HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLEBOGAMMA 10% DIF safely and effectively. See full prescribing information for FLEBOGAMMA 10% DIF

FLEBOGAMMA 10% DIF (immune globulin intravenous [Human]), solution for intravenous administration
Initial U.S. Approval: 2010

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis administer FLEBOGAMMA 10% DIF 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 of hyperviscosity.**
- **Renal dysfunction, acute renal failure, osmotic nephrosis and death may occur with the administration of human immune globulin intravenous (IGIV) products, particularly those products that contain sucrose. FLEBOGAMMA 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer FLEBOGAMMA 10% DIF at the minimum dose and infusion rate practicable. (5.2)**

----------RECENT MAJOR CHANGES----------
Indications and Usage (1), Dosage and Administration (2) XX/XXXX

----------INDICATIONS AND USAGE----------
Flebogamma 10% DIF is an immune globulin intravenous (human), indicated for treatment of:

- Primary (inherited) Immunodeficiency (PI). (1.1)
- Chronic Primary Immune Thrombocytopenia (ITP) in patients 2 years of age and older. (1.2)

----------DOSAGE AND ADMINISTRATION----------
For Intravenous Use Only

Indication	Dose	Initial Infusion Rate	Maintenance Infusion Rate (if tolerated)
PI	300-600 mg per kg every 3-4 weeks	0.01 mL per kg per minute (1 mg/kg/min)	0.08 mL per kg per minute (8 mg per kg per min)
ITP	1 g per kg daily for 2 consecutive days	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)

- Ensure that patients with pre-existing renal insufficiency are not volume-depleted and discontinue Flebogamma 10% DIF if renal function deteriorates. (5.2)
- For patients at risk of renal dysfunction or thrombosis, administer Flebogamma 10% DIF at the minimum dose and infusion rate practicable. (5.2, 5.4)

----------DOSAGE FORMS AND STRENGTHS----------
Solution for intravenous injection containing 10% IgG (100 mg per mL). (3)

----------CONTRAINDICATIONS----------

- History of anaphylactic or severe systemic reactions to human immunoglobulin. (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity. (4)

----------WARNINGS AND PRECAUTIONS ----------

- IgA deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. (5.1)
- Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma 10% DIF therapy. (5.3)
- Aseptic meningitis syndrome (AMS) may occur in patients receiving Flebogamma 10% DIF therapy, especially with high doses or rapid infusion rates. (5.5)
- Hemolysis, either intravascular or due to enhanced red blood cell sequestration, can develop subsequent to Flebogamma 10% DIF treatment. Risk factors include high doses and non-O blood group. Monitor patients for hemolysis and hemolytic anemia. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI). (5.7)
- Patients receiving Flebogamma 10% 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 development of fever, chills, nausea, and vomiting. (5.8)
- Flebogamma 10% DIF is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.9)
- Passive transfer of antibodies may confound serologic testing. (5.11)
- Flebogamma 10% DIF contains sorbitol. The presence of sorbitol presents a risk to those with hereditary fructose intolerance (HFI). (5.12)

----------ADVERSE REACTIONS----------
The most common adverse reactions (reported in ≥5% of clinical trial subjects) were:
PI: headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and pain in extremities.
ITP: headache, pyrexia, nausea, chills, vomiting, body temperature increased, dizziness, back pain, hypotension, hypertension, heart rate increased and diarrhea. (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, such as measles, mumps, and rubella. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: no human or animal data. (8.1)
- Pediatrics: increased risk of adverse reactions compared with adults. (8.4)
- Geriatric: in patients aged 65 years or older or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose. Infuse Flebogamma 10% DIF at the minimum dose and infusion rate practicable and at <0.04 mL per kg per min (<4 mg per kg per min). (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: MM/YYYY

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FULL PRESCRIBING INFORMATION

WARNING: THROMBOSIS, RENAL DYSFUNCTION, and ACUTE RENAL FAILURE

- **Thrombosis may occur with immune globulin products, including FLEBOGAMMA 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. *(see Warnings and Precautions (5.4)* and *Patient Counseling Information (17))***
- **For patients at risk of thrombosis, administer FLEBOGAMMA 10% DIF 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 patient at risk for hyperviscosity. *(see Dosage and Administration (2.3)* and *Warnings and Precautions (5.4))***
- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death[1] have been related to intravenous immune globulin (IGIV) products. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.**
- **Administer FLEBOGAMMA 10% DIF at the minimum dose and rate of infusion practicable in patients at risk for renal dysfunction or failure.**
- **Reports of renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose as a stabilizer. They account for a disproportionate share of the total number of reported cases of renal dysfunction and acute renal failure. FLEBOGAMMA 10% DIF does not contain sucrose. *(see Dosage and Administration (2.3)* and *Warnings and Precautions (5.2))***

1 INDICATIONS AND USAGE

Flebogamma 10% DIF is an immune globulin intravenous (human) solution indicated for the treatment of:

1.1 Primary Immunodeficiency (PI)

Flebogamma 10% DIF is indicated as replacement therapy in primary immunodeficiency (PI) including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

1.2 Primary Immune Thrombocytopenia (ITP)

Flebogamma 10% DIF is indicated for the treatment of patients 2 years of age and older with chronic primary immune thrombocytopenia to raise platelet count.

2. DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Dosage

Table 1. Recommended Infusion Rates for Flebogamma 10% DIF

Indication	Dose	Initial Infusion Rate	Maintenance Dose Rate (if tolerated)
PI	300 to 600 mg per kg body weight (3.0 to 6.0 mL per kg) administered every 3 to 4 weeks	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)
ITP	1 g per kg body weight (10 mL per kg) daily for 2 consecutive days	0.01 mL per kg per minute (1 mg per kg per min)	0.08 mL per kg per minute (8 mg per kg per min)

As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Adjust the dose according to clinical response.

Adjust the dosage over time to achieve the desired serum trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.

2.2 Preparation and Handling

- Inspect Flebogamma 10% DIF visually for particulate matter and color prior to administration. Do not use the vial if particles are detected. Do not use if turbid.
- Several vials of Flebogamma 10% DIF may be pooled into an empty sterile solution container by using aseptic technique, if large doses are to be administered.
- Do not dilute with intravenous fluids. Do not inject other medications into intravenous tubing being used for Flebogamma 10% DIF.
- Infuse Flebogamma 10% DIF through a separate intravenous line. Do not add any medications or intravenous fluids to the Flebogamma 10% DIF infusion container. Do not mix IGIV products of different formulations or from different manufacturers.
- Discard unused contents and administration devices after use.
- Use promptly any vial that has been entered.
- Discard partially used vials. Do not save for future use because the solution contains no preservative.
- Do not use solution that has been frozen.

2.3 Administration

The recommended initial infusion rate of Flebogamma 10% DIF is 0.01 mL per kg body weight per minute (1 mg per kg per min) for the first thirty minutes. If tolerated, the rate may be gradually increased to 0.04 mL per kg body weight per minute (4 mg per kg per min) and if

tolerated, gradually increased to a maximum of 0.08 mL per kg body weight per min (8 mg per kg per min).

Monitor patient vital signs throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient.

For the first 2-3 infusions, Flebogamma 10% DIF may be administered at infusion rates slower than recommended rates. If after administration of the first few infusions no adverse drug reactions are observed, the infusion rate for subsequent infusions may be slowly increased to the maximum rate. For patients experiencing adverse drug reactions, reduce the infusion rate in subsequent infusions or administer IGIV at 5% concentration.

3. DOSAGE FORMS AND STRENGTHS

Flebogamma 10% DIF is a liquid preparation containing 10% IgG (100 mg per mL).

4 CONTRAINDICATIONS

- Flebogamma 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic hypersensitivity reactions to the administration of human immune globulin.
- Flebogamma 10% DIF is contraindicated in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. *(see Warnings and Precautions (5.1))*

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions and anaphylactic reactions with a fall in blood pressure may occur, even in patients who tolerated treatment with IGIV in the past. *(see Contraindications (4))* If a hypersensitivity reaction develops, discontinue Flebogamma 10% DIF infusion immediately and institute appropriate treatment.

Flebogamma 10% DIF contains trace amounts of IgA (less than 100 µg/mL). *(see Description (11))* Patients with antibodies to IgA have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Flebogamma 10% DIF is contraindicated in patients with antibodies against IgA and a history of hypersensitivity reaction. *(see Contraindications (4))*

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular nephropathy, osmotic nephrosis and death have been reported in patients receiving IGIV, particularly those products containing sucrose.[2] Flebogamma 10% DIF does not contain sucrose.

Ensure that patients are not volume-depleted before administering Flebogamma 10% DIF. 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 years, volume depletion, sepsis, paraproteinemia or patients receiving known nephrotoxic drugs, administer Flebogamma 10% DIF at the minimum dose and rate of infusion practicable.[3] *(see Boxed Warning) (see Dosing and Administration* (2.3)*)*

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma 10% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of the product.

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma 10% DIF therapy. It is critical to distinguish true hyponatremia from pseudohyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolarity or elevated osmolar gap. This is because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and increased risk of thrombosis.

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including Flebogamma 10% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

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. *(see Warnings and Precautions (5.10))* For patients at risk of thrombosis, administer Flebogamma 10% DIF 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 Boxed Warning, Dosage and Administration* (2.3) *and Patient Counseling Information* (17)*)*

5.5 Aseptic Meningitis Syndrome (AMS)

AMS has been reported to occur following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.[4,5] The symptoms of AMS usually begin within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. *(see Patient Counseling Information* (17)*)* Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL but negative culture results. Conduct a thorough neurological examination of patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently following high doses (e.g., >2 g per kg body weight) or rapid infusion of IGIV.

5.6 Hemolysis

Flebogamma 10% DIF may contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct

antiglobulin test (DAT) (Coombs' test) and hemolysis.[6,7] Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration and acute hemolysis, consistent with intravascular hemolysis.[8] Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of IGIV.

The following risk factors may be associated with the development of hemolysis following IGIV administration: high doses (e.g., >2 g per kg), given either as a single administration or divided over several days, and non-O blood group.[9] Other individual patient factors, such as an underlying inflammatory state (as may be reflected by, for example, elevated C-reactive protein or erythrocyte sedimentation rate), have been hypothesized to increase the risk of hemolysis following administration of IGIV,[10] but their role is uncertain. Hemolysis has been reported following administration of IGIV for a variety of indications, including ITP and PI.[11] Monitor patients for clinical signs and symptoms of hemolysis, particularly patients with risk factors noted above. Consider appropriate laboratory testing in higher risk patients, including measurement of hemoglobin or hematocrit prior to infusion and within 36 to 96 hours post infusion. If clinical signs and symptoms of hemolysis or a significant drop in hemoglobin or hematocrit have been observed, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. *(see Patient Counseling Information* (17)*)*

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Non-cardiogenic pulmonary edema has been reported in patients following IGIV treatment.[12] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. *(see Patient Counseling Information* (17)*)* If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Infusion Reactions

Individuals receiving Flebogamma 10% 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 fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events. *(see Dosage and Administration (2.3))*

5.9 Transmissible Infectious Agents

Because Flebogamma 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and theoretically, the Creutzfeldt-Jakob (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. No cases of transmission of viral diseases or CJD have been associated with the use of Flebogamma 10% DIF. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 1-888-474-3657. Before prescribing or

administering Flebogamma 10% DIF, the physician should discuss the risks and benefits of its use with the patient. *(see Patient Counseling Information* (17)*)*

5.10 Monitoring: 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 BUN and serum creatinine, before the initial infusion of Flebogamma 10% DIF 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 potential for increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma 10% DIF, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

5.11 Interference with 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.

5.12 Hereditary Fructose Intolerance

Flebogamma 10% DIF 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 becomes symptomatic after breast feeding. Flebogamma 10% DIF must not be administered to subjects with HFI.

6 ADVERSE REACTIONS

The most common adverse reactions (reported in ≥5% of clinical trial subjects) were:
PI: headache, fever/pyrexia, shaking, tachycardia, hypotension, back pain, myalgia, hypertension, chest pain, pain, nausea, infusion site reactions and pain in extremities.
ITP: headache, pyrexia, nausea, chills, vomiting, body temperature increased, dizziness, back pain, hypotension, hypertension, heart rate increased and diarrhea.

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 Trials 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.

Primary Immunodeficiency (PI)

In a multicenter, open-label, non-randomized, historically controlled clinical study, 46 individuals with PI received infusions of Flebogamma 10% DIF at doses of 300 to

600 mg/kg body weight every 3 weeks (mean dose 469 mg/kg) or 4 weeks (mean dose 457 mg/kg) for up to 12 months. *(see Clinical Studies (14.1))*

One subject experienced four serious adverse events (SAE) (bacterial pneumonia, subcutaneous abscess and two episodes of cellulitis) and withdrew from the study. Two other subjects discontinued prematurely due to AEs (back pain/chest pain/headache; and chills/tachycardia). Three subjects experienced four SAEs (drug abuse/depression; hernia; and sinusitis) unrelated to the product.

One or more product-related adverse reactions were reported in 38 (83%) subjects. Adverse reaction intensity was reported as mild in 117 infusions, moderate in 74 infusions, and severe in 8 infusions. The percentage of infusions associated with mild, moderate or severe adverse reactions was 19.5% (upper bound 95% CI=22.9%), 12.3 % (upper bound 95% CI=15.2%) and 1.3% (upper bound 95% CI=2.6%), respectively.

The total number of temporally associated adverse reactions (i.e., reported within 72 hours post-infusion) was 291. Since a total of 601 infusions were administered, the rate of temporally associated adverse reactions per infusion was 0.48 (upper bound of the 1-sided 95% confidence interval: 0.52). A total of 166 infusions (30.3%, 1-sided 95% upper bound CI = 37.6%) were associated with one or more temporally associated adverse reactions. In the 21 subjects who received pre-medication, 12 (57%) reported temporally associated adverse reactions for 48 of 130 infusions (37%).

Adverse reactions that occurred with an incidence of ≥5% on a per-subject basis are summarized in Table 2.

Table 2. Adverse Reactions Occurring in ≥5% of Subjects

Adverse Reaction	Subjects (%) N=46	Number of Events
Headache	24 (52.2)	71
Pyrexia[a]	19 (41.3)	11
Rigors	17 (37.0)	38
Tachycardia/heart rate increased	11 (23.9)	20
Hypotension	9 (19.6)	11
Back Pain	8 (17.4)	27
Myalgia	8 (17.4)	21
Hypertension[b]	7 (15.2)	12
Chest pain[c]	6 (13)	25
Pain	4 (8.7)	8
Nausea	4 (8.7)	6
Infusion site reaction	3 (6.5)	6
Pain in extremities	3 (6.5)	3

a. includes combined reported terms of pyrexia and body temperature increase.
b. includes combined reported terms of hypertension, diastolic hypertension, blood pressure increased, systolic blood pressure increased and systolic hypertension.
c. includes combined reported terms of chest pain and chest discomfort.

Other common adverse drug reactions reported in <5% of the subjects included flatulence, fatigue, feeling cold, malaise, neck pain, dizziness, wheezing, muscle spasms/tightness and abdominal distension/pain.

Forty-three of 46 subjects had a negative Coombs' test at baseline. Of these 43 subjects, 10 (23.3%) developed a positive Coombs' test at some time during the study. However, no subjects showed evidence of hemolytic anemia.

Chronic Primary Immune Thrombocytopenia (ITP)

In a prospective, open-label, multicenter study, 58 subjects (46 adult and 12 pediatric) with chronic ITP were treated with Flebogamma 10% DIF, administered intravenously at a dose of 1 g per kg per day for 2 consecutive days, for a total dose of 2 g per kg, at a starting rate of 0.01 mL per kg per minute for 30 minutes.

Three SAEs of moderate to severe intensity were reported in 3 adult subjects during the 30 day follow-up period: soft tissue inflammation (unrelated) of unknown etiology in one subject on Day 29 and headache in two subjects (possibly related) on Day 2. All subjects recovered without sequelae.

Forty-eight (82.8%) subjects had one or more product related adverse reactions at some time during the study. Adverse reactions that occurred with an incidence of at least 5% on a per subject basis are summarized in Table 3. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Pediatric Use (8.4) and Clinical Studies (14.2))*

Table 3. Adverse Reactions Occurring in ≥5% of Subjects

Adverse Reaction	Adults (N = 46)		Pediatrics (N = 12)		All Subjects (N = 58)	
	n (%)	Number of Events	n (%)	Number of Events	n (%)	Number of Events
Headache	24 (52.2)	34	11 (91.7)	19	35 (60.3)	53
Nausea	4 (8.7)	4	8 (66.7)	9	12 (20.7)	13
Pyrexia	8 (17.4)	11	4 (33.3)	5	12 (20.7)	16
Chills	7 (15.2)	8	4 (33.3)	4	11 (19.0)	12
Vomiting	4 (8.7)	4	5 (41.7)	5	9 (15.5)	9
Body temperature increased	3 (6.5)	3	2 (16.7)	2	5 (8.6)	5
Back pain	2 (4.3)	2	2 (16.7)	2	4 (6.9)	4
Dizziness	4 (8.7)	4	0	0	4 (6.9)	4
Diarrhoea	3 (6.5)	3	0	0	3 (5.2)	3
Heart rate increased	1 (2.2)	1	2 (16.7)	2	3 (5.2)	3
Hypertension	2 (4.3)	2	1 (8.3)	1	3 (5.2)	3
Hypotension	1 (2.2)	1	2 (16.7)	3	3 (5.2)	4

In a supportive study of Flebogamma 10% DIF in adults (N=18) with ITP, three SAEs in 2 subjects were reported over the 3 month follow-up period: one case of thrombosis (possibly related) in one subject, and leukopenia (from 5.3 x 10^9/L pre-infusion to 2.7 x 10^9/L at Day 3; probably related) and decreased hemoglobin (from 11.7 g/dL pre-infusion to 9.8 g/dL on Day 2; probably related) in a second subject. All subjects recovered without sequelae.

6.2 Post-marketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse reactions have been identified during post-approval use of IGIV products,[13-14] including Flebogamma 5% and 10% DIF.

Infusion reactions	Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
Renal	Acute renal dysfunction/failure, osmotic nephropathy
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, aseptic meningitis syndrome
Integumentary	Stevens-Johnson Syndrome, epidermolysis, erythema multiformae, dermatitis (e.g., 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

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps and rubella. Inform the immunizing physician of recent therapy with Flebogamma 10% DIF so that appropriate measures can be taken. *(see Patient Counseling Information* (17)*)*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies of Flebogamma 10% DIF use in pregnant women. Animal reproduction studies have not been performed with Flebogamma 10% DIF. It is also not known whether Flebogamma 10% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation. Flebogamma 10% DIF should be given to a pregnant woman only if clearly needed.

8.2 Lactation

Risk Summary

There is no information regarding the presence of Flebogamma 10% DIF in human milk, its effects on the breastfed infant, or its effects on milk production The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Flebogamma 10% DIF and any potential adverse effects on the breastfed infant from Flebogamma 10% DIF or from the underlying maternal condition.

8.4 Pediatric Use

Primary Immunodeficiency (PI)

Three (3) pediatric subjects with PI (two between the ages of 6 and 10, and one 16 years old) were included in the clinical evaluation of Flebogamma 10% DIF. This number is too small to establish safety and efficacy in the pediatric population. *(see Clinical Studies (14))*

Chronic Primary Immune Thrombocytopenia (ITP)

Twelve (12) pediatric subjects with chronic ITP were enrolled and treated with Flebogamma 10% DIF in a clinical trial. Of the 12 subjects enrolled and treated, 4 were children and 8 were adolescents. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Clinical Trials Experience (6.1))*

The safety and effectiveness of Flebogamma 10% DIF has not been established in pediatric subjects under the age of 2.

8.5 Geriatric Use

Limited information is available for the geriatric use of Flebogamma 10% DIF. Clinical studies of Flebogamma 10% DIF did not include sufficient numbers of subjects aged ≥65 years to determine whether they respond differently from younger subjects. Use caution when administering Flebogamma 10% DIF to patients aged ≥65 years who are judged to be at increased risk for developing thrombosis or renal insufficiency. Do not exceed the recommended dose, and infuse Flebogamma 10% DIF at the minimum dose and infusion rate practicable and at less than 0.04 mL per kg per minute (4 mg per kg per min). *(see Boxed Warning, Warning and Precautions (5.2, 5.4) and Dosage and Administration (2.3))*

10 OVERDOSAGE

Overdose may lead to fluid overload and hyperviscosity. Patients at particular risk of complications of fluid overload and hyperviscosity include elderly patients and patients with cardiac or renal impairment.

11 DESCRIPTION

Flebogamma 10% DIF is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold ethanol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment and Planova nanofiltration using 20 nanometer (nm) filters.

Flebogamma 10% DIF is a purified (at least 97% IgG), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG_1, 27.9% IgG_2, 3.0% IgG_3 and 2.5% IgG_4. Flebogamma 10% DIF contains trace amounts of IgA (typically less than 100 µg/mL) and trace amounts of sodium and IgM.

Flebogamma 10% DIF contains 10 g human normal immunoglobulin and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, and ≤ 6 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.

Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collections and plasma preparation. Each individual plasma donation used in the manufacture of Flebogamma 10% DIF is collected only at FDA-approved blood establishments and is tested by FDA licensed serological test for hepatitis B surface antigen (HBsAg), and for antibodies to human immunodeficiency virus (HIV-1/HIV-2) and hepatitis C virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, mini-pools of plasma are tested for the presence of HBV, HIV-1 and HCV by FDA licensed nucleic acid testing (NAT) and found to be negative. In addition, plasma is tested by in-process NAT for hepatitis A virus (HAV) and parvovirus B19 (B19) on mini-pools and the viral load limit for B19 in the manufacturing pool is set not to exceed 10^4 IU/mL. NAT for the presence of HCV and HIV in the manufacturing plasma pool is also performed and found to be negative.

To further improve the margin of safety, three dedicated, independent virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely pasteurization at 60 ºC, 10 hours, solvent-detergent treatment for 6 hours and nanofiltration down to 20 nm Planova filters.

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed on seven steps of the production process (pasteurization, solvent-detergent treatment, nanofiltration, Fraction I precipitation, Fraction II+III precipitation, 4% PEG precipitation and pH treatment for 4 hours at 37 ºC).

The viral reduction data (in $\log_{10}$) from these experiments are summarized in Table 4.

Table 4. Flebogamma 10% DIF: viral reduction capacity of combined steps ($\log_{10}$)

Target virus	**HIV-1, HIV-2 (env. RNA)**	**HBV Herpesvirus (env. DNA)**		**HCV (env. RNA)**		**WNV (env. RNA)**	**HAV (non-env. RNA)**	**B19 Virus (non-env. DNA)**
Model virus	HIV-1	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 nanometer	≥ 4.81	≥ 4.63	nd	≥ 4.67	nd	≥ 3.63	≥ 5.92	4.61

Overall Reduction Capacity	≥ 25.11	≥ 27.78	≥ 6.33	≥ 21.28	≥ 6.49	≥ 17.42	≥ 19.25	15.04

*When the RF is <1 $\log_{10}$, 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.
Abbreviations: HIV= Human immunodeficiency virus; PRV= Pseudorabies virus; IBR= Infectious bovine rhinotracheitis virus, BVDV; Bovine viral diarrhoea 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 individual production steps in the Flebogamma 10% DIF manufacturing process have been shown to decrease TSE infectivity of an experimental model agent. TSE reduction steps include 4% polyethylene glycol precipitation [at least 6.19 $\log_{10}$] and Planova nanofiltration using a 20 nanometer filter [at least 5.45 $\log_{10}$]. 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

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

Chronic ITP: the mechanism of action of immunoglobulins in the treatment of chronic ITP has not been fully elucidated.

12.3 Pharmacokinetics

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

The mean dose (range) for those on the 21-day schedule was 476 mg/kg (range: 339-597) and 496 mg/kg (range: 434-588) for those on the 28-day schedule. Blood samples for PK analysis were obtained after Infusion #7 for subjects on a 28-day schedule and after Infusion #9 for subjects on a 21-day schedule. Table 5 summarizes the pharmacokinetic parameters of Flebogamma 10% DIF, measured as serum concentrations of total IgG. The half-life of IgG can vary considerably among patients.

Table 5. Pharmacokinetic Variables of Total IgG in Subjects with PI

Variable	3-Week Dosing Interval (n=10)		4-Week Dosing Interval (n=9)	
	Mean ± SD	Range	Mean ± SD	Range
Cmax (mg/mL)	19.50 ± 2.83	15.10 – 24.40	20.92 ± 3.66	16.80 – 29.20
AUC_{0-last} (day·mg/mL)	339.51 ± 45.27	241.12 – 380.21	342.37 ± 39.72	276.83 – 408.25

Clearance (mL/day)	115 ± 31	81 – 186	144 ± 47	77 – 237
Half-life (days)[a]	34 ± 10	21 – 58	37 ± 13	24 – 59
Trough IgG level (mg/mL)[b]	9.76 ± 1.65	6.45 – 11.40	8.77 ± 1.26	7.59 – 11.70

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility

No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of Flebogamma 10% 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 per kg body weight with infusion rates 6-37 times higher than the maximum rates recommended for humans. The most common clinical observations in mice studies were piloerection, ptosis, ataxia and increase in respiration all lasting 90 minutes or less. 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 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 macroscopic and microscopic analysis. This phenomenon was ascribed to hemolysis that occurred when the 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.

14 CLINICAL STUDIES

14.1 Treatment of Primary Immunodeficiency (PI)

A phase 3, multicenter, open-label, historically controlled study to assess the efficacy, safety and pharmacokinetics of Flebogamma 10% DIF in subjects with PI was conducted in the United States. Forty-six subjects were treated with Flebogamma 10% DIF for 12 months at a 3-week or 4-week dosing interval. Subjects ranged in age from 6 to 65 years; 65% were male and 35% were female; 96% were Caucasian and 4% were Hispanic. Pre-medication to alleviate potential adverse drug reactions was only allowed after the first infusions only in those subjects that exhibited adverse reactions. Of 601 infusions administered during the study, 130 (22%) infusions in 21 (47%) subjects were preceded by pre-medication (antipyretic, antihistamine, or antiemetic agent) because of experience with consecutive infusion-related adverse reactions.

If the infusion was well tolerated (no adverse reaction temporally associated with the infusion), the infusion rate was increased to 0.02 mL per kg per minute for 30 minutes and then to 0.04 mL per kg per minute for another 30 minutes. If well tolerated, additional increments of 0.02 mL per kg per minute were made at 30-minute intervals up to a maximum rate of 0.08 mL per kg per minute.

Since 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 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 468.5 mg per kg per month for subjects in the 3-week schedule (N=16, range 320-597 mg per kg per month) and 457.4 mg per kg per month for subjects in the 4-week schedule (N=30, range 307-588 mg per kg per month). Subjects received a total of 601 infusions of Flebogamma 10% DIF. The maximum infusion rate allowed during the study was 0.08 mL per kg per minute.

During the study period, 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 0.025 (upper 1-sided 98% confidence interval: 0.001 to 0.133). One subject had one episode of bacterial pneumonia. There were no other serious bacterial infections (Table 6).

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

Infections	**Subjects (N=46) N (%)**	**Episodes**	**Estimates[a]**	**98% CI[b]**
Bacterial pneumonia	1 (2.2)	1		
Bacteremia or sepsis	0 (0.0)	0		
Osteomyelitis/septic arthritis	0 (0.0)	0		
Visceral abscess	0 (0.0)	0		
Bacterial meningitis	0 (0.0)	0		
Subjects with at least 1 serious bacterial infection	**1 (2.2)**	**1**	**0.025**	**(0.001, 0.133)**

a. Estimate = Total episodes/Total subject years.
b. The confidence interval is obtained by using a generalized linear model procedure for Poisson distribution

The number of days of work/school missed, hospitalizations and days of each hospitalization, the number of visits to physicians or emergency rooms, other infections documented by positive radiographic findings and fever, and days on therapeutic and prophylactic oral/parenteral antibiotic use also were evaluated. These variables were annualized by using subject-years exposure data of those subjects experiencing the events, but not the entire study cohort. The mean rate of other validated infections was <2 days per subject per year (this calculation used all subjects, including those who had no infections). (Table 7)

Table 7. Summary of Annualized Efficacy Variables

Variable	**Subjects**		**Mean number of events, days or visits per subject per year[a]**
	N	**%**	
Work/school days missed	20	43.5	3.0
Days in hospital	5	11.0	0.6
Visits to physician/ER	24	52.2	2.1
Number of other documented infectious episodes	7	15.2	0.2
Days of therapeutic oral antibiotic use	36	78.3	56.4

Days of therapeutic parenteral antibiotic use	2	4.3	1.3
Days of other therapeutic antibiotic use	14	30.4	60.5
Days of prophylactic oral antibiotic use	19	41.3	45.8
Days of prophylactic parenteral antibiotic use	1	2.2	0.02
Days of other prophylactic antibiotic use	1	2.2	3.3

a. Days of work/school missed per subject 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.

14.2 Treatment of Chronic Primary Immune Thrombocytopenia (ITP)

A phase 3, prospective, open-label, single-arm, multicenter study assessed the efficacy, safety and tolerability of Flebogamma 10% DIF in 58 subjects (46 adult and 12 pediatrics) with chronic ITP and a platelet count of $\leq 20 \times 10^9$/L. Subjects ranged in age from 3 to 70 years (median age: 28 years). Females (67.2%) outnumbered males (32.8%). A majority of the subjects were Asian (67.4%); the remainder was Caucasian (26.1%), Hispanic (4.3%) and African American (2.2%).

Median age of the pediatric cohort was 13 years. The ratio of males to females was 1:1. Only Caucasian subjects were enrolled. See Table 8 for the number pediatric subjects stratified by age.

Table 8. Summary of Pediatric Subjects by Age Groups

Age group	Number of subjects (N)
3-5 years	1
6-11 years	3
12-16 years	8

Subjects received a 2 g per kg dose of Flebogamma 10% DIF administered intravenously as 1 g per kg on 2 consecutive days. Pre-medication to alleviate potential adverse drug reactions was not allowed. The starting rate of 0.01 mL per kg per minute was to be maintained for 30 minutes. If the infusion was well tolerated, the infusion rate was increased to 0.02 mL per kg per minute for 30 minutes and then to 0.04 mL per kg per minute for another 30 minutes. If well tolerated, additional increments of 0.02 mL per kg per minute were made at 30-minute intervals up to a maximum rate of 0.08 mL per kg per minute.

Platelet counts were measured on infusion visits (Days 1 and 2), in clinical follow-up visits (Day 3, Day 5 ± 1, Day 8 ± 1, Day 15 ± 1, Day 22 ± 1), at final study visit (Day 30 ± 1) and daily on Day 4 through Day 8 or until counts reached or exceeded 50×10^9/L, whichever occurred first, and then every 4 ± 1 days through Day 22 ± 1.

The primary efficacy endpoint was the response rate, defined as the proportion of treated subjects in whom platelet counts increased from $\leq 20 \times 10^9$/L to $\geq 50 \times 10^9$/L by Day 8 ± 1 (the day of the first infusion was Day 1) in the modified intent-to-treat population (mITT). The mITT consisted of all subjects who received at least one infusion (at any dose) of Flebogamma 10% DIF.

Table 9. Response Rate (mITT Population)

	Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders (%)	35 (76.1)	12 (100.0)	47 (81.0)
95% confidence interval[a]	(63.5, 86.0)	(77.9, 100.0)	(70.6, 89.0)

mITT: modified intention to treat; N: number of subjects.
a. The lower and upper bound of the exact one-sided 95% confidence interval.

Secondary efficacy endpoints included:

- Time to platelet count recovery, as determined by the number of days elapsed from Day 1 to the day on which the platelet count was first found to be $\geq 50 \times 10^9$/L during the clinical follow-up period ending on Day 30 ± 1.
- Duration of response, as determined by the number of consecutive days for which the platelet count remained $\geq 50 \times 10^9$/L during the clinical follow-up period ending on Day 30 ± 1.
- Regression of hemorrhage/bleeding, as determined by the proportion of treated subjects with hemorrhage/bleeding on Day 1 who improved their diathesis, assessed using a categorized rating scale, during the clinical follow-up period ending on Day 15 ± 1.

A total of 47 out of 58 subjects (81%) in the mITT population were responders. The responder rate was 76.1% (35/46) in adults and 100% (12/12) in children. Analysis of the primary efficacy endpoint showed that the lower limit of the exact one-sided 95% CI was 70.6%, which was above the predefined response rate of 50%.

Mean time to platelet count recovery ($\geq 50 \times 10^9$/L) was ≤ 1.7 days among all responders (≤ 1.8 days in adults and ≤ 1.4 days in pediatrics). Median time to platelet count recovery was ≤ 2 days for all responders and adults, and ≤ 1 day for pediatrics. (The symbol "≤" is used because actual time to platelet count recovery could have occurred prior to the study visit since this endpoint was assessed only at study visits.)

Table 10. Time to Platelet Count Recovery in Responders (mITT Population)

		Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders		35	12	47
Time to platelet count recovery (days)	Mean ± SD	1.8 ± 1.0	1.4 ± 0.5	1.7 ± 0.9
	Median (Min, Max)	2 (0, 4)	1 (1, 2)	2 (0, 4)

mITT=modified intention to treat; N=number of subjects; SD=standard deviation of the mean; Min=minimum; Max=maximum.

Mean duration of response was ≥ 10.8 days among all responders, ≥ 9.6 days in adult responders and ≥ 14.3 days in pediatric responders. (The symbol "≥" is used because actual duration of response could have persisted after the study visit since this endpoint was assessed only at study visits.)

Table 11. Duration of Response in Responders (mITT Population)

	Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Number of responders	35	12	47

Duration of response (days)	Mean ± SD	9.6 ± 7.8	14.3 ± 8.0	10.8 ± 8.0
	Median (Min, Max)	7 (1, 29)	14 (3, 29)	10 (1, 29)

mITT= modified intention to treat; N= number of subjects; SD=standard deviation of the mean; Min= minimum; Max=maximum.

Approximately 67% of all subjects (39/58) presented with signs of hemorrhage/bleeding at Day 1 before the first infusion of Flebogamma DIF 10%. This cohort included 59% of adults (27/46) and all pediatric subjects (12/12, 100%). Approximately 92% of these subjects experienced improvement in bleeding diathesis during the follow-up period by Day 15 regardless of whether they were responders in terms of platelet count.

Table 12. Regression of Hemorrhage (mITT population)

Parameters	Adults (N = 46)	Pediatrics (N = 12)	All Subjects (N = 58)
Subjects with hemorrhage at Day 1	27	12	39
Improvement in diathesis of subjects with hemorrhage at Day 1	24/27 (88.9%)	12/12 (100.0%)	36/39 (92.3%)
95% confidence interval[a]	(70.8, 97.6)	(73.5, 100.0)	(79.1, 98.4)

mITT: modified intention to treat; N: number of subjects.
a. Lower and upper bound of the exact two-sided 95% confidence interval.

Mean maximum platelet count among all responders ranged from 205.3×10^9/L (adults) to 335.2×10^9/L (pediatrics). All responders, adults and pediatrics combined, showed a mean maximum platelet count of 238.4×10^9/L. All responders, including adult and pediatric responders, had a mean time to maximum platelet count of 4.8 days. Maximum platelet count was 4.7 days for adult responders and 5.3 days for pediatric responders. The mean maximum increase in platelet count in all responders was 226.3×10^9/L, with 193.3×10^9/L in adult responders and 322.6×10^9/L in pediatric responders.

Three SAEs were reported in the adult cohort, 1 case of soft-tissue inflammation and 2 cases of headache. No SAEs were reported in the pediatric cohort but the incidence of treatment-emergent adverse events was higher in pediatric subjects than in adults. *(see Adverse Events (6.1))*

A supportive, prospective, open-label, single-arm, multicenter study assessed the efficacy, safety and tolerability of Flebogamma 10% DIF in 18 adult subjects with chronic ITP and a platelet count of $\leq 20 \times 10^9$/L. A total of 12 females and 6 males ranging in age from 18 to 82 years were enrolled. Their median age was 43 years. All subjects were Caucasian.

The primary efficacy endpoint was the response rate, defined as the proportion of treated subjects in whom platelet counts increased from $\leq 20 \times 10^9$/L to $\geq 50 \times 10^9$/L at any time during the study period. The study achieved its primary endpoint: 13/18 subjects (72.2%; 95% confidence interval: 50.2, 88.4) met the criteria for treatment responders.

Three SAEs were reported in two subjects and assessed as possibly related: leukopenia (mild) and decreased hemoglobin (mild) in the one subject and axillary vein thrombosis (severe) in the second subject. Both subjects recovered without sequelae. The proportion of subjects who experienced treatment-emergent adverse events (TEAE) was higher in the pediatric cohort than in the adult cohort. *(see Clinical Trials Experience, (6.1) and Pediatric Use (8.4))*

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16 HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma 10% DIF is supplied in single-use, individually laser-etched vials containing the labeled amount of functionally active IgG.

The following presentations of Flebogamma 10% DIF are available:

NDC Number	Fill Size	Grams Protein
61953-0005-1	50 mL	5 g
61953-0005-2	100 mL	10 g
61953-0005-3	200 mL	20 g

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

Flebogamma 10% DIF may be stored at room temperature at 2 to 25 ºC (36 to 77 ºF) for up to 24 months, as indicated by the expiration date printed on the outer carton and container label. Discard after expiration date. **Do not freeze.**

Keep Flebogamma 10% DIF in its original carton to protect it from light.

Not made with natural rubber latex

17 PATIENT COUNSELING INFORMATION

Instruct patients to immediately report the following signs and symptoms to their physician:

- Decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath *(see Renal Failure (5.2))*
- Symptoms of thrombosis which may include: pain and/or swelling of an arm or leg with warmth over the affected area, discoloration of an arm or leg, unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body *(see Thrombosis (5.4))*
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea and vomiting *(see Aseptic Meningitis Syndrome (5.5))*
- Increased heart rate, fatigue, yellowing of 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 10% DIF is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). The risk of Flebogamma 10% DIF transmitting an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma, and inactivating and/or removing certain viruses during manufacturing. *(see Warnings and Precautions (5.8))* Instruct patients to report any symptoms that concern them and might be caused by infections.

Inform patients that Flebogamma 10% DIF may interfere with their immune response to live viral vaccines such as measles, mumps and rubella. Inform patients to notify their health care professional of this potential interaction when they are receiving vaccinations. *(see Drug Interactions (7))*

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