**WARNINGS AND PRECAUTIONS**

- IgA deficient patients with antibodies to IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. (5.1)
- Monitor renal function, including blood urea nitrogen, serum creatinine and urine output in patients at risk of developing acute renal failure. (5.2)
- Hypoalbuminemia, increased serum viscosity and hyponatremia may occur in patients receiving Flebogamma 5% DI therapy. (5.3)
- Thrombosis may occur. Monitor patients with known risk factors for thrombosis and consider baseline assessment of blood viscosity for those at risk of hyperviscosity. (5.4)
- Aseptic Meningitis Syndrome (AMS) may occur in patients receiving Flebogamma 5% DI therapy, especially with high doses or rapid infusion. (5.5)
- Hemolytic anemia can develop subsequent to Flebogamma 5% DI treatment. Monitor patients for signs and symptoms of hemolysis and hemolytic anemia. (5.6)
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury, TRALI). (5.7)
- Patients receiving Flebogamma 5% DI for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks may be at a higher risk for development of fever, chills, nausea, and vomiting. (5.8)
- Flebogamma 5% DI is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.9)
- Passive transfer of antibodies may confound serologic testing. (5.11)

The most common adverse reactions reported in ≥ 5% of clinical trial subjects were: headache, pyrexia/fever, pain, infusion site reactions, dizziness, rashes or chills, urticaria and infusion site inflammation. (6)

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

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**ADVERSE REACTIONS**

Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines, such as measles, mumps, and rubella. (7)

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**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 5% DI at the minimum infusion rate practicable and less than 0.06 mL/kg/minute (3 mg/kg/minute). (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2013
WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION

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

2. DOSAGE AND ADMINISTRATION
For Intravenous Use

2.1 Dosage Treatment of Primary Immunodeficiency

Dose

<table>
<thead>
<tr>
<th>Initial Infusion Rate</th>
<th>Maintenance Dose Rate (t tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01 mL/kg/min</td>
<td>0.01 to 0.04 mL/kg/min</td>
</tr>
<tr>
<td>0.05 mL/kg/min</td>
<td>0.05 to 0.20 mL/kg/min</td>
</tr>
</tbody>
</table>

3. DOSAGE FORMS AND STRENGTHS
Flebogamma 5% DIF is a liquid preparation containing 5% IgG (50 mg/mL).

4. CONTRAINDICATIONS
Flebogamma 5% DIF is contraindicated in patients who have had a history of anaphylactic or severe hypersensitivity reactions to the administration of human immunoglobulin.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions and anaphylactic reactions with a mortality in blood pressure may occur, even in patients who had not tolerated previous treatment with IVIG (see Contraindications (4)). If an hypersensitivity reaction develops, discontinue Flebogamma 5% DIF infusion immediately and institute appropriate treatment.

Flebogamma 5% DIF contains traces amount of IgG less than 50 µg/mL (see Description (13)). Patients with antibodies to IgG have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Flebogamma 5% DIF is contraindicated in patients with antibodies against IgG and a history of hypersensitivity reaction. (See Contraindications (4)).

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, acute tubular necrosis, proximal tubular necrosis, cortical necrosis and death have been reported in patients receiving IVIG, particularly those products containing sucrose (7-10). Flebogamma 5% DIF does not contain sucrose.

Ensure that patients are not volume-depleted before administering Flebogamma 5% DIF. For patients judged to be at risk for developing acute renal failure, 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 tolerable for the patient.

5.3 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

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

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 5% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuation of Flebogamma 5% DIF.

Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. (See Dosage and Administration (2.3) and Warnings and Precautions (5.4))

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 thrombosis, use of anticoagulants, hypertriglyceridemia, and cardiac and vascular risk factors. Thrombosis may occur in the absence of known 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 for hyperviscosity. (See Dosage and Administration (2.3) and Warnings and Precautions (5.4))

Flebogamma 5% DIF includes: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of anticoagulants, hypertriglyceridemia, and cardiac and vascular risk factors. Thrombosis may occur in the absence of known risk factors.

6. ADVERSE REACTIONS

Individuals receiving active immunizations (reported in ≤ 5% of clinical trial subjects) were headache, pyrexia/fever, pain, infusion site reactions, diarrhea, rigors, chills, urticaria, and infusion site infection.

To report SUSPECTED ADVERSE REACTIONS, contact British Biologics at 1-888-GRIFFOLS (1-888-477-4657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Clinical Trials Experience

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

7. PATIENT EDUCATION

See Patient Counseling Information

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Flebogamma 5% DIF is not known to cause harm to the developing human fetus. (See Animal Data (14.1)). Flebogamma 5% DIF contains IgG-containing immunoglobulin products whose effects on fetal development are not known.

8.2 Lactation

Flebogamma 5% DIF is not known to cause harm to the nursing infant. (See Animal Data (14.1)). Flebogamma 5% DIF contains IgG-containing immunoglobulin products whose effects on the nursing infant are not known.

8.3 Children

Flebogamma 5% DIF was not evaluated in clinical studies in children.

8.4 Elderly

Flebogamma 5% DIF is not expected to differ from Flebogamma 5% in the elderly with regard to adverse reactions. (See Clinical Pharmacology (12)).

9. DRUG INTERACTIONS

Flebogamma 5% DIF is a human immunoglobulin that is not known to induce drug interactions.
6.2 Post-marketing Experience
Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure.

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

7 DRUG INTERACTIONS
Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines, such as measles, mumps and rubella. Inform the immunizing physician of recent therapy with Flebogamma 5% DIF so that appropriate measures can be taken (see Patient Counseling Information [17]).

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

8.3 Nursing Mothers
Use of Flebogamma 5% DIF has not been evaluated in nursing mothers.

8.4 Pediatric Use
Clinical studies of Flebogamma 5% DIF for the treatment of PI did not include sufficient numbers of subjects aged 16 and younger to determine whether they respond differently from adults. Efficacy and safety in pediatric patients have not been established (see Clinical Studies [14]).

8.5 Geriatric Use
Limited information is available for the geriatric use of Flebogamma 5% DIF. Clinical studies of Flebogamma 5% DIF did not include sufficient numbers of subjects over the age of 65 to determine whether they respond differently from younger subjects. Use caution when administering Flebogamma 5% DIF to geriatric patients who are known or suspected to be receiving drugs that could potentially influence renal function or that could prevent diuresis. In geriatric patients with a history of renal impairment, dose reductions may be necessary.

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

11 DESCRIPTION
Flebogamma 5% DIF is a ready to use, sterile, clear or slightly opalescent and colorless to pale yellow, liquid preparation of purified immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold ethanol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurization, solvent detergent treatment and Planovia nano-filtration using 20 nanometer (nm) filters.

Flebogamma 5% DIF is a 5% (w/v) solution, human IgG. The distribution of the four IgG subclasses is approximately 68% IgG4, 28% IgG1, 2% IgG2, and 2% IgG3. Flebogamma 5% DIF contains trace amounts of ADA (typically < 50 μg/mL) and trace amounts of sodium and thymol.

Flebogamma 5% DIF contains 5 g human normal immunoglobulin G and 5 g D-sorbitol (as stabilizer) in 100 mL of water for injection, pH 5.45-6.95. These studies provide reasonable assurance that low levels of CJD/vCJD infectivity, if present in the starting material, would be removed.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Immune Globulin Intravenous (Human), Flebogamma 5% DIF is a replacement therapy for PI. 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 with cells such as erythrocytes. 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 mg 1 000 mg/kg) to subjects every 3 (n=12) or 4 (n=11) weeks for 12 months. The pharmacokinetics of total IVIG was determined after the 7th infusion for 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 toxicity studies were performed in mice and rats at doses up to 25 kg body weight with injection rates 6 to 7 1 in excess of the maximum recommended dose for humans. The most common clinical observations in mice were phlebitis, ataxia, and increase in respiration lasting 10 minutes or less. No relevant adverse effects were confirmed leading to histopathological, circulatory, renal, autonomic and central nervous systems, somatomotor activity, and behavior of the treated mice and rats.

Five out of 25 rats treated with the highest dose of approximately 6 times the maximum injection rate recommended for humans, showed a transient "red hump" sign which was not confirmed as a relevant basically causing phenomenon after renal macro and microscopic analysis. This phenomenon was ascribed to hemolysis when serum was analyzed, suggesting a possible relation to cross reactivity of any red cells with human antibodies. No "red hump" was detected in any mouse, a much smaller animal where the ratio of injection was comparatively much higher than in rats. The macroscopic inspection of all treated mice did not show any renal 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 10-75 years (63% male, 37% female) were enrolled, and were treated with Flebogamma 5% DIF at a dose of 300-600 mg/kg per infusion every 3 or 4 weeks for 12 months.

Since the subjects in the clinical study were assigned to 2 different treatment intervals (3-weeks 4-weeks infusion schedules), the dosages had to be adjusted to ensure that the subjects received approximately the same dose on an annualized basis. Therefore, subjects in the 3-weeks protocol received 4% of the total antibody (4-weeks) dose per infusion. This resulted in a mean total dose of 451 mg/kg/month for subjects in the 3-weeks schedule (n=13, range 288-586 mg/kg/month) and 446 mg/kg/month for subjects in the 4-weeks schedule (n=33, range 288-581 mg/kg/month).

During the study period, the mean level of acute serum bacterial infection, defined as bacterial pneumonia, bacteremia or sepsis, osteomyelitis, arthritis, visceral abscesses and bacterial meningitis per subject per year, was 0.07 (with an upper 1-sided 95% confidence interval of 0.01 to 0.21). One subject had one episode of bacterial pneumonia and there were no other episodes of serious bacterial infections reported (Table 4).
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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work/school days missed</td>
<td>23</td>
<td>50.8 12.95</td>
</tr>
<tr>
<td>Days of normal activities missed</td>
<td>18</td>
<td>39.1 7.28</td>
</tr>
<tr>
<td>Days in hospital</td>
<td>4</td>
<td>8.7 0.77</td>
</tr>
<tr>
<td>Visits to physician/ER</td>
<td>29</td>
<td>63.0 4.31</td>
</tr>
<tr>
<td>Number of other documented infectious episodes</td>
<td>33</td>
<td>71.7 1.96</td>
</tr>
<tr>
<td>Days of therapeutic oral antibiotic use</td>
<td>36</td>
<td>76.1 55.52</td>
</tr>
<tr>
<td>Days of therapeutic parenteral antibiotic use</td>
<td>2</td>
<td>4.3 0.14</td>
</tr>
<tr>
<td>Days of other therapeutic oral antibiotic use</td>
<td>16</td>
<td>34.8 44.38</td>
</tr>
<tr>
<td>Days of prophylactic oral antibiotic use</td>
<td>19</td>
<td>41.3 81.08</td>
</tr>
<tr>
<td>Days of prophylactic parenteral antibiotic use</td>
<td>1</td>
<td>2.3 0.02</td>
</tr>
<tr>
<td>Days of other prophylactic antibiotic use</td>
<td>0</td>
<td>0.0 0.00</td>
</tr>
</tbody>
</table>

Table 4. Summary of Bacterial Infections (Intention-to-Treat Population, N = 46)

<table>
<thead>
<tr>
<th>Infections</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>
</tr>
<tr>
<td>Bacteremia or sepsis</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis/arthritic</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>0 (0.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>1 (2.2)</td>
<td>1</td>
<td>0.021 (0.001-0.112)</td>
</tr>
</tbody>
</table>


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

The days of work/school missed, hospitalizations and days of each hospitalization, the number of visits to physicians or emergency rooms, other infections documented by positive radiographic findings and fever, and days on therapeutic and prophylactic oral/parenteral antibiotic use were also evaluated. These variables were annualized by using the subject-years exposure data of those 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).