The dosage recommendations are summarised in the following table:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement therapy: Primary Immunodeficiency (PI) diseases</td>
<td>- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg</td>
<td>every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/L</td>
</tr>
<tr>
<td>Symptomatic hypogammaglobulinaemia secondary to underlying disease or treatment</td>
<td>0.2 - 0.4 g/kg</td>
<td>every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/L</td>
</tr>
<tr>
<td>Immunomodulation: Idiopathic thrombocytopenic purpura</td>
<td>0.8 - 1 g/kg</td>
<td>on day 1, possibly repeated once within 3 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>for 2 - 5 days</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>for 3 - 7 days</td>
</tr>
<tr>
<td>Guillain Barre syndrome</td>
<td>0.4 g/kg/d</td>
<td>in several doses for 2 - 5 days in association with acetylsalicylic acid</td>
</tr>
<tr>
<td>Kawasaki disease</td>
<td>1.6 - 2 g/kg or 2 g/kg</td>
<td>in one dose in association with acetylsalicylic acid</td>
</tr>
</tbody>
</table>

Method of administration

The product should be brought to room or body temperature before use. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Flebogamma 10% DIF should be infused intravenously at an initial rate of 0.01 ml/kg/min (1 mg/kg/min) for the first thirty minutes. If tolerated, advance to 0.02 ml/kg/min (2 mg/kg/min) for the second thirty minutes. Again, if tolerated, advance to 0.04 ml/kg/min (4 mg/kg/min) for the third thirty minutes. If the patient tolerates the infusion well, additional increments of 0.02 ml/kg/min may be made at 30-minute intervals up to a maximum of 0.08 ml/kg/min (8 mg/kg/min).

It has been reported that the frequency of adverse reactions to IVIG increases with the infusion rate. Infusion rates during the initial infusions should be slow. If there are no adverse reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate. For patients experiencing adverse reactions, it is advisable to reduce the infusion rate in subsequent infusions and limit the maximum rate to 0.04 ml/kg/min or administer IVIG at a 5% concentration (see section Precautions).

This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line.

Product is for use in one patient only. Discard any residue.

Any unused product or waste material should be disposed of in accordance with local requirements.

OversDose

Overdose may lead to fluid overload and hyper viscosity, particularly in patients at risk, including elderly patients or patients with renal impairment.

Contact poisons information centre on 131126 for advice on management.

Presentation

Flebogamma 10% DIF is a solution for infusion supplied in a type II glass vial closed with a chlor-butyl-rubber stopper.

Flebogamma 10% DIF is supplied as 5 g/50 ml, 10/100 ml and 20/200 ml vials.

Pack size: 1 vial

Not all pack sizes may be marketed.

Storage Conditions

Shelf life is 2 years.

Store below 30 °C. Do not freeze. Protect from light.

Contains no antimicrobial preservative. Use in one container on one occasion only.

Do not use after expiry date.

NAME AND ADDRESS OF THE SPONSOR

Grifols Australia Pty Ltd
5/90 Fairbank Road,
Clayton South,
Victoria, Australia
3168

NAME AND ADDRESS OF THE MANUFACTURER

Instituto Grifols, S.A., Can Guasch, 2 - Poles del Vallés
08150 Barcelona - Spain

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 12 February 2013

Instituto Grifols, S.A. Can Guasch, 2 - Poles del Vallés 08150 Barcelona - SPAIN 3036029

Flebogamma 10% DIF

Solution for infusion

Human normal immunoglobulin (IVg) 100 mg/ml

DESCRIPTION

Flebogamma 10% DIF (dual inactivation plus nanofiltration) (IVg) is a sterile, clear or slightly opalescent, and colourless to pale yellow, liquid ready to use, preparation of highly purified human immunoglobulin (IgG) obtained from human plasma pools. The purification process includes cold alcohol fractionation, gelatine glycine precipitation, to exchange chromatography, low pH treatment, pasteurisation, andalent derivate treatment and two sequential nanofiltrations through 35 nm and 20 nm pore size nanofilters connected in series.

Flebogamma 10% DIF is a highly purified (≥ 97% IgG) and unmodified human IgG that contains the antibody specificities found in the donor population. IgG subclasses are fully represented with the following approximate percentages of total IgG: IgG1, 66.6%; IgG2, 27.9%; IgG3, 3.0%; and IgG4, 5.5%. Flebogamma 10% DIF contains only trace amounts of IgA (lower than 100 micrograms/ml). In the final formulation, Flebogamma 10% DIF contains ≤ 10 human normal immunoglobulin and ≤ 5 yeast derived (as stabilizer) ≤ 100 mg/ml of yeast DNA. There is no preservative in the formulation. The pH of the solution ranges from 5.0 to 6.0 and the osmolality from 250 to 350 mOsm/kg, which is within the normal physiologic range. The Fe and Fab functions are maintained in Flebogamma 10% DIF.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravenous administration, ATC code: J06AB02.

Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donors. It has a distribution of immunoglobulin G subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low normal immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Pharmacokinetic properties

Human normal immunoglobulin is immediately and completely bioavailable in the recipient’s circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3 - 5 days equilibrium is reached between the intra- and extravascular compartments.

One multicenter trial to determine the clinical efficacy, pharmacokinetics and safety was performed in 45 patients with primary immunodeficiency. From the average levels and other standard pharmacokinetic parameters such as serum Cmax, half-life, clearance and volume of distribution for total IgG, IgG subclasses were determined in a subgroup of 15 patients (18 - 58 years, 10 male). Mean trough IgG level ranged from 880 to 970 mg/dl for 21-day infusion schedule patients and from 800 to 862 mg/dl for 28-day infusion schedule patients. The mean serum half-life for total IgG was 34 and 37 days for the 21 and 28 day dosing schedule, respectively, and the mean clearances were 115 and 144 ml/day. For IgG subclasses the mean serum half-life ranged from 29 to 53 days. For both dosing schedules, the mean AUC levels for the total IgG was around 34.000 day*mg/ml, the mean Cmax levels was around 2000 mg/ml, and the mean volume of distribution between 5.4 and 7.4 L.

Half-life may vary from patient to patient, in particular in primary immunodeficiency.

IgG and IgG-complexes are broken down in cells of the reticuloendothelial system.

CLINICAL TRIALS

Primary immunodeficiency disease

One clinical trial (ID 304) was performed with the objective of evaluating the clinical efficacy and the safety of the product. To achieve the primary objective it was used the Food and Drug Administration (FDA) efficacy criterion which includes as primary outcome the rate of serious bacterial infections of ≤ 1 serious bacterial infection/patient/year. The definition of serious bacterial infections includes the following infections: bacteremia or sepsis, bacterial meningitis, and acute bacterial sinusitis. The study was designed as a multi-center, open-label, non-randomized, clinical study in patients with PID diseases requiring antibody replacement therapy and who have been receiving IVIG replacement therapy at a steady dose for at least 3 months prior to entry. Patients participated in the study for 12 months (13 to 17 infusions based on individual dose intervals). Study participants have received Flebogamma 10% DIF intravenously at a dose of 100 to 500 mg/kg per infusion, administered every 21 to 28 days (4 - 7 days). Early-sea patients were enrolled in the study and received at least 1 infusion of Flebogamma 10% DIF. Thirty-seven patients (80.5%) completed the study. The results obtained from the trial with Flebogamma 10% DIF in PID (study IG104) show that patients who received Flebogamma 10% DIF infusions of 300 - 600 mg/kg had a serious bacterial infection rate of 0.025 infections/patient/year (1 serious bacterial infection reported; 98% CI: 0.001 - 0.313).

Chronic idiopathic thrombocytopenia

Twenty-seven patients, eighteen adults at least 18 years of age, and nine children aged 3 - 15 years were enrolled in 2 open trials in which patients with chronic ITTP were treated with a total dose of 2 g/kg of Flebogamma 10% DIF. The primary efficacy response was the proportion of patients with increase in platelet count ≥ 50 x 10^9/L.

Twenty-four patients overall (89%) responded. The proportion of adult responders was 83% (15/18), the proportion of paediatric responders was 100% (9/9). The median time to response was 2 ± 7 days for all the patients. The median duration of response was 12 days in all the patients. Responders recorded a median maximum platelet count of 277 ± 195%, which is within the normal physiologic range. The Fe and Fab functions are maintained in Flebogamma 10% DIF.
INDICATIONS
Replacement therapy indications:
- Primary Immune Deficiency Diseases
- Symptomatic hypogammaglobulinemia secondary to underlying disease or treatment.

Immunomodulation indications:
- Idiopathic thrombocytopenia purpura (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain-Barré syndrome.
- Kawasaki disease.

CONTRAINdications
Hypersensitivity to the active substance or to any of the excipients (see section Precautions).
Hypersensitivity to human immunoglobulins, especially in very rare cases of IgA deficiency, when the patient is at risk of anaphylactic shock.
Hereditary fructose intolerance. In babies and young children hereditary fructose intolerance may not be diagnosed and may be fatal, thus, they should not receive this medicinal product.

PRECAUTIONS
An apparent increase in the rate of adverse events was observed in clinical trials with Flebogamma 10% DIF compared to Flebogamma 3% DIF.
Flebogamma 10% DIF should be infused intravenously at an initial rate of 0.01 ml/kg/min (1 mg/kg/min) for the first thirty minutes. If tolerated, advance to 0.02 ml/kg/min (2 mg/kg/min) for the second 30 minutes. If tolerated, advance to 0.04 ml/kg/min (4 mg/kg/min) for the total 30 minutes. If the patient tolerates the infusion well, additional increments of 0.02 ml/kg/min may be made at 30-minute intervals until a maximum of 0.08 ml/kg/min (8 mg/kg/min).
SPECIAL WARNINGS AND INSTRUCTIONS FOR USERS:
- If necessary, blood pressure should be continuously monitored during infusion.
- Patients with rare hereditary problems of fructose intolerance should not take this medicine.

When human normal immunoglobulin is used for immunoglobulin replacement therapy, the possibility of transmitting infective agents cannot be totally excluded. The risk of such transfers is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing human normal immunoglobulin.

The treatment required depends on the nature and severity of the adverse reactions.

In case of shock, standard medical treatment for shock should be implemented.
In all patients, IgG administration should:
- be adequately hydrated prior to the initiation of the infusion of IgG.
- monitor urine output.
- monitoring of serum creatinine levels.
- avoidance of concomitant use of loop diuretics.

Hypersensitivity
True hypersensitivity reactions are rare. They can occur in the very seldom cases of IgA deficiency with anti-IgA antibodies.
Rarely, human normal immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who had tolerated previous treatment with human normal immunoglobulin.

Thromboembolism
There is clinical evidence of an association between IgG administration and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thromboses which is assumed to be related to a relative increase in blood viscosity through the high influx of immunoglobulin in at-risk patients. Caution should be exercised in prescribing and infusing IgG in obese patients and in patients with pre-existing risk factors for thrombotic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thromboembolic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilization, severely hypoalbuminemic patients, and patients with diseases which increase blood viscosity).

In patients at risk for thromboembolic adverse reactions, IgG products should be administered at the minimum rate of infusion and dose practicable.

Acute renal failure
Cases of acute renal failure have been reported in patients receiving IgG therapy. In most cases, renal factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypalbuminemia, overhydration, concomitant nephrotic syndromes or age over 65.
In case of renal impairment, the use of IgG products should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IgG products, those containing sucrose as an excipient accounted for 97% of these reports.

In patients at risk for acute renal failure, IgG products should be administered at the minimum rate of infusion and dose practicable.

Haemolytic anaemia
IgG products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red cells with immunoglobulin, causing a reduced rate of clearance (Coomb’s test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to IgG therapy due to enhanced red blood cells (RBCC) sequestration. IgG recipients should be monitored for clinical signs and symptoms of RBCC sequestration.

Transfusion-related acute lung injury (TRALI)
TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate to severe back pain have been observed.

Musculoskeletal and connective tissue disorders
- back pain, myalgia

Number of patients studied: 46 patients.

Very rarely, thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thromboses have been observed with human normal immunoglobulin.

System Organ Class
Cardiac disorders
Tachycardia
Common
Ear and labyrinth disorders
Ear pain
Uncommon
Eye disorders
- Conjunctivitis, maculopathy

Gastrointestinal disorders
Nausea
Common
Abdominal distension, abdominal pain, flatulence
Uncommon
General disorders and administration site conditions
- Infusion site reaction, pain, pruritus, rash

Infections and infestations
- Infections, urinary tract infection

Investigations
Blood pressure increased, blood pressure systolic increased, heart rate increased

Musculoskeletal and connective tissue disorders
Arthralgia, muscle pains, muscle tightness, neck pain, pain in extremity

Nervous system disorder
Headache
Very uncommon
Dizziness, syncope vasovagal,.tremor

Respiratory, thoracic and mediastinal disorders
- Pneumothorax, sinus pain, wheezing

Skin and subcutaneous tissue disorders
Acne
Uncommon

Vascular disorders
- Diastolic hypertension, hypertensive crisis, systolic hypertenion

Number of patients studied: 46 patients.