Highly Purified IGIV
- Trace amounts of IgA: $0.0028 \pm 0.0016$ mg/mL
- Appropriate for patients with restricted sodium intake
- Sorbitol stabilized, sucrose and maltose free

Demonstrated Benefits in Replacement Therapy
- In the pre-approval clinical trial\(^2\):
  - Only 0.021 serious bacterial infections/patient/year
  - None of the patients participating withdrew from the study due to a treatment-related adverse event

One Step Beyond in Viral Safety Margin
- Seven validated viral elimination steps including:
  - 20 nm nanofiltration
  - Double specific inactivation
- Highly effective process:
  - $\geq 15.04$ log reduction of PPV (B19 model virus)
  - $\geq 13.33$ log reduction of EMCV (HAV model virus)

\(^{\dagger}\) Laser etched identifier number may at times be covered by the label.
(1) Mean value from 97 consecutive lots, data on file, Instituto Grifols, S.A.

For further information call Grifols USA, LLC Professional Service: 888-GRIFOLS (888-474-3657)
Customer Service: 888-325-8579 Fax: 323-441-7068 www.grifols.com
Flebogamma® 5% DIF is indicated for replacement therapy in primary humoral immunodeficiency disorders.

Important Safety Information

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 PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. Flebogamma® 5% DIF should not be administered to individuals with a history of severe or anaphylactic reactions to blood or blood-derived products. Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using Flebogamma® 5% DIF even though it contains low amounts of IgA (typically < 50 µg/mL). If patients are known to be intolerant to any component of Flebogamma® 5% DIF, such as sorbitol (i.e., intolerance to fructose), they should not receive the product. An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. AMS may occur more frequently in association with high-dose (e.g., > 1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. There have been reports of non-cardiogenic pulmonary edema (Transfusion-Related Acute Lung Injury (TRALI)) in patients administered IGIV. Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Reported adverse reactions with Flebogamma® 5% DIF and other IGIV products include: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema, often beginning within 60 minutes of the start of the infusion. Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented. Please refer to adjacent Brief Summary of the Prescribing Information.
Immune Globulin Intravenous (Human)
Flebogamma® 5% DIF
For intravenous use only
Rx only

BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Flebogamma® 5% DIF is indicated for replacement therapy in primary (inherited) humoral immunodeficiency disorders.

DOSEAGE AND ADMINISTRATION
The usual dose of Flebogamma® 5% DIF for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight administered every 3 to 4 weeks.

An in-line filter with a pore size of 15 to 20 microns is recommended for the infusion. Antibacterial filters (0.2 micron) may also be used. Discard unused contents and administration devices after use.

The infusion of Flebogamma® 5% DIF should be initiated at a rate of 0.01 mL/kg body weight/minute (0.5 mg/kg/minute). If, during the first 30 minutes, the patient does not experience any discomfort, the rate may be gradually increased to a maximum of 0.10 mL/kg/minute (5 mg/kg/minute).

For patients judged to be at risk for developing renal dysfunction or considered to be at increased risk of thrombotic/thromboembolic events, it may be prudent to limit the infusion rate to a maximum rate less than 0.06 mL/kg body weight/minute (3 mg/kg/minute). Reduction in dose, concentration, and/or rate of infusion in patients at risk of acute renal failure, which includes patients over 65, has been proposed in the literature in order to reduce the risk of acute renal failure.

CONTRAINDICATIONS
Flebogamma® 5% DIF should not be administered to individuals with a history of severe or anaphylactic reactions to blood or blood-derived products. Patients with severe selective IgA deficiency (IgA < 0.05 g/L) may develop anti-IgA antibodies that can result in a severe anaphylactic reaction. Anaphylaxis can occur using Flebogamma® 5% DIF even though it contains low amounts of IgA (typically < 50 µg/mL). Such patients should only receive intravenous immune globulin with utmost caution and in a setting where supportive care is available for treating life-threatening reactions. If patients are known to be intolerant to any component of Flebogamma® 5% DIF, such as sorbitol (i.e., intolerance to fructose), they should not receive the product.

WARRNS

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, paraproteinemias, 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION sections for important information intended to reduce the risk of acute renal failure.

Flebogamma® 5% DIF is made from human plasma. As with all plasma derived products, the risk of transmission of infectious agents, including viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated. The risk that such products will transmit an infectious agent has been greatly reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologics at 888-GRIFOLS (888-474-3657). All patients, but especially individuals receiving Flebogamma® 5% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at risk for the development of inflammatory reactions characterized by fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations may reduce the risk of these types of events.

Appropriate supportive care, including immediate access to epinephrine injection, should be available for the management of acute anaphylactic reactions.

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

Ensure that patients are not volume-depleted before the initiation of the infusion of IGIV.

Renal Function:
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. Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma® 5% DIF and again at appropriate intervals thereafter. If renal function deteriorates, discontinuation of the product should be considered.

For patients judged to be at risk for developing renal dysfunction, it may be prudent to reduce the amount of product infused per unit time by infusing Flebogamma® 5% DIF at a maximum rate less than 0.06 mL/kg (3 mg/kg) body weight/minute.

Aseptic Meningitis Syndrome:
An aseptic meningitis syndrome (AMS) has been reported to occur infrequently in association with IGIV treatment. The syndrome usually begins within several hours to 2 days following IGIV treatment. It is characterized by symptoms and signs including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting. Cerebrospinal fluid (CSF) studies are generally positive with pleocytosis up to several thousand cells per cubic milliliter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL. Patients exhibiting such symptoms and signs should receive a thorough neurological examination, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high-dose (e.g., > 1.0 g/kg body weight) and/or rapid-infusion IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis:
Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration [See ADVERSE REACTIONS]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See PRECAUTIONS: Laboratory Tests].

Thrombotic Events:
Thrombotic events have been reported in association with IGIV [See ADVERSE REACTIONS]. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammapathies [See PRECAUTIONS: Laboratory Tests].

Transfusion-Related Acute Lung Injury (TRALI):
There have been reports of non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1 to 6 hours after transfusion. Patients with TRALI may be managed by using oxygen therapy with adequate ventilatory support. IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum [See PRECAUTIONS: Laboratory Tests].

Information For Patients:
Patients should be instructed to immediately report symptoms of decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage) to their physicians. It is recommended that the lot number of the vials used be recorded when Flebogamma® 5% DIF is administered.

Laboratory Tests:
Renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, should be assessed before the initial infusion of Flebogamma® 5% DIF in patients judged to have a potential increased risk for developing acute renal failure and again at appropriate intervals thereafter.
Following infusion of Flebogamma® 5% DIF, there may be a transitory rise of various antibody titers that may result in misleading positive results in serological testing. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triglycerides (triglycerides), or monoclonal gammapathies. If TRALI is suspected, appropriate tests should be performed for the presence of antineutrophil antibodies in both the product and patient serum.

Pregnancy Category C:
Animal reproduction studies have not been performed with Flebogamma® 5% DIF. It is also not known whether Flebogamma® 5% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma® 5% DIF should be given to a pregnant woman only if clearly needed.

Drug Interactions:
Antibodies in Flebogamma® 5% DIF may interfere with the response to live viral vaccines, such as measles, mumps, and rubella. Physicians should be informed of recent therapy with Immune Globulin Intravenous (Human) so that administration of live viral vaccines, if indicated, can be appropriately delayed 3 or more months from the time of IGIV administration.

Pediatric Use:
The above mentioned clinical trial with Flebogamma® 5% DIF enrolled only a very limited number of children (0) and adolescents (3) with primary humoral immune deficiency, a number insufficient to fully characterize and establish the efficacy and safety in pediatric patients.

Geriatric Use:
Subjects over 65 are at increased risk of renal failure with IGIV treatment. For these subjects, and for any other subjects at risk of renal failure, the infusion rate of Flebogamma® 5% DIF should be limited to < 0.06 mL/kg/min (3 mg/kg/min).

Adverse Reactions
Increases of creatinine and blood urea nitrogen (BUN) have been observed as soon as 1 to 2 days following infusion of IGIV. Progression to oliguria and anuria requiring dialysis has been observed, although some patients have improved spontaneously following cessation of treatment. Types of severe renal adverse reactions that have been seen following IGIV therapy include: acute renal failure, acute tubular necrosis, proximal tubular nephropathy, and osmotic nephrosis. Certain severe adverse reactions may be related to the rate of infusion. The recommended infusion rate [See DOSAGE AND ADMINISTRATION] must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. Adverse reactions may occur more frequently when a high infusion rate is used, the treatment is the initial exposure to immunoglobulin, the immunoglobulin product has been changed to that of a different manufacturer, or there has been a long interval (more than 8 weeks) since the previous infusion. Slowing or stopping an infusion usually results in the prompt disappearance of symptoms.

Post-Marketing:
The following adverse reactions have been identified and reported during the post-approval use of IGIV products.

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

Because post-marketing reporting of these reactions is voluntary and the at-risk populations are of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to exposure to the product. Such is also the case with literature reports authored independently.

Adverse events were reported in a study of 46 individuals with primary humoral immunodeficiency diseases receiving infusions every 3 to 4 weeks of 300 to 600 mg/kg body weight. Forty-three (94%) subjects experienced at least 1 adverse event irrespective of the relationship with the product, and these subjects reported a total of 595 adverse events. None of the 46 subjects who participated in this study discontinued the study prematurely due to an adverse experience related to the study drug. One subject had treatment-emergent bronchiectasis, mild, ongoing, after infusion #10; and one subject had recurrent moderate leukopenia after the 7th and 12th infusions. No adverse events occurred with an incidence of > 2% on a per infusion basis.

Table 1. Adverse Events Occurring with an Incidence of > 15%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of AEs</th>
<th>Number of Subjects with AEs</th>
<th>Percent of Subjects with AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Bronchitis</td>
<td>19</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Cough and productive cough</td>
<td>10</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Diarrhea NOS</td>
<td>14</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Headache NOS and sinus headache</td>
<td>46</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>11</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Injection site reaction NOS</td>
<td>13</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>27</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Sinusitis NOS</td>
<td>38</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Wheezing and asthma aggravated</td>
<td>24</td>
<td>10</td>
<td>22</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Severity of AE</th>
<th>No. 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>

Reported adverse reactions with Flebogamma® 5% DIF and other IGIV products include: headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema, often beginning within 60 minutes of the start of the infusion. Rarely, Immune Globulin Intravenous (Human) can induce a severe fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with IGIV. In the case of shock, the current standard medical treatment for shock should be implemented.

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

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Assessment Criteria</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST Above 3x the ULN</td>
<td>3</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>ALT Above 3x the ULN</td>
<td>1</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

a. ULN = upper limit of normal.

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

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