1. PRODUCT NAME

Flebogamma 5% DIF
Human normal immunoglobulin (IVIg) 50 mg/ml - Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human normal immunoglobulin (IVIg)

One ml contains:
Human normal immunoglobulin……..50 mg
(purity of at least 97% IgG)

Each vial of 10 ml contains: 0.5 g of human normal immunoglobulin
Each vial of 50 ml contains: 2.5 g of human normal immunoglobulin
Each vial of 100 ml contains: 5 g of human normal immunoglobulin
Each vial of 200 ml contains: 10 g of human normal immunoglobulin
Each vial of 400 ml contains: 20 g of human normal immunoglobulin

Distribution of the IgG subclasses (approx. values):
IgG_1 66.6%
IgG_2 28.5%
IgG_3 2.7%
IgG_4 2.2%

The maximum IgA content is 50 micrograms/ml.

Produced from the plasma of human donors.

Excipient with known effect:

One ml contains 50 mg of D-sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

The solution is clear or slightly opalescent and colourless to pale yellow.

Flebogamma DIF is isotonic, with an osmolality from 250 to 350 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flebogamma 5% DIF is indicated for:

Replacement therapy in:

Primary immunodeficiency syndromes such as:
- congenital agammaglobulinaemia and hypogammaglobulinaemia
- common variable immunodeficiency
- severe combined immunodeficiency
- Wiskott Aldrich syndrome

Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia 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 Barré syndrome.

Allogeneic bone marrow transplantation.

4.2 Dose and method of administration

Dose

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 the 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 varies from 2 - 4 weeks.

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

Replacement therapy in myeloma 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.

Idiopathic thrombocytopenic purpura

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.

Guillain Barré syndrome

0.4 g/kg/day for 3 to 7 days.

Experience in children is limited.

Allogeneic 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 3 months after transplantation.

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:

Indication	**Dose**	**Frequency**
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 2 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Replacement therapy in secondary immunodeficiency	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 4 - 6 g/l
Children with AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Immunomodulation:		
Idiopathic thrombocytopenic purpura	0.8 - 1 g/kg or 0.4 g/kg/d	on day 1, possibly repeated once within 3 days for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 3 - 7 days
Allogeneic bone marrow transplantation:		

-	treatment of infections and prophylaxis of graft versus host disease	0.5 g/kg	every week from day -7 up to 3 months after transplantation
-	persistent lack of antibody production	0.5 g/kg	every month until antibody levels return to normal

Paediatric population

The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above mentioned conditions.

Method of administration

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

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

4.3 Contraindications

Hypersensitivity to any of the components (see section 4.4).

Hypersensitivity to homologous immunoglobulins, especially in very rare cases of IgA deficiency, when the patient has antibodies against IgA.

Fructose intolerance (see section 4.4).

4.4 Special warnings and precautions for use

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.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to viral safety.

It is strongly recommended that every time Flebogamma 5% DIF is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Special warnings about excipients: This medicinal product contains 50 mg of sorbitol per ml as excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Special precautions should be taken with babies and young children because this fructose intolerance may not yet be diagnosed and may be fatal. Interferences with determination of blood glucose levels are not expected.

Infusion/administration

Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given under "Dosage and administration" must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period.

Certain adverse reactions may occur more frequently:

- in case of high rate of infusion,
- in patients with hypo- or agammaglobulinaemia with or without IgA deficiency,
- in patients who receive human normal immunoglobulin for the first time, or in rare cases, when the human normal immunoglobulin product is switched or when there has been a long interval since the previous infusion.

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.

Potential complications can often be avoided by ensuring:

- that patients are not sensitive to human normal immunoglobulin by first injecting the product slowly at an initial rate of 0.01 - 0.02 ml/kg/min;
- that patients are carefully monitored for any symptoms throughout the infusion period. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion, in order to detect potential adverse signs. All other patients should be observed for at least 20 minutes after administration.

Association with Thromboembolic phenomenon

There is clinical evidence of an association between IVIg 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 IVIg 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 thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, and patients with diseases which increase blood viscosity).

Renal failure

Cases of acute renal failure have been reported in patients receiving IVIg therapy. In most cases, risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant nephrotoxic medicinal products or age over 65.

In case of renal impairment, IVIg discontinuation should be considered.

While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IVIg products, those containing sucrose as a stabiliser accounted for a disproportionate share of the total number. In patients at risk, the use of IVIg products that do not contain sucrose may be considered.

In patients at risk for acute renal failure or thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

In all patients, IVIg administration requires:
- adequate hydration prior to the initiation of the infusion of IVIg
- monitoring of urine output
- monitoring of serum creatinine levels
- avoidance of concomitant use of loop diuretics

In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.

The treatment required depends on the nature and severity of the side effect.

In case of shock, standard medical treatment for shock should be implemented.

Interference with serological testing

After injection of immunoglobulin the transitory rise of the various passively transferred antibodies in the patients blood may result in misleading positive results in serological testing.

Passive transmission of antibodies to erythrocyte antigens, e.g. A, B, D, may interfere with some serological tests for red cell antibodies, for example the antiglobulin test (Coomb's test).

4.5 Interaction with other medicines and other forms of interaction

Live attenuated virus vaccines

Immunoglobulin administration may impair for a period of at least 6 weeks and up to 3 months the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore patients receiving measles vaccine should have their antibody status checked.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Breast-feeding
Immunoglobulins are excreted in breast milk. The safety of this product for use during lactation has not been established in controlled clinical trials. Flebogamma 5% DIF should, therefore, only be given with caution to breastfeeding mothers.

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

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

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

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 thromboses.

Two multicenter clinical trials were performed, one of them in children (n= 3) 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 806 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. Pyrexia 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	**Body System Preferred Term**	**ADR frequency evaluation**
Investigations	Coombs test positive, blood pressure systolic decreased, blood pressure systolic increased, body temperature increased	Uncommon
Nervous system disorder	Headache	Common
	Dizziness	Uncommon
Respiratory, thoracic and mediastinal disorder	Bronchitis, cough, wheezing	Uncommon
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, abdominal pain, abdominal pain upper	Uncommon
Skin and subcutaneous tissue disorders	Urticaria, rash pruritic, dermatitis contact	Uncommon
Musculoskeletal and connective tissue disorder	Back pain, arthralgia, myalgia, muscle cramp	Uncommon
Vascular disorders	Hypotension, hypertension, diastolic hypertension, blood pressure fluctuations	Uncommon
General disorders & administration site conditions	Pyrexia, injection site reaction	Common
	Rigors, asthenia, pain, infusion site inflammation, injection site oedema, injection site pain, injection site pruritus, injection site swelling, migration of implant	Uncommon

For safety with respect to transmissible agents, see section 4.4.

Paediatric population

The safety results for 3 paediatric patients (those ≤ 16 years old) included in the PID study appeared to be generally similar to those for the overall patient population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration, ATC code: J06BA02.

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 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.

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 0.021 infections/subject/year (98% CI = 0.001 to 0.112). The annualized mean number of days of work/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 10^9/l). A total of 19 patients with ITP were included (age: 18-85 years; 13 females). Patients received a total dose of 400 mg/kg body weight for 5 consecutive days and were followed for 3 months. Fourteen (14) patients presented a response (platelet count ≥ 50 x 10^9/l) being the rate of responders as 14/19 (74%). The platelet counts was ≥ 50 x 10^9/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 10^9/l to the last measurement that the subject had still a platelet count over that level. A total of 18/19 (95%) patients had a regression of bleedings on day 10 and 17/19 (89%) on day 14 after treatment.

5.2 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. Trough IgG levels and other standard pharmacokinetic parameters such as serum C_{max}, 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 level ranged from 773 to 1143 mg/dl for 21-day infusion schedule patients and from 777 to 1137 mg/dl 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, and the mean clearances were 139 and 109 ml/day. For IgG subclasses the mean serum half-life ranged from 26 to 40 days. For both dosing schedules, the mean AUC levels for the total IgG was around 32000 day*mg/dl, the mean C_{max} levels was around 2000 mg/dl, 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.

5.3 Preclinical safety data

Single dose toxicity studies were carried out in rats and mice. The absence of mortality in the non-clinical studies performed with Flebogamma DIF with doses up to 2500 mg/kg, and the lack of any confirmed relevant adverse sign affecting respiratory, circulatory and central nervous system, of the treated animals supports the safety of Flebogamma DIF.

Repeated dose toxicity testing and embryo-foetal toxicity studies are impracticable due to induction of, and interference with antibodies. Effects of the product on the immune system of the newborn have not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

D-sorbitol
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30 ºC. Do not freeze. Protect from light.
Contains no antimicrobial preservative. Use in one patient on one occasion only.
Do not use after expiry date.

6.5 Nature and contents of container

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644, New Zealand
Phone (09) 918 5100

9. DATE OF FIRST APPROVAL

16 December 2010

10. DATE OF REVISION OF THE TEXT

Date of preparation: 16 Dec 2024