In case of persistent lack of antibody production, dosage of 0.5 g/kg/month is recommended until antibody level returns to normal. The dosage recommendations are summarised in the following table:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
</table>
| Replacement therapy in primary immunodeficiency | - starting dose: 0.4 - 0.8 g/kg  
- thereafter: 0.2 - 0.8 g/kg  
- 0.2 - 0.4 g/kg  
- 0.2 - 0.4 g/kg  
- 0.2 - 0.4 g/kg | every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l every 3 - 4 weeks |
| Replacement therapy in secondary immunodeficiency | 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d | for 2 - 5 days for 3 - 7 days |
| Children with AIDS                       | 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d | for 3 - 7 days |
| Guillain Barre syndrome                  | 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d  
- 0.4 g/kg/d | for 3 - 7 days |
| Allogeneic bone marrow transplantation:  | 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg | every week from day -7 up to 3 months after transplantation |
| - treatment of infections and prophylaxis of graft versus host disease | 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg  
- 0.5 g/kg | every month until antibody levels return to normal |

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 5% DIF should be infused intravenously at an initial rate of 0.01 - 0.02 m/kg/min for the first thirty minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.1 m/kg/min.

This medicinal product must not be mixed with other medicinal products or intravenous fluids. It should be administered by a separate intravenous line. Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

Overdose may lead to fluid overload and hyper viscosity, particularly in patients at risk, including elderly patients or patients with renal impairment. Contact poison information centre on 131126 for advice on management.

PRESENTATION

Flebogamma 5% DIF is a solution for infusion supplied in a Type II glass vial closed with a chloro-butyl-rubber stopper.

STORAGE CONDITIONS

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

Flebogamma 5% DIF is supplied as 0.5 g/10 ml, 2.5 g/50 ml, 5 g/100 ml, 10 g/200 ml and 20 g/400 ml vials.

Pack size: 1 vial

Flebogamma 5% DIF contains 5 g human normal immunoglobulin and 5 g pergalbin (as stabiliser) in 100 ml of water for injection. There is no preservation in the formulation. The pH of the solution ranges from 5.6 to 6.6 and the osmolality from 250 to 350 mOsm/kg, which is within the normal physiological range. The Fc and Fab functions are maintained in Flebogamma 5% DIF.

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: immune serum 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 less 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 reduce abnormally low 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 46 patients with primary immunodeficiency. Through IgG levels and other standard pharmacokinetic parameters such as serum Cmax, AUC, half-life, clearance and volume of distribution for total IgG and subclass IgG were determined in a subgroup of 20 patients (17-75 years; 11 female). Mean trough IgG levels ranged from 773 to 1134 mg/l for 21-day infusion schedule patients and from 777 to 1137 mg/l for 28-day infusion schedule patients. The mean serum half-life for total IgG was 30 and 32 days for the 21 and 28 day dosing schedule, respectively. The mean IgG levels were 1.93 and 1.09 mg/l for IgG subclasses the mean serum half-life ranged from 26 to 42 days. For both dosing schedules, the mean AUC levels for the total IgG was around 32000 day/mg/l, the mean Cmax levels was around 2000 mg/l and the mean volume of distribution between 4.9 and 5.5 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

One multicenter clinical trial was performed in children (n = 3) and adults with primary immune deficiency. Forty-six patients were included and 41 completed the study (15-75 years; 29 males). They were followed during 1 year of treatment at a dose of 300-600 mg/kg every 3 to 4 weeks. The results showed that subjects had a serious acute bacterial infection rate of 0.01 infections/subject/year (95% CI: 0.001 to 0.130). The annualized mean number of days of school missed was 12.95 ± 40 and the annualized mean number of days of hospitalization was 0.77 ± 3.5. One multicenter clinical trial was performed in patients with chronic immune thrombocytopenic purpura in acute phase (platelet count < 20 x 10⁹ /l) in total of 10 patients with IP with IFP were included (age: 18-83 years; 13 females). Patients received a total dose of 400 mg/kg body weight for 5 consecutive days and were followed for 3 months. Fifteen (10) patients presented a response (platelet count ≥ 30 x 10⁹ /l on day 5 and the duration of response had a mean result of 14/19 (74%). The platelet count was ≥ 50 x 10⁹ /l by day 5 and the duration of response had a mean result of ≥ 14.3 ± 24 days (median of 7 range 1 - 92 days) estimated from the first measurement that the subject had a platelet count greater than or equal to 50 x 10⁹ /l in the last measurement that the subject had a platelet count over that level. A total of 19/19 (95%) patients had a regression of bleedings on day 10 and 17/19 (89%) on day 14 after treatment.

INDICATIONS

Flebogamma 5% DIF is indicated for replacement therapy in:

Primary immunodeficiency syndromes such as:
- congenital agammaglobulinemia and hypogammaglobulinemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott–Aldrich syndrome
- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinemia and recurrent infections.

Children with congenital AIDS and recurrent infections.

Immunomodulation

Idiopathic thrombocytopenic purpura (ITP), in children or adults at high risk of bleeding or prior to surgery to correct the platelet count.

Guillain Barre syndrome.

Aplastic bone marrow transplantation.

CONTRAINDICATIONS

Hypersensitivity to any of the components (see section Precautions).

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency. Fructose intolerance (see section Precautions).

PRECAUTIONS

Transmission of infectious agents

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.

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POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL: 10/2008

DATE OF MOST RECENT AMENDMENT: 01/2012.

Flebogamma 5% DIF

Solution for infusion

Human normal immunoglobulin (IgG) 50 mg/ml

.DESCRIPTION

Flebogamma 5% DIF (dual inactivation plus nanofiltration) (IV IgG) is a sterile, clear or slightly opalescent and colourless to pale yellow, liquid ready to use, preparation of highly purified IgG obtained from human plasma pools. The purification process includes cold alcohol fractionation, polyethylene glycol precipitation, ion exchange chromatography, low pH treatment, pasteurisation, solvent detergent treatment and two sequential nanofiltrations through 35 nm and 10 nm pore size nanofilters connected in series. Flebogamma 5% DIF is a highly purified (≥ 97% IgG), 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 is 66.6%, IgG2, 28.5%, IgG3, 2.7%, and IgG4, 2.2%. Flebogamma 5% DIF contains only trace amounts of IgA (< 0.05 mg/ml).

In the final formulation Flebogamma 5% DIF contains 5 g human normal immunoglobulin and 5 g pergalbin (as stabiliser) in 100 ml of water for injection. There is no preservation in the formulation. The pH of the solution ranges from 5.6 to 6.6 and the osmolality from 250 to 350 mOsm/kg, which is within the normal physiological range. The Fc and Fab functions are maintained in Flebogamma 5% DIF.

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3043409
Effects on fertility
No fertility effects have been conducted in animals on Flebogamma 5% DIF.

ADVERSE EFFECTS
Adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and moderate low back pain may occasionally occur.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis.

Two multicenter clinical trials were performed, one of them in children (n = 5) and adults with primary immune deficiency and the second one in patients with chronic immune thrombocytopenic purpura in acute phase. Forty-six patients were included in the first trial and 41 completed the study. They were followed during 1 year of treatment at a dose of 300-600 mg/kg every 3 to 4 weeks. A total of 20 patients were included in the second study. Patients received a total dose of 400 mg/kg body weight for 5 consecutive days and were followed for 3 months. Therefore, a total of 66 patients have been exposed to Flebogamma 5% DIF and they have received 966 infusions. Data from both studies indicate a good tolerability of the product as incidence of adverse events was low and most of them were mild to moderate in intensity. Of the 806 infusions administered in patients enrolled in both studies 10.8% (1-sided 95% CI upper bound = 12.9%) were associated with an adverse event suspected to be related to the product. No patients died, only 6 patients withdrew from the studies but none of them because of potentially related adverse events. Four patients experienced 8 serious adverse events that were considered not related to the study medicinal product.

Pain and headache were the most frequently reported adverse events potentially related to the medicinal product in both studies.

The adverse drug reactions reported in the 2 trials by at least the 5% of the patients are summarised and categorised according to the MedDRA system organ class in the table below.

Frequency has been determined using the following criteria:
- very common: ≥1/10
- common: ≥1/100 to <1/10
- uncommon: ≥1/1,000 to <1/100
- rare: ≥1/10,000 to <1/1,000
- very rare: <1/10,000, not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing of seriousness.

System Organ Class

<table>
<thead>
<tr>
<th>Body System Preferred Term</th>
<th>ADR frequency evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorder</td>
<td>Headache</td>
</tr>
<tr>
<td>Respiratory, thoracic and</td>
<td>Bronchitis, cough, wheezing</td>
</tr>
<tr>
<td>medical disorder</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea, nausea, vomiting, abdominal pain, abdominal pain upper</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Urticaria, rash pruritic, dermatitis contact</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorder</td>
<td>Back pain, arthralgia, myalgia, muscle cramp</td>
</tr>
<tr>
<td>General disorders &amp; administration site conditions</td>
<td>Pyrexia, injection site reaction</td>
</tr>
</tbody>
</table>

Dosage

The dose and dosage regimen is dependent on the indication.

In replacement therapy the dosage may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.

Replacement therapy in primary immunodeficiency syndromes

The dosage regimen should achieve a trough level of IgG (measured before the next infusion) of at least 4 - 6 g/l. Three to six months are required after initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 - 0.8 g/kg followed by at least 0.2 g/kg every three weeks.

The dose required to achieve a trough level of 6 g/l is of the order of 0.2 - 0.8 g/kg/month. The dosage interval when steady state has been reached may vary from 2 - 4 weeks.

Trough levels should be measured in order to adjust the dose and dosage interval.

Replacement therapy in aplastic anaemia or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections; replacement therapy in children with AIDS and recurrent infections

The recommended dose is 0.2 - 0.4 g/kg every three to four weeks.

Hypothalamic/thyroid dysfunction:

For the treatment of an acute episode, 0.8 - 1 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg daily for two to five days. The treatment can be repeated if relapse occurs.

Sulindac breastfeeding

0.4 mg/kg/day for up to 1 year.

Experience is limited in children.

Allergic bone marrow transplantation

Human normal immunoglobulin treatment can be used as part of the conditioning regimen and after the transplant.

For the treatment of infections and prophylaxis of graft versus host disease, dosage is individually tailored. The starting dose is normally 0.5 g/kg/week, starting seven days before transplantation and for up to 5 months after transplantation.

For safety with respect to transmissible agents, see section Precautions.