Special REPORT

Flebogamma® DIF: A Highly Purified Intravenous Immunoglobulin

Summary

Flebogamma® DIF (dual inactivation and filtration) is a ready-to-use liquid formulation of intravenous immunoglobulin (IVIG), and the only liquid IVIG licensed in the United States at both 5% and 10% concentrations. Derived from fraction II + III of the Cohn cold ethanol fractionation process, the starting material for Flebogamma® DIF is further purified by a sequential series of selective steps (polyethylene glycol [PEG] precipitation and anion exchange chromatography), resulting in a highly purified, fully functional immunoglobulin with demonstrated efficacy. The unique Flebogamma® DIF manufacturing process includes 7 validated viral elimination steps, including 3—pasteurization, solvent/detergent (S/D) treatment, and Planova™ 20-nm nanofiltration—that are specific pathogen elimination steps. Flebogamma® DIF is the only pasteurized IVIG licensed in the United States. Pasteurization has been shown to inactivate enveloped and nonenveloped viruses as well as clotting enzymes, a potential contaminant of IVIG products implicated in thromboembolic events.
Introduction

Intravenous immunoglobulin (IVIG) products vary widely with regard to the methods used in their manufacture. Such differences in the way immunoglobulin G (IgG) is purified from pools of human plasma account in large measure for the purity and ultimate tolerability of the final product. For example, the presence of containing vasoactive proteins, such as prekallikrein activator and kallikrein, may contribute to some of the infusion-related reactions (eg, pain at the injection site, flushing, chest tightness, hypotension) associated with IVIG administration.\(^2\)\(^-\)\(^5\)

Although infrequent thromboembolic events, including deep vein thrombosis and stroke, have been associated with IVIG therapy.\(^2\)\(^-\)\(^3\) Such complications of IVIG therapy have been attributed to certain patient risk factors (eg, advanced age, diabetes), hypersensitivity of the IVIG preparation, and increased blood viscosity as a result of the IgG infusion.\(^2\)\(^-\)\(^3\)\(^1\)\(^-\)\(^1\(^1\)

However, contaminating clotting factors also may be implicated in these thrombotic episodes.\(^5\) Indeed, IVIG contaminated with factor XI/activated factor XI (factor Xla) from several manufacturers has been reported\(^1\(^2\): the degree of factor Xla contamination correlated with the manufacturer, implying that specific manufacturing processes, and possibly the plasma fractions used as starting material, may account for the differences found. Moreover, a recent product recall because of an increased incidence of thromboembolic events was believed by the manufacturer to be due to an unanticipated increase in factor Xla in the final product.\(^1\(^3\)\(^-\)\(^1\(^4\)\) This event underscores the need for constant vigilance in the measures taken to assure product purity.

Flebogamma® DIF (dual inactivation and filtration) is a pasteurized, ready-to-use liquid formulation of IVIG, available at both 5% and 10% concentrations. The Flebogamma® DIF manufacturing process involves proprietary cutting-edge technology that can be relied upon to result in an IVIG product of high quality and purity. This monograph provides a review of how this level of purity is achieved.

The Flebogamma® DIF Manufacturing Process

The Flebogamma® DIF manufacturing process involves a series of highly selective purification steps that result in a liquid formulation of highly purified, fully functional immunoglobulin with demonstrated efficacy. Protein and other impurities are removed primarily through sequential PEG precipitation and ion exchange chromatography (Table). Pasteurization—1 of 3 specific viral elimination steps—also has been shown to inactivate clotting enzymes.\(^1\(^5\)

Potential viral contaminants of plasma-derived products include both DNA and RNA viruses (with and without lipid envelopes), as well as viruses of varying size. Therefore, multiple viral elimination steps with differing modes of action are utilized in the production of Flebogamma® DIF. The Flebogamma® DIF manufacturing process includes 7 validated viral elimination steps. Three of these—pasteurization, S/D treatment, and Planova™ 20-nm nanofiltration—are specific pathogen elimination steps, whereas the other 4, including fraction I precipitation, fraction II + III alcohol incubation, PEG precipitation, and acid treatment (pH 4 for 4 hours at 37°C), are nonspecific. The combination of these steps provides an overall viral reduction capacity ranging from ≥13.3 to ≥23.2 log\(_{10}\)/mL, depending on the type of virus.\(^1\(^6\)\(^-\)\(^1\(^7\)

The sequential steps in the Flebogamma® DIF manufacturing process (Figure) are described below.

Approved Plasma Source

All source plasma used in the manufacture of Flebogamma® DIF is collected at FDA-approved plasmapheresis centers in the United States. In addition to rigorous donor screening, each plasma unit collected is tested by enzyme-linked immunoabsorbent assay, and must be found negative for the presence of hepatitis B surface antigen and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Plasma units, as well as final manufacturing plasma pools, must also be found negative on nucleic acid amplification testing for HCV and HIV.

Cohn Cold Ethanol Fractionation

For most IVIG products currently in use, the purification of IgG from human plasma begins with cold ethanol fractionation, a process that was developed during the 1940s as a means of separating albumin and other proteins from human plasma.\(^1\(^8\)

The process, which is based on the differential solubility of plasma proteins at varying protein and ethanol concentrations, pH, temperature, and ionic strength, includes a series of selective precipitation, centrifugation, and filtration steps.\(^5\) Flebogamma® DIF is produced by a proprietary modification of the Cohn process and is derived from fraction II + III (a purer starting material than fraction I + II + III).\(^1\(^9\)\) IgG-rich fraction II + III, however, also contains protein impurities, as well as IgG aggregates, which must be removed before the product can be safely used intravenously. For example, the presence of IgG aggregates can cause aggregate-induced complement activation, potentially resulting in anaphylactoid reactions on IV administration.\(^2\)\(^-\)\(^3\) Therefore, additional purification steps are required to remove such impurities. Additionally, although the alcohol incubation/fractionation steps effectively clear HIV and contribute to the clearance of other viruses, cold ethanol fractionation alone is insufficient to ensure a broad safety margin with regard to other viral pathogens.\(^2\)\(^-\)\(^2\)\(^9\)

PEG Precipitation

The synthetic polymer PEG is a chemically inert, nontoxic, non-denaturing protein precipitating agent used in the separation of IgG from other plasma proteins.\(^2\)\(^-\)\(^4\) PEG precipitation of protein is rapid and can be accomplished without rigorous temperature control.\(^2\) The mechanism of PEG precipitation is not completely understood. However, proteins appear to be separated by virtue of differences in their relative solubility. It has been postulated that PEG acts as an “inert solvent sponge” that reduces solvent availability; thus, with
increasing concentration of PEG, the effective concentration of a given protein is increased until its solubility is exceeded and precipitation occurs. In addition to PEG concentration, multiple factors including polymer size as well as protein size, charge, and concentration, have been shown to affect the precipitation process. A second hypothesis emphasizes the importance of protein charge, wherein more highly charged (hydrophilic) proteins are more easily precipitated than hydrophobic ones.

Among liquid IVIG products, Flebogamma® DIF is unique in regard to the incorporation of PEG precipitation into the manufacturing process. PEG precipitation is employed twice, initially for the purification of fraction II + III, and again following pasteurization and S/D treatment. In addition to removing contaminating proteins (Table), PEG fractionation also removes aggregated IgG and immunocomplexes, yielding monomeric IgG.

Moreover, PEG precipitation also has been shown to be a
robust viral elimination procedure. During the manufacture of Flebogamma® DIF, the viral reduction capacity of PEG precipitation is ≥5 to ≥6 log₁₀/mL, eliminating both enveloped and nonenveloped viruses. Finally, PEG precipitation can effectively clear the infectivity of transmissible spongiform encephalopathy (TSE) agents, as demonstrated by studies in which a prion protein model agent was experimentally spiked into a laboratory-scale model of the Flebogamma® DIF manufacturing process. Hamster scrapie strain 263K was used as the TSE model agent because it partitions by PEG precipitation along with the variant Creutzfeldt-Jakob disease (vCJD) agent, an emerging pathogen of potential concern for plasma-derived products. By bioassay assessment—the “gold standard” for detection of TSE infectivity—PEG precipitation provided a reduction factor of 6.19 log₁₀/mL or greater.

**Ion Exchange Chromatography**

Following PEG precipitation, further purification is accomplished through ion exchange chromatography—a process that separates protein molecules based on their net electrical charge. Specifically, Flebogamma® DIF is purified by anion exchange chromatography on columns filled with a positively charged resin, diethylaminoethyl (DEAE) cellulose.

In this process, negatively charged molecules contained in solution are retained by the positively charged matrix as they pass through the column. Anionic exchange chromatography is generally performed at a slightly acidic pH. The isoelectric point (the pH at which a molecule carries no net charge) of IgG is between 6.4 and 9.0. Thus, at a slightly acidic pH range, IgG is positively charged and passes through the column while negatively charged protein impurities are retained.

At a slightly acidic pH, about 90% of plasma proteins are negatively charged and are consequently bound to the anion exchanger. Certain clotting factors, however, are positively charged and therefore co-elute with IgG. These include factors XI and Xa (isoelectric point near 9.1) and thrombin (isoelectric point between 7 and 7.6). Therefore, additional purification steps are required to eliminate these impurities in order to reduce the thrombogenic potential of the final product. Indeed, as noted above, an increase in the level of factor Xa has been implicated in causing an increase in IVIG-associated thromboembolic events.

**Sorbitol Stabilizer**

Sorbitol is a polyol stabilizer that is added to Flebogamma® DIF during the manufacturing process, specifically prior to pasteurization, to prevent aggregation of IgG molecules (Figure). Sorbitol prevents denaturation and preserves the biologic function of IgG during pasteurization. Compared with sucrose, sorbitol has been demonstrated to be superior in preventing the generation of IgG polymers and anticomplementary activity during pasteurization. In addition, Flebogamma® DIF is formulated with 5% sorbitol to prevent IgG aggregation during storage at room temperature for as long as 24 months, without requiring formulation at a lower pH.

Sorbitol plays a physiologic protective role in mammalian kidneys. Sorbitol is 1 of 5 organic osmolytes used by the kidneys to maintain osmotic equilibrium with the hypertonic extracellular environment. The kidneys synthesize sorbitol from glucose in response to extracellular hypertoncity. In addition, sorbitol is metabolized by the kidneys when the total concentration of organic osmolytes is sufficient for osmotic regulation, thereby preventing excess accumulation. These dynamics may in part explain the relatively low incidence of renal failure associated with sorbitol-stabilized IVIG products.

**Pasteurization**

Pasteurization—heat treatment at 60°C for 10 hours—inactivates both enveloped and nonenveloped viruses. During the manufacture of Flebogamma® DIF, the viral reduction capacity of pasteurization ranges from ≥4 to 6 log₁₀/mL or greater, depending on the virus. In the presence of sorbitol, IgG is not denatured and retains full functionality during the pasteurization process. Importantly, pasteurization also has been shown to inactivate clotting enzymes and coagulation factor activation markers during Flebogamma® DIF production. Specifically, although other clotting factor activities were below the limit of detection following intermediate purification steps (such as PEG precipitation), factor XI clotting activity was still present; however, after pasteurization, factor XI clotting activity fell below the quantification limit, even in concentrated samples. Additionally, any remaining kallikrein activity and thrombin generation capacity were eliminated following pasteurization. These results are significant in that factor XI appears to play a dual role in both thrombin generation and in the inhibition of fibrinolysis. Thus, factor XI, which can be activated by thrombin, is not only a procoagulant, but also protects the clot against lysis once it is formed. Moreover, elevated factor XI levels have been shown to be a risk factor for venous thrombosis, whereas a severe factor XI deficiency is associated with a reduced incidence of deep vein thrombosis. Therefore, even low levels of contaminating factor XI may contribute to the risk for thrombosis following IVIG therapy, particularly in individuals at risk for thrombotic complications.

Therefore, pasteurization provides a dual benefit of viral inactivation and inactivation of clotting enzyme activity. Flebogamma® DIF is currently the only IVIG licensed in the United States that is pasteurized.

**Solvent/Detergent Treatment**

S/D treatment is an established viral inactivation technology that has been used for more than 20 years to inactivate lipid-enveloped viruses, including HIV, hepatitis B virus, and HCV, in plasma-derived products. S/D treatment inactivates lipid-enveloped viruses by destroying their lipid envelope and associated virus-binding sites. During Flebogamma® DIF production, the viral reduction capacity of S/D treatment ranges from ≥4 to almost 7 log₁₀/mL.
Nanofiltration

Nanofiltration is a size-dependent viral elimination step, effective in the removal of both enveloped and nonenveloped viruses. The manufacturing process for Flebogamma® DIF includes Planova™ 20-nm nanofiltration (Asahi), which can remove even the smallest known nonenveloped viruses such as hepatitis A virus (HAV) (25-30 nm) and parvovirus B19 (B19V) (18-24 nm). Using porcine parvovirus, a model virus for B19V, the Flebogamma® DIF reduction factor after Planova™ 20-nm nanofiltration is 4.6 log_{10}/mL.48

Nanofiltration with a 35-nm filter also has been reported to effectively remove HAV and B19V; however, viral removal was dependent on the formation of virus–antibody complexes to increase the effective size of the viruses.49,50 Elimination of viruses smaller than 35 nm with Planova™ 20-nm nanofiltration is independent of the presence of specific antibodies or virus aggregation.

Although initially aimed at viral removal, nanofiltration also has been found to be effective in removal of prions from biological solutions, possibly based on both a sieving mechanism and adsorption onto the membrane.48 In the Flebogamma® DIF production process, Planova™ 20-nm nanofiltration has been shown, by bioassay assessment, to achieve a reduction factor of ≥5.45 log_{10} of the TSE model agent hamster scrapie strain 263.29 Therefore, the Flebogamma® DIF manufacturing process contains 2 steps—PEG precipitation and Planova™ 20-nm nanofiltration—that have been proven effective in eliminating known prions.16,17

Flebogamma® DIF: A Highly Purified and Functional IVIG

The Flebogamma® DIF manufacturing process results in a highly purified IVIG product, with >99.4% and >99.9% of IgG in monomeric and dimeric forms in Flebogamma® 5% DIF and Flebogamma® 10% DIF, respectively. The IgG subclass distribution is similar to that found in normal serum.16,17

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**Table. Mean Values of Trace Proteins in Flebogamma® 10% DIF and Flebogamma® 5% DIF**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Flebogamma 10% DIF Mean Value (n=3)</th>
<th>Flebogamma 5% DIF Mean Value (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKA, IU/mL</td>
<td>&lt;2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transferrin, mg/mL</td>
<td>≤0.004 – 0.006</td>
<td>≤0.002 – 0.004</td>
</tr>
<tr>
<td>Albumin, mg/mL</td>
<td>≤0.005</td>
<td>≤0.002</td>
</tr>
<tr>
<td>Haptoglobin, mg/mL</td>
<td>≤0.007</td>
<td>≤0.004</td>
</tr>
<tr>
<td>IgM, mg/mL</td>
<td>≤0.006</td>
<td>≤0.002</td>
</tr>
<tr>
<td>IgA, mg/mL</td>
<td>≤0.006&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.003&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>n=220 for mean PKA and IgA values

<sup>b</sup>PKA specification value = ≤10 IU/mL (Flebogamma 10% DIF); ≤10 IU/mL (Flebogamma 5% DIF)

<sup>c</sup>IgA specification value = ≤0.05 mg/mL (Flebogamma 10% DIF); ≤0.00 mg/mL (Flebogamma 5% DIF)

Ig, immunoglobulin; PKA, prekallikrein activator

Based on reference 51.
Demonstrated Efficacy and Tolerability

In a multicenter, prospective, open-label, historically controlled study of Flebogamma® 10% DIF in 46 patients with primary immunodeficiency disease (PID), who received doses of 300 to 600 mg/kg per infusion every 3 or 4 weeks for 12 months, the annualized number of serious bacterial infections was 0.025 infections per patient per year (98% confidence interval [CI], 0.001-0.133). This rate falls well below the FDA standard of less than 1 infection per patient per year for IVIG products. In a similar study of Flebogamma® 5% DIF in 46 patients with PID, the rate of serious bacterial infections per patient per year was 0.021 (98% CI, 0.001-0.112).

Flebogamma® DIF is well tolerated. In the multicenter trial of Flebogamma® 10% DIF, patients received 601 infusions (mean of 13 per patient). Out of 723 reported adverse events (AEs), 57% were not treatment-related. The average percentage of infusions associated with AEs, occurring during or within 72 hours after an infusion for each patient, was 36.7%. The majority of treatment-related AEs were graded as mild (59%) or moderate (36%). Similarly, in the Flebogamma® 5% DIF study in patients with PID, most treatment-related AEs were graded as mild to moderate.

Dosing Flexibility and Convenience

Flebogamma® DIF is the only liquid IVIG available in the United States at both 5% and 10% concentrations, with a range of vial sizes for customized dosing. Flebogamma® DIF can be stored at room temperature (2°C to 25°C) for its entire 2-year shelf life.

Flebogamma® 5% DIF may be an appropriate choice for patients who have frequent adverse reactions to infusions of IVIG; this concentration also may be suitable for patients who would benefit from additional fluid. Because Flebogamma® 10% DIF can be infused in a lower volume, it may meet the needs of patients at risk for volume overload, including the elderly, neonates, and patients with heart failure or renal dysfunction.

Full Product Traceability

Grifols has instituted several procedures, integral to its manufacturing and final packaging processes, to ensure that each vial of Flebogamma® DIF is authentic and fully traceable. Additionally, Grifols has made it possible for health care providers to access detailed information about each vial of Flebogamma® DIF, from plasma donation to final product.

Laser-Etched Vials

Each vial of Flebogamma® DIF is laser etched with a unique identifier number that correlates with a video of the entire filling process.
sequence, ensuring full traceability. The identifier number also links each vial to its original plasma derivatives. Additionally, there is a Grifols-exclusive holographic safety seal on every opening tab of the packaging. These packaging features help to deter counterfeiting and tampering.

**PediGri® On Line**

In September 2008, Grifols launched its proprietary PediGri® On Line system in the United States to provide health care professionals with access to unparalleled levels of specific information about each vial of Flebogamma® DIF. This transparency of information is made possible because Grifols codes each unit of plasma that is collected, which is then electronically traced from the beginning of the manufacturing process until it becomes part of the final product.

To access the PediGri® On Line Web portal, health care providers—including physicians, nurses, and pharmacists—must register online (www.pedigri.grifols.com) and obtain a confidential username and password. By simply entering the lot number from a particular vial of Flebogamma® DIF, registered users can view specific quality and safety information about each plasma donation used in the production of that vial (i.e., the donation number and viral screening at the origin). Additionally, specific information for each product lot (number of plasma units, total volume of plasma, as well as a certificate of analysis) is made available. The certificate of analysis includes the plasma origin, viral screenings of donations and subsequent viral testing of pooled source plasma, and the biochemical characteristics of the finished product. Finally, users also can access the applicable product package insert.

**Reliable Supply of IVIG**

The demand for IVIG continues to grow, and Grifols has made the commitment to ensure that the company can provide a reliable, consistent supply of IVIG. Grifols is the world leader in plasma collection with 147 plasma collection centers across the United States. Grifols also has its own US-based plasma-testing laboratory, with a second one scheduled to be operational this year. The Flebogamma® DIF production facility in Barcelona, Spain, was designed and built by an in-house team of engineers. A second Flebogamma® DIF production facility, scheduled to open in 2013 in Los Angeles, CA, will almost double current production capacity.
Flebogamma® 10% DIF, Immune Globulin Intravenous (Human), Important Safety Information

Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immune deficiency (PI), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.

**WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

- Use of immune globulin intravenous (IGIV) products, particularly those containing sucrose, has been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death (1). Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or those receiving known nephrotoxic drugs (see Warnings and Precautions [5.2]). Flebogamma® 10% DIF does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer Flebogamma® 10% DIF at the minimum infusion rate practicable (see Dosage and Administration [2.3], Warnings and Precautions [5.2]).

Flebogamma® 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin and in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

In patients at risk for developing acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine, and urine output.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma® 10% DIF therapy.

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF. Monitor patients at risk for thrombotic events, including those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with Flebogamma® 10% DIF treatment. AMS may occur more frequently following high doses and/or rapid infusion of IGIV.

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

Non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] may occur in patients following Flebogamma® 10% DIF treatment. 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.

All patients, but especially 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.

Because Flebogamma® 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma® 10% DIF.

The most common adverse reactions (reported in ≤5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion 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. The most serious adverse reactions observed with Flebogamma® 10% DIF were back pain, chest discomfort, and headache (2 patients); and chest pain, maculopathy, rigors, tachycardia, bacterial pneumonia, and vasovagal syncope (1 patient).

Please refer to Flebogamma® 10% DIF full prescribing information for full prescribing details, including comprehensive adverse event profile and black box warning.
Flebogamma® 5% DIF, Immune Globulin Intravenous (Human), Important Safety Information

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.

**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. 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.)

Flebogamma® 5% DIF is contraindicated in patients with a history of anaphylactic or severe systemic reactions to human immune globulin and in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reaction.

In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine.

Hyperproteinemia, increased serum viscosity, and hypotension may occur in patients receiving Flebogamma® 5% DIF.

Thrombotic events may occur during or following IGIV treatment. Monitor patients at risk for thrombotic events, including 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.

Aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. AMS may occur more frequently with high doses and/or rapid infusion of IGIV.

Flebogamma® 5% DIF may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.

Non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient serum.

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.

In the pre-approval clinical trial, the most common temporally related adverse reactions with Flebogamma® 5% DIF 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, often beginning within 60 minutes of the start of the infusion.

Please refer to Flebogamma® 5% DIF full prescribing information for full prescribing details, including comprehensive adverse event profile and black box warning.
References


51. Data on file, Instituto Grifols S.A.


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WARNING: ACUTE RENAL DYSFUNCTION AND FAILURE

See full prescribing information for complete boxed warning.

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of human immune globulin intravenous (IGIV) products.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV 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 infusion rate practicable.

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DOSAGE AND ADMINISTRATION

For Intravenous Use Only

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg every 3-4 weeks</td>
<td>0.01 mL/kg/minute (1 mg/kg/min)</td>
<td>0.08 mL/kg/minute (8 mg/kg/min)</td>
</tr>
</tbody>
</table>

Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Flebogamma 10% DIF if renal function deteriorates. [5.2]

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DOSAGE FORMS AND STRENGTHS

Flebogamma 10% DIF is a liquid solution containing 10% IgG (100 mg/mL).

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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]

---

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 5% of subjects were headache, chills, fever, shivering, 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]

Serious adverse reactions included back pain, chest discomfort, headache, chest pain, malacopathy, rigors, tachycardia, and vasovagal syncope.

To report SUSPECTED ADVERSE REACTIONS, contact Gelifte Biologicals at 1-888-GRIFOLS (1-888-474-3607) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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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. Use only if clearly needed. [8.1]
- Geriatric: In patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Flebogamma 10% DIF at the minimum infusion rate practicable. [8.5]

Set 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2010

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* Sections or subsections omitted from the full prescribing information are not listed.
1 INDICATIONS AND USAGE

Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immunodeficiency (PI) including the humoral immune deficiency, variable immunodeficiency, X-linked agammaglobulinemia, and Wiskott-Aldrich syndrome.

2. DOSAGE AND ADMINISTRATION

For Intravenous Use Only

2.1 Preparation and Handling

• Flebogamma® 10% DIF is a clear or slightly opalescent, colorless solution. Inspect the drug product visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy, turbid, or if it contains particulates.

• Do not shake.

• Do not freeze.

• Flebogamma® 10% DIF should be administered at room temperature.

The solution is for single-use only.

• Flebogamma® 10% DIF contains no preservative. Once the vial has been entered under aseptic conditions, its contents should be used promptly. Because the solution contains no preservative, Flebogamma® 10% DIF should be infused as soon as possible.

• Do not mix Flebogamma® 10% DIF with other IV products or other intravenous medications.

• Use Flebogamma® 10% DIF in the original vial for infusion.

• If a larger dose of Flebogamma® 10% DIF is to be administered, several vials may be connected into sterile intravenous lines using aseptic technique.

2.2 Dose

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, as judged according to the clinical response.

The recommended dose of Flebogamma® 10% DIF for patients with PI is 300 to 600 mg/kg body weight (3.0 to 6.0 g/kg) administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical response. randomized controlled data are available to determine an optimum target serum IgG level.

2.3 Administration

It has been reported that the frequency of adverse drug reactions to IgG increases with the infusion rate. Initial infusion rates should be slow. If necessary, the infusion rate may be adjusted accordingly.

3. DOSAGE FORMS AND STRENGTHS

Flebogamma® 10% DIF is a liquid solution containing 10% (100 mg/mL).

4. CONTRAINDICATIONS

• Flebogamma® 10% DIF is contraindicated in patients who have a history of asplenia or severe systemic reactions to the administration of human immune globulin.

• Flebogamma® 10% DIF is contraindicated in IGG deficient patients with antibodies to IgA and a history of hypersensitivity.

5. WARNINGS AND PRECAUTIONS

• Weigh the potential risks and benefits of Flebogamma® 10% DIF against those of alternative therapies in all patients for whom Flebogamma® 10% DIF is being considered.

• Before prescribing Flebogamma® 10% DIF, the physician should discuss risks and benefits of its use with patients.

6. HYPERSENSITIVITY

Severe hypersensitivity reactions may occur (see Contraindications [4]). In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Flebogamma® 10% DIF contains trace amounts of IgA (less than 150 μg/mL) (see Description [17]). Patients with antibodies to IgA have a greater risk of developing possibly severe hypersensitivity and anaphylactic reactions. Flebogamma® 10% DIF is contraindicated in patients with antibodies against IgA and a history of hypersensitivity (see Contraindications [4]).

6.2 Renal Dysfunction/Failure

Acute renal dysfunction, azotemia, and nephropathy, and death may occur upon use of Flebogamma® 10% DIF. Ensure that patients are not volume-depleted before administering Flebogamma® 10% DIF in patients who are at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, age greater than 65 years, volume depletion, sepsis, paraproteinemia, use of concurrent nephrotoxic drugs, etc.). Administer Flebogamma® 10% DIF at 10% of the maximum rate of infusion practice (see Dosage 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. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma® 10% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinue use of Flebogamma® 10% DIF.

6.3 Hypersensitivity Reactions

6.3.1 Anaphylaxis

Hypersensitivity reactions, especially and hyperglobulinemia and hypotension, may occur when receiving Flebogamma® 10% DIF therapy. It is clinically critical to distinguish that hypotension from a pseudohypotension that is temporarily or casually related to hypotension with concurrent decreased calculated serum osmolarity or elevated osmol gap, because treatment aimed at decreasing serum free water in patients with pseudohypotension may lead to volume depletion, a further increase in serum osmolality and a high risk of hypertensive events.

6.4 Thrombotic Events

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF (see table). Patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hypercoagulability.

Baseline consideration of blood viscosity in patients at risk for hypercoagulability, including those with cryoglobulinemia, fasting chyomicrons/very low triglyceride lipoproteins, or monoclonal gammopathies. For patients judged at high risk of developing thrombotic events, administer Flebogamma® 10% DIF at the minimum rate of infusion practicable (see Dosage and Administration [2.3]).

Table 1. Recommended Infusion Rates for Flebogamma® 10% DIF

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose (mg/kg)</th>
<th>Initial Infusion Rate (mg/kg)</th>
<th>Maintenance Infusion Rate (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viroids</td>
<td>300</td>
<td>0.01 mg/kg/min</td>
<td>0.08 mg/kg/min</td>
</tr>
<tr>
<td>Viroids</td>
<td>600</td>
<td>0.01 mg/kg/min</td>
<td>0.08 mg/kg/min</td>
</tr>
<tr>
<td>Viroids</td>
<td>900</td>
<td>0.01 mg/kg/min</td>
<td>0.08 mg/kg/min</td>
</tr>
</tbody>
</table>

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.

Ensure that patients with pre-existing renal insufficiency are not volume-depleted. Patients judged to be at risk for renal dysfunction or thrombotic events, administer Flebogamma® 10% DIF at the minimum infusion rate practicable, and consider discontinuation of oral medications and administration of diuretics if renal failure develops subsequent to infusion of IgG.

7. ADVERSE REACTIONS

As reported in clinical studies, adverse events were observed in patients receiving Flebogamma® 10% DIF. However, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice. Because Flebogamma® 10% DIF contains human gamma globulin, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent. Individuals with a history of transfusion-related acute lung injury (TRALI) may be at higher risk of developing allergic reactions if transfused with Flebogamma® 10% DIF. If a patient experiences an allergic reaction, it should be discontinued and institution of appropriate therapy for Triglyceride-induced adult respiratory distress syndrome (ARDS; see table).

Table 2. Treatment-related Adverse Events occurring in ≥5% of Patients with PI during a Flebogamma® 10% DIF Infusion within 72 Hours after the End of an Infusion

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Subjects (%)</th>
<th>Infusions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (N=46)</td>
<td>Infusions (N=601)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>24 (52%)</td>
<td>67 (11%)</td>
</tr>
<tr>
<td>Rigors</td>
<td>17 (37%)</td>
<td>37 (6%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15 (33%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>10 (22%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9 (20%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>8 (17%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Body temperature increased</td>
<td>8 (17%)</td>
<td>17 (3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (9%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Pain</td>
<td>4 (9%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>3 (7%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (7%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>3 (7%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3 (7%)</td>
<td>3 (0.5%)</td>
</tr>
</tbody>
</table>
Drug Interactions

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps, and rubella, or impair the immunizing properties of recent therapy with Flebo gamma 10% DIF so that appropriate measures may be taken (see Patient Counseling Information [17]).

Use in Specific Populations

8.1 Pregnancy

Pregnancy Category C: Animal reproduction studies have not been performed with Flebo gamma 10% DIF. It is also not known whether Flebo gamma 10% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebo gamma 10% DIF should be given to a pregnant woman only if clearly needed. Infusions cross the placenta from maternal circulation increasingly after 30 weeks of gestation.

8.3 Nursing Mothers

Use of Flebo gamma 10% DIF has not been evaluated in nursing mothers.

8.4 Pediatric Use

There are no pediatric patients with primary humoral immunodeficiency (less than the age of 6 and 10), and 16-46 year-old were included in the clinical evaluation of Flebo gamma 10% DIF. This number of subjects is too small to establish safety and efficacy in the pediatric population (see Clinical Studies [14]).

11 DESCRIPTION

Flebo gamma 10% DIF is a ready-to-use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of highly purified immunoglobulin G 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.

Flebo gamma 10% DIF is a purified (97%), unmodified, human IgG. The distribution of the four IgG subclasses is approximately 66.6% IgG1, 27.9% IgG2, 3.0% IgG3 and 2.5% IgG4. Flebo gamma 10% DIF contains trace amounts of lgA (typically ≤ 0.50g/L), and trace amounts of immunoglobulin M (IgM).

Flebo gamma 10% DIF contains 10g human normal immunoglobulin G and 5g sodium dextrose (as stabilizer) in 100mL of water for injection, and a 46mg polyethylene glycol, there is no presence in the formulation. The pH of the solution ranges from 5 to 6 and the osmolality from 240 to 370mg/mos/kg, which is within the normal physiological range. The IgF and Fab functionality is maintained in Flebo gamma 10% DIF.

All Source Plasma used in the manufacture of Flebo gamma 10% DIF was collected only by FDA approved plasma 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 HIV and HBV. An irreversible nat for HIV for HBV is also performed on all plasma. The significance of a negative result has not been established. Additionally, plasma is tested by test nat for hepatitis A virus (Hav), parvovirus B19, and cytomegalovirus and the viral load test for B19 in the manufacturing pool is not set to exceed 106 IU/mL. 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 toward viral safety of the final product. The effectiveness of these steps to screen or inactivate viruses from the product was 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. Flebo gamma 10% DIF production process includes the following specific virus inactivation removal steps:

- Pasteurization at 60°C, 10 hours
- Solvent detergent treatment for 6 hours
- Nanofiltration through 10 nm Planova Filters

The following purification processes can also reduce the risk of final transmission:

- Fractionation
- Precipitation
- 5% PEG precipitation
- pH 4 precipitation for 4 at 37°C

The viral load results (in log10) for B19 experiments are summarized in Table 4.

Table 4. Flebo gamma 10% DIF: viral reduction capacity of combined steps (log10)

<table>
<thead>
<tr>
<th>Target virus</th>
<th>HCV 1</th>
<th>HCV 2 (non-ccma. RNA)</th>
<th>HBS (non-ccma. DNA)</th>
<th>HIV 1</th>
<th>HIV 2</th>
<th>HIV 3</th>
<th>HIV 4</th>
<th>B19 virus (non-ccma. DNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model virus</td>
<td>HCV-1</td>
<td>PRV</td>
<td>BPR</td>
<td>WWV</td>
<td>WKV</td>
<td>WNV</td>
<td>EMV</td>
<td>PMV</td>
</tr>
<tr>
<td>Fraction 1</td>
<td>&lt;1.00&lt;</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>2.78</td>
<td>nd</td>
<td>1.00&lt;</td>
</tr>
<tr>
<td>Ethanol treatment</td>
<td>1.48</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>&lt;1.00&lt;</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Peg precipitation</td>
<td>6.10</td>
<td>6.92</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Acid pH treatment</td>
<td>2.47</td>
<td>5.32</td>
<td>nd</td>
<td>&lt;1.00&lt;</td>
<td>nd</td>
<td>nd</td>
<td>&lt;1.06&lt;</td>
<td>nd</td>
</tr>
<tr>
<td>Solvent detergent</td>
<td>6.84</td>
<td>6.98</td>
<td>6.33</td>
<td>6.46</td>
<td>6.49</td>
<td>8.42</td>
<td>8.56</td>
<td>4.08</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

Possible drug interactions may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps, and rubella, or impair the immunizing properties of recent therapy with Flebo gamma 10% DIF so that appropriate measures may be taken (see Patient Counseling Information [17]).
In the clinical study assessing safety and efficacy in primary immunodeficiency disease (PI), the pharmacokinetics of Flebogamma 10% DIF showed a transient "reddish urine" sign which was not confirmed as a relevant toxicity causing phenomenon after renal macro and microscopic examination.

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.

**Table 7. Summary of Annualized Efficacy Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subjects</th>
<th>Mean number of events, days or visits/subject/year [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work/school days missed</td>
<td>20</td>
<td>43.5</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>5</td>
<td>11.0</td>
</tr>
<tr>
<td>Visits to physician/ER</td>
<td>24</td>
<td>52.2</td>
</tr>
<tr>
<td>Number of other documented infectious episodes</td>
<td>7</td>
<td>15.2</td>
</tr>
<tr>
<td>Days of therapeutic oral antibiotic use</td>
<td>36</td>
<td>78.3</td>
</tr>
<tr>
<td>Days of therapeutic parenteral antibiotic use</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Days of other therapeutic antibiotic use</td>
<td>14</td>
<td>30.4</td>
</tr>
<tr>
<td>Days of prophylactic oral antibiotic use</td>
<td>19</td>
<td>41.3</td>
</tr>
<tr>
<td>Days of prophylactic parenteral antibiotic use</td>
<td>1</td>
<td>2.2</td>
</tr>
</tbody>
</table>

[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.

**15 REFERENCES**


**16 HOW SUPPLIED/STORAGE AND HANDLING**

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

The following presentations of Flebogamma 10% DIF are available:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Fill Size</th>
<th>Grams Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>61853-0005-1</td>
<td>50 mL</td>
<td>5 g</td>
</tr>
<tr>
<td>61853-0005-2</td>
<td>100 mL</td>
<td>10 g</td>
</tr>
<tr>
<td>61853-0005-3</td>
<td>200 mL</td>
<td>20 g</td>
</tr>
</tbody>
</table>

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number. DO NOT FREEZE.

When stored at room temperature (up to 25°C [77°F]), Flebogamma 10% DIF is stable for up to 24 months, as indicated by the expiration date printed on the outer carton and container label.

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

**17 PATIENT COUNSELING INSTRUCTIONS**

Inform 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 Warnings and Precautions [5.4])
- Acute chest pain, shortness of breath, leg pain, and swelling of the legs (see Warnings and Precautions [5.4])
- Severe headache, neck stiffness, dizziness, fever, sensitivity to light, plural edema movements, nausea and vomiting (see Warnings and Precautions [5.4])
- Increased heart rate, fatigue, yellowing of skin or eyes, dark-colored urine (see Warnings and Precautions [5.4])
- Trouble breathing, chest pain, blue lips or extremities, fever (see Warnings and Precautions [5.4])

Inform patients that Flebogamma 10% DIF is made from human plasma and may contain endogenous agents that can cause disease (e.g., viruses, and, theoretically, the CJD agent). While the risk that Flebogamma/HIG DIF may transmit an infection has been reduced by screening plasma donors for prior exposure, testing donated plasma and inactivating and/or removing certain viruses during manufacturing, patients should report any symptoms that concern them (see Warnings and Precautions [5.8]).

Inform patients that Flebogamma 10% DIF can interfere with the response to live viral vaccines such as measles, mumps and rubella, and instruct patients to notify their healthcare professional of this potential interaction when they are receiving vaccinations (see Drug Interactions [7]).
Flebogamma® 5% DIF

Immune Globulin Intravenous (Human)

Flebogamma® 5% DIF

5% Liquid Preparation

DOSAGE AND ADMINISTRATION

- Treatment of Primary Humoral Immunodeficiency (2.2)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI 300-600 mg/kg every 3-4 weeks</td>
<td>0.01 mL/kg/minute (0.5 mg/kg/min)</td>
<td>Increase to 0.10 mL/kg/minute (5 mg/kg/min)</td>
</tr>
</tbody>
</table>

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

DOSE FORMS AND STRENGTHS

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 g</td>
<td>10 mL</td>
</tr>
<tr>
<td>2.5 g</td>
<td>50 mL</td>
</tr>
<tr>
<td>5 g</td>
<td>100 mL</td>
</tr>
<tr>
<td>10 g</td>
<td>200 mL</td>
</tr>
<tr>
<td>20 g</td>
<td>400 mL</td>
</tr>
</tbody>
</table>

CONTRAINDICATIONS

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

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

<table>
<thead>
<tr>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>2.1</td>
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<tr>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>5.1</td>
</tr>
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<td>5.2</td>
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<td>5.3</td>
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<td>5.6</td>
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<td>5.7</td>
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<td>5.8</td>
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<tr>
<td>5.9</td>
</tr>
<tr>
<td>5.10</td>
</tr>
</tbody>
</table>

ADVERSE REACTIONS

6

1. Clinical Trials Experience
2. Post-marketing Experience
7

DRUG INTERACTIONS

8

9

10

11

12

12.1

12.2

12.3

13

13.1

13.2

14

15

16

17

DESCRIPTION

CLINICAL PHARMACOLOGY

Mechanism of Action

Pharmacodynamics

Pharmacokinetics

NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, impairment of fertility

Animal Toxicology and/or Pharmacology

CLINICAL STUDIES

REFERENCES

HOW SUPPLIED/STORAGE AND HANDLING

PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed
**Immune Globulin Intravenous (Human) Flebogamma® 5% DIF**

**5% Liquid Preparation**

**WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

**1 INSTRUCTIONS AND USAGE**

Flebogamma® 5% DIF is an immune globulin intravenous (Human) 5% preparation that is indicated for the treatment of primary hypogammaglobulinemia, severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Preparation and Handling**

Flebogamma® 5% DIF should be inspected visually for particulate matter and color prior to administration. If particles are detected in the vial, the solution should not be used. Use for intravenous injection only. Do not use for intramuscular injection.

**2.2 Treatment of Primary Humoral Immunodeficiency (PI)**

As there are significant differences in the half-life of IgG among patients with primary hypogammaglobulinemia, the frequency and amount of IgG infusions may vary. Intravenous immunoglobulin should be administered at the minimum rate practicable.

The usual dose of Flebogamma® 5% DIF for patients with PI is 300 to 600 mg/kg body weight/day (6 to 12 mg/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels. A recommended initial control total serum IgG level is 500 mg/dL.

**2.3 Administration**

The recommended initial infusion rate of Flebogamma® 5% DIF is 0.1 mL/kg body weight minute (0.05 mg/kg/min). If the infusion is well-tolerated, the infusion rate may be gradually increased to a maximum of 0.1 mL/kg body weight minute (0.05 mg/kg/min). 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, 5.3)

**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

**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. Discontinue immune globulin immediately available for treatment of acute severe hypersensitivity reactions.

Flebogamma® 5% DIF contains trace amounts of IgA (less than 20 μg/mL). Patients with known antibodies to IgA may have a greater risk of developing potentially severe 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. So do not use if turbid. Solution that has been frozen should not be used.

**5.2 Renal Failure**

Assure that patients are not volume depleted prior to the infusion 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 discontinuing 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. (See Warnings and Precautions 5.2, 5.3)

**5.3 Hypergammaglobulinemia**

Hypergammaglobulinemia, increased serum viscosity and hyaluronidase may occur in patients receiving Flebogamma® 5% DIF. It is clinically critical to distinguish true hypergammaglobulinemia from a pseudoplasmatoma that is caused by a decreased calculated serum viscosity or a direct serum viscosity measurement.

**5.4 Thromboembolic Events**

Thrombotic events may occur during or following IGIV treatment (5.1 and 5.2). 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, recent surgery, previous history of thromboembolic disease, malignancy, or patients with an inherited predisposition to thrombosis or hypercoagulability, including those with cryoglobulinaemia, fasting glycaemia/creatinine ratio 5:1, high fibrinogen (hyperfibrinogenaemia), or polyglucosaminuria. For patients judged to be at risk for developing thrombotic events, administer Flebogamma® 5% DIF at the minimum rate of infusion practicable.

**5.5 Aseptic Meningitis Syndromes**

AMS may occur infrequently with IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae (5.6). AMS usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by the following symptoms: severe headache, nuchal rigidity, photophobia, changes in mental status, nausea and vomiting, photophobia, confusion, and altered levels of consciousness. AMS has been reported to occur even in asymptomatic patients. AMS may occur frequently following high-dose IgG (greater than 10 g/kg body weight) and/or rapid infusion IGIV treatment. Patients with a history of migraine may be more susceptible. (See Warnings and Precautions 5.1, 5.2)

**5.6 Hemolysis**

Flebogamma® 5% DIF may contain small blood group antibodies which may act on hemolytic and induce in case coating of red blood cells (A,R,B,A,R,B,A,R). If patients are allergic to the substance (i.e., IgA deficiency), administration of Flebogamma® 5% DIF should be avoided.
Number of infusions for which AE onset occurred during an infusion or within 72 hours post-infusion.

- Includes reported preferred terms of Bronchitis NOS, Bronchitis NOS, and Bronchitis acute NOS.
- Corresponds to preferred term of injection site reaction. NOS. If combined to include infusion site information, injection site edema, injection site pain, injection site pruritus, injection site reaction NOS, and injection site swelling, there are 9 (3) subjects and 17 (2) infusions.
- Includes reported preferred terms of Bursitis, Chondromalacia patellae, Eczematoid, Joint sprain, Joint swelling, Tenosynovitis, and Trigger finger.

The total number of AEs of impregnation of attribution reported whose onset were within 72 hours after the end of an infusion of FleboGamm® 5% DIF was 216. There were a total of 708 infusions, resulting in a rate of 0.30% (upper bound 0.54±0.12%) temporally associated other AE. There were 144 infusions (53.5%) in 1-sided 0.05% upper bound (3.24%) 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

<table>
<thead>
<tr>
<th>Severity of AE</th>
<th>No. of infusions with AE</th>
<th>Adjusted %</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>58</td>
<td>7.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
<td>3.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

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

* The 5% upper bound for the adjusted % of infusions is 0.30% (upper bound 0.54±0.12%) temporally associated other AE.

6.2 Post-marketing experience

The following adverse reactions have been identified during the post-approval use of the product, including FleboGamm® 5% DIF (see references). 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.

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Apnea, Acute Respiratory Distress Syndrome (ARDS), Infection-Related Acute Lung Injury (PALS), cyanosis, pterygium, pulmonary edema, dyspnea, pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Cardiac arrest, cardiogenic shock, cardiovascular collapse, hypertensive crisis</td>
</tr>
<tr>
<td>Neurological</td>
<td>Coma, loss of consciousness, seizures, tremor</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Stevens-Johnson Syndrome, epidermolysis, erythema multiforme, furunculosis, dermatitis herpetiformis, Pancytopenia, leukopenia, hemotysis, pseudo-diease fibrinogen (Coombs test)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatic dysfunction, abdominal pain</td>
</tr>
</tbody>
</table>

### Table 3. Number (%) of Subjects with Treatment-Emergent Rashes in ASL or ALT in N = 46

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Assessment Criteria</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>Above the ULN</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>ALT</td>
<td>Above the ULN</td>
<td>2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* ULN = upper limit of normal.

None of these subjects had a concomitant treatment-emergent rise in liver enzymes.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FleboGamm® 5% DIF supplied is a broad spectrum of opsonic and neutralising IgG antibodies against bacteria, viral, parasitic, and mycoplasma ligands and their toxins. The mechanism of action in PI has not been fully elucidated.

12.2 Pharmacodynamics

FleboGamm® 5% DIF contains antigenic material and, when used in patients with a history of drug allergy, may cause a local or systemic reaction.

12.3 Pharmacokinetics

In the clinical study assessing safety and efficacy in primary immunodeficiency disease (PI), FleboGamm® 5% DIF was administered as an IV infusion (500 to 600 mg/kg) to patients with PI, with a 3-week interval and after the 5th infusion for 12 weeks. The pharmacokinetics of total IgG was determined after the 7th infusion of the 3-week dosing interval and after the 5th infusion for 4 weeks (Table 5 and Table 6).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>3-Week Dosing Interval (n=8)</th>
<th>4-Week Dosing Interval (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/dL)</td>
<td>1,920</td>
<td>2,069</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1,290–2,800</td>
<td>2,280</td>
</tr>
<tr>
<td>Cmin (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>2,480–4,010</td>
<td></td>
</tr>
<tr>
<td>Clearance (mL/d)</td>
<td>31,159</td>
<td>32,934</td>
</tr>
<tr>
<td>AUC (area under curve)</td>
<td>20,049–23,104</td>
<td>27,650–41,894</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>138</td>
<td>57</td>
</tr>
<tr>
<td>Trough IgG level (mg/dL)</td>
<td>951.38</td>
<td>132.42</td>
</tr>
</tbody>
</table>

* The number of bradycardia are the minimum and maximum values.

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

* For subjects on a 4-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 deaths (16 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.
The number of days of therapeutic and prophylactic oral antibiotic use was also monitored. Although the NOAD 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 Flebogamma® 5% DIF or its effects on fertility. Inform patients that Flebogamma® 5% DIF is made from human plasma and may contain infectious agents that can cause disease.

Table 6. Summary of Bacterial Infections (Intention-to-Treat Population, N = 40)

<table>
<thead>
<tr>
<th>Infections</th>
<th>Patients (N=40)</th>
<th>Episodes</th>
<th>Estimates [1]</th>
<th>95% CI (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>1.2 (0.0)</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>0.0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis/septic arthritis</td>
<td>0.0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>0.0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>1 (2.2)</td>
<td>0.021</td>
<td>0.001-0.112</td>
<td></td>
</tr>
</tbody>
</table>

[2] The confidence interval is defined 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 such 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 analyzed by using the subject-years-exposure data only of those subjects experiencing the endpoints, not WIT-age study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days/subject-year. The calculation includes all subjects, including those who had no infections, see Table 7.

Table 7. Summary of Secondary Efficacy Variables

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

[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 defined in Table 8.

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

<table>
<thead>
<tr>
<th>Statistic</th>
<th>3-Week Dosing Interval</th>
<th>4-Week Dosing Interval</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>33</td>
<td>46</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>451 (98.72)</td>
<td>448 (81.83)</td>
<td>449 (85.96)</td>
</tr>
<tr>
<td>Median</td>
<td>440</td>
<td>453</td>
<td>449</td>
</tr>
<tr>
<td>Q1, Q3*</td>
<td>384.2, 540.5</td>
<td>379.5, 511.1</td>
<td>380.9, 518.8</td>
</tr>
<tr>
<td>Min, Max</td>
<td>288.4, 598.2</td>
<td>298.2, 591.1</td>
<td>288.4, 591.1</td>
</tr>
</tbody>
</table>

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