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 5% 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 5% 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 5% DIF does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer FLEBOGAMMA 5% DIF at the minimum infusion rate practicable. [5.2]

DOSAGE AND ADMINISTRATION
For Intravenous Use Only

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Initial Infusion Rate</th>
<th>Maintenance Dose Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>300-600 mg/kg every 3-4 weeks</td>
<td>0.01 mL/kg/minute (0.3 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 thrombosis, administer FLEBOGAMMA 5% DIF at 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
Liquid preparation containing 5% IgG (50 mg/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]
- 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 5% DIF at the minimum infusion rate practicable and less than 0.06 mL/kg/minute (3 mg/kg/minute). [8.5]

ADVERSE REACTIONS
The most common adverse reactions (reported in ≥ 1% of clinical trial subjects) were: headache, pyrexia/fever, pain, infusion site reactions, diarrhea, rashes or chills, urticaria and infusion site inflammation. [6]

USE IN SPECIFIC POPULATIONS
- Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, and rubella. [7]

See 17 for PATIENT COUNSELING INFORMATION.

REVISED: 09/2013

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

1 INDICATIONS AND USAGE
Flebogamma 5% DIF is an Immune Globulin Intravenous (Human) 5% preparation that is indicated for the treatment of Primary Immunodeficiency (PI) (including the humoral immune defect in common variable immunodeficiency, i.e. agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome).

2 DOSAGE AND ADMINISTRATION
For Intravenous Use

2.1 Doseage

Dose

Initial Infusion Rate

Dose

Maintenance Dose Rate

(1 tolerated)

300 to 600 mg/kg body weight (6.0 to 12.0 mL/kg) administered every 3 to 4 weeks

0.01 mL/kg body weight/minute (0.5 mg/kg/minute)

Increase to 0.10 mL/kg/minute

As there are significant differences in the half-life of IgG among patients with HIV, the frequency and amount of immunotherapy may vary from patient to patient. Dosage should be adjusted according to the clinical response. The dosage may be adjusted over time to achieve the desired levels during clinical trials and control results. No randomized controlled trials are available to determine an optimum target trough serum level IgG.

WARNING: THROMBOSIS, RENAL DYSFUNCTION, AND ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin products, including Flebogamma 5% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thromboembolism, congenital heart disease, pregnancy, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. (See Warnings and Precautions (5.4) and Warnings and Precautions (5.4).

For patients at risk of thrombosis, administer Flebogamma 5% DIF at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis, including blood in the patient's urine, in the absence of known risk factors. (See Warnings and Precautions (5.3) and Warnings and Precautions (5.4).

Renal dysfunction, acute renal failure, sepsis, nephrotic syndrome, and death have been reported in patients receiving IGIV. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.

Administer Flebogamma 5% DIF at the minimum dose of infusion practicable in patients at risk for renal dysfunction or failure.

An increased risk of renal dysfunction and acute renal failure occurs more commonly in patients receiving IGIV containing sucrose (see Warnings and Precautions (5.4)). Flebogamma 5% DIF does not contain sucrose.

(See Dosage and Administration (2.3) and Warnings and Precautions (5.4).

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing renal dysfunction or failure.

5.4 Thrombosis

Thrombosis may occur following treatment with immune globulin products, including Flebogamma 5% DIF. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thromboembolism, use of ethanol, intravenous central vascular catheters, hypercoagulability, 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 (5.4)). 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 (5.4)).

The most common other adverse drug reactions reported in 5% of the subjects included hypertension, sinusitis, nausea/vomiting, abdominal pain, headache, back pain, abdominal pain, diarrhea, nausea/vomiting, and headache. Pain scores were generally low and were not considered to be clinically important.

The total number of adverse reactions reported whose onset were between 72 hours after the end of an infusion of Flebogamma 5% DIF was 107. There were a total of 709 infusions, resulting in a rate of 0.15% temporally associated adverse reactions per infusion (15/1090 infusions). There were 709 infusions, 9/1090 infusions (0.8%). There were 709 infusions, 9/1090 infusions (0.8%). There were 709 infusions, 9/1090 infusions (0.8%).

The most common other adverse drug reactions reported in fewer than 5% of the subjects included hypertension, sinusitis, nausea/vomiting, abdominal pain, headache, back pain, abdominal pain, diarrhea, nausea/vomiting, and headache. Pain scores were generally low and were not considered to be clinically important.

The total number of adverse reactions reported whose onset were between 72 hours after the end of an infusion of Flebogamma 5% DIF was 107. There were a total of 709 infusions, resulting in a rate of 0.15% temporally associated adverse reactions per infusion (15/1090 infusions). There were 709 infusions, 9/1090 infusions (0.8%). There were 709 infusions, 9/1090 infusions (0.8%). There were 709 infusions, 9/1090 infusions (0.8%).
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
relate a reaction to drug exposure. Therefore, information on reported adverse reactions is desirable.

The following adverse reactions have been identified during the post-approval use of IVIG products (16-17), including
Flebogamma 5% DIF:

Table 2. Flebogamma 5% DIF: viral reduction capacity of combined steps (log10)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Model virus</td>
<td>HIV-1</td>
<td>PRV</td>
<td>IBR</td>
<td>BDV</td>
<td>SNEIB</td>
<td>WWIV</td>
<td>ECV</td>
</tr>
<tr>
<td>Interplacental</td>
<td>1.00*</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ethanol treatment</td>
<td>1.06</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Pegylation</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Acid pH treatment</td>
<td>2.47</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Nanofiltration 20 nanometer</td>
<td>4.81</td>
<td>4.81</td>
<td>4.81</td>
<td>4.81</td>
<td>4.81</td>
<td>4.81</td>
<td>4.81</td>
</tr>
<tr>
<td>Overall Reduction Capacity</td>
<td>≥25.11</td>
<td>≥27.78</td>
<td>≥6.33</td>
<td>≥21.28</td>
<td>≥6.49</td>
<td>≥17.42</td>
<td>≥19.25</td>
</tr>
</tbody>
</table>

Risk factors for primary hyperimmunoglobulinemia: IgM, IgG1, IgG2, IgG3, IgG4. Flebogamma 5% DIF contains trace amounts of IgA (typically
< 50 µg/mL) and trace amounts of sodium and IgM.

11 Contraception
Flebogamma 5% DIF is a ready-to-use, sterile, clear or slightly opalescent 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, pH treatment, precipitation, solvent detergent treatment and Flebogamma 5% DIF nanofiltration using 20 nanometer (nm) filters.

Flebogamma 5% DIF is a 10% preparation of human immunoglobulin G (IgG) in a sterile, pyrogen-free, non-pyrogenic solution of 140 mmol/L sodium chloride (NaCl) with a pH of 6.4-7.4. Flebogamma 5% DIF is intended for intravenous administration only.

12 Clinical PHARMACOLOGY
12.1 Mechanism of Action
Immunoglobulin In Intravenous (Human) (Flebogamma 5% DIF) is a replacement therapy for FI. It supplies a broad spectrum of opposing and neutralizing IgG antibodies against a wide variety of bacterial and viral agents. Flebogamma 5% DIF also contains a spectrum of antibodies capable of neutralizing cell surface antigens. The role of these antibodies and the mechanisms of action of IgG in Flebogamma 5% DIF have not been fully elucidated.

12.2 Pharmacokinetics
In the clinical study assessing safety and efficacy in PI, Flebogamma 5% DIF was administered as an IV infusion (300 to 600 mg/kg) to subjects every 3 to 4 (n=12) or 4 to 6 (n=23) weeks for 12 months. The pharmacokinetics of total IgG was determined after the 7th infusion and the 3-week dosing interval and after the 9th infusion for the 4-week dosing interval (Table 3).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenicity, Mutagenesis, Impairment of Fertility
No animal studies were conducted to evaluate the carcinogenic or mutagenic effect of Flebogamma 5% DIF or its effects on fertility.

13.2 Animal Toxicology and/or Pharmacology
Acute toxicology studies were performed in mice and rats at doses up to 5 kg body weight with injury rates of 6 to 77 times higher than the maximum rates recommended for humans. The most common clinical observations in mice were tremor, piloerection, ataxia and increase in respiration in all tested animals, but no relevant adverse effects could be confirmed after histological examination, gross necropsy, and microscopic analysis. This phenomenon was an indication of hypothermia when serum was analyzed, suggesting a possible relationship to increased thermoregulatory activity instead of reduced thermoregulatory activity. Three adverse effects were detected in any mouse, a much smaller animal where the rate of injury was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any relevant alteration.

14 CLINICAL STUDIES
A multicenter, open-label, historically controlled study was conducted in the United States to assess the efficacy, safety and pharmacokinetics of Flebogamma 5% DIF in adult and pediatric subjects with PI. A total of 46 subjects aged 16 years or older were enrolled, and were treated with Flebogamma 5% DIF at a dose of 300-600 mg/kg per infusion every 3 or 4 weeks for 12 months.

Since the subjects in the clinical study were assigned to two different treatment intervals (3-weeks vs 4-week infusion schedules), the dosing had to be adjusted to ensure that the subjects received approximately the same dose on an annualized basis. Therefore, subjects in the 3-week schedule received the same amount of antibody (66 mg/kg) per infusion. This resulted in a mean total dose of 451 mg/kg/month for subjects in the 3-week schedule (n=13, range 288-588 mg/kg/month) and 448 mg/kg/month for subjects in the 4-week schedule (n=23, range 288-589 mg/kg/month).
Table 4. Summary of Bacterial Infections (Intention-to-Treat Population, N = 46)

<table>
<thead>
<tr>
<th>Infections</th>
<th>Patients (N=46)</th>
<th>Episodes</th>
<th>Estimates (1)</th>
<th>95% CI (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>1 (2.2)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia or sepsis</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorioamnionitis/septic arthritis</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>1 (2.2)</td>
<td>1</td>
<td>0.021</td>
<td>0.001-0.112</td>
</tr>
</tbody>
</table>


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/prophylactic antibiotic use were also evaluated. These variables were annualized by using the subject-years exposure data of the subjects experiencing the events, but not the entire study cohort. With regard to the number of other validated infections, the mean rate was less than 2 days/subject/year (the calculation used all subjects, including those who had no infections; see Table 5).

Table 5. 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>23</td>
<td>12.95</td>
</tr>
<tr>
<td>Days of normal activities missed</td>
<td>18</td>
<td>7.28</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>4</td>
<td>0.77</td>
</tr>
<tr>
<td>Visits to physician/ER</td>
<td>29</td>
<td>4.31</td>
</tr>
<tr>
<td>Number of other documented infectious episodes</td>
<td>33</td>
<td>1.96</td>
</tr>
<tr>
<td>Days of therapeutic oral antibiotic use</td>
<td>36</td>
<td>55.52</td>
</tr>
<tr>
<td>Days of therapeutic parenteral antibiotic use</td>
<td>2</td>
<td>9.14</td>
</tr>
<tr>
<td>Days of other therapeutic antibiotic use</td>
<td>16</td>
<td>44.38</td>
</tr>
<tr>
<td>Days of prophylactic oral antibiotic use</td>
<td>19</td>
<td>43.10</td>
</tr>
<tr>
<td>Days of prophylactic parenteral antibiotic use</td>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>Days of other prophylactic antibiotic use</td>
<td>0</td>
<td>0.00</td>
</tr>
</tbody>
</table>

[1] Days of work/school missed per patient year are annualized 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 Inclusion 2 and Inclusion 3), these number of days in this period is not counted in the denominator. All other endpoints are defined similarly.

19 REFERENCES


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, and/or shortness of breath (see Renal Failure [3.2]).
- 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 [3.4]).
- Severe headache, neck stiffness, drowsiness, fever, sensitivity to light, painful eye movements, nausea, and vomiting (see Aseptic Meningitis Syndrome [5.5]).
- Fatigue, increased heart rate, yellowing of the skin or eyes, and dark-colored urine (see Hemolysis [5.6]).
- Trouble breathing, chest pain, blue lips or extremities, fever (see TRALI [5.7]).

Inform patients that Flebogamma 5% DIF is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the HIV). The risk of Flebogamma 5% DIF transmitting an infectious agent has been reduced by screening plasma donors for prior exposure, testing the 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 might be caused by infections.

Inform patients that Flebogamma 5% DIF may interfere with their immune response to live viral vaccines such as measles, mumps and rubella. Instruct patients to notify their health care professionals of this potential interaction when they are receiving vaccinations (see Drug Interactions [7.3]).

Manufactured by:
INSTITUTO GRIFOLS, S.A.
BARCELONA - SPAIN
U.S. License No. 1981
U.S. Distributor
GRIFOLS BIOLOGICS Inc.
LOS ANGELES - CA 90032, U.S.A.
U.S. License No. 1904

16 HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma 5% DIF is supplied in single-use, individually laser etched vials containing the labeled amount of functionally active IgG. The following presentations of Flebogamma 5% DIF are available:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
<th>Grams Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>61953-0004-1</td>
<td>50 ml</td>
<td>0.5 g</td>
</tr>
<tr>
<td>61953-0004-2</td>
<td>50 ml</td>
<td>2.5 g</td>
</tr>
<tr>
<td>61953-0004-3</td>
<td>100 ml</td>
<td>5.0 g</td>
</tr>
<tr>
<td>61953-0004-4</td>
<td>200 ml</td>
<td>10.0 g</td>
</tr>
<tr>
<td>61953-0004-5</td>
<td>400 ml</td>
<td>20.0 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.

Flebogamma 5% DIF may be stored at room temperature at 2 to 25 °C (36 to 77 °F) for 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 5% DIF in its original carton to protect it from light.