean Total Dose (mg/kg) of Flebogamma® 5% DIF Administered Per Infusion

Statistic	3-Week Dosing Interval	4-Week Dosing Interval	Total
N	13	33	46
Mean (SD)	451 (98.72)	448 (81.93)	449 (85.96)
Median	440	453	449
Q1, Q3*	384.2, 540.5	379.5, 511.1	380.9, 518.8
Min, Max	288.4, 588.2	298.2, 591.1	288.4, 591.1

a. Q1 is the 25th percentile, and Q3 is the 75th percentile.

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16 HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma® 5% DIF is supplied in single-use, individually laser etched vials containing the labeled amount of functionally active IgG.

The following dosage forms are available:

NDC Number	Size	Grams Protein
61953-0004-1	10 mL	0.5 g
61953-0004-2	50 mL	2.5 g
61953-0004-3	100 mL	5.0 g
61953-0004-4	200 mL	10.0 g
61953-0004-5	400 mL	20.0 g

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number.

When stored at room temperature (up to 25 °C [77 °F]), Flebogamma® 5% DIF is stable for 24 months, as indicated by the expiration date printed on the outer carton and container label. Store at +2 to +25 °C (36 to 77 °F). Do not freeze. Discard after expiration date.

17 PATIENT COUNSELING INFORMATION

Inform patients to immediately report the following to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath. (See *Renal Failure* (5.2)).
 - Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting. (See *Aseptic Meningitis Syndrome* (5.5)).
 - Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine. (See *Hemolysis* (5.6)).
 - Trouble breathing, chest pain, blue lips or extremities, fever. (See *TRALI* (5.7)).
- Inform patients that Flebogamma® 5% DIF is made from human plasma and may contain infectious agents that can cause disease. Explain that the risk Flebogamma® 5% DIF may transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing the donated plasma for certain virus infections and by inactivating and/or removing certain viruses during manufacturing (see *Warnings and Precautions* (5.8)). Patients should report any symptoms that concern them.
- Inform patients that Flebogamma® 5% DIF may interfere with their immune response to live viral vaccines (i.e., MMR) and instruct patients to notify their health care provider of this potential interaction when they are receiving vaccinations. It is recommended that the lot number of the vials used be recorded when Flebogamma® 5% DIF is administered.

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