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The following information is intended for healthcare professionals only (see section 3 for further information):

Posology and method of administration

The dose and dose regimen is dependent on the indication.
In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dosage regimens are given as a guideline.
The dose recommendations are summarised in the following table:

Indication	Dose	Frequency of injections
Replacement therapy in primary immunodeficiency	- starting dose: 0.4 - 0.8 g/kg - thereafter: 0.2 - 0.8 g/kg	every 3 - 4 weeks to obtain IgG trough level of at least 5 - 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 5 - 6 g/l
Congenital AIDS	0.2 - 0.4 g/kg	every 3 - 4 weeks
Hypogammaglobulinaemia (< 4 g/l) in patients after allogeneic haematopoietic stem cell transplantation	0.2 - 0.4 g/kg	every 3 - 4 weeks to obtain IgG trough level above 5 g/l
Immunomodulation:		
Primary immune thrombocytopenia	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 5 days
Kawasaki disease	1.6 - 2 g/kg or 2 g/kg	in divided doses over 2 - 5 days in association with acetylsalicylic acid in one dose in association with acetylsalicylic acid

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.
A significant increase in median platelet levels was achieved in a clinical trial in chronic ITP patients (64,000/µl) although it did not reach normal levels.

Paediatric population
As the dosage for each indication is given by body weight and adjusted to the clinical outcome of the above-mentioned conditions, the dosage in children is not considered to be different to that of adults.

Incompatibilities

Flebogamma 5% DIF should not be mixed with other medicines or intravenous solutions and it should be administered by a separate intravenous line.

Special precautions

Sorbitol
Each ml of this medicinal product contains 50 mg of sorbitol. Patients with rare hereditary problems of fructose intolerance must not take this medicine.
In babies and young children (aged 0-2 years) hereditary fructose intolerance (HFI) may not yet be diagnosed and may be fatal, thus, they must not receive this medicinal product.
In persons more than 2 years old with HFI, a spontaneous aversion for fructose-containing foods develops and may be combined with the onset of symptoms (vomiting, gastro-intestinal disorders, apathy, height and weight retardation). Therefore a detailed history with regard to HFI symptoms has to be taken of each patient prior to receiving Flebogamma 5% DIF.
In case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.

Interferences with determination of blood glucose levels are not expected.

It is strongly recommended that every time that 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.

Instructions for handling and disposal

The product should be brought at room temperature (no more than 30 ºC) before use.
The solution should be clear or slightly opalescent. Do not use Flebogamma 5% DIF if you notice that the solution is cloudy or has deposits.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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GRIFOLS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Flebogamma 5% DIF

Solution for infusion

HUMAN NORMAL IMMUNOGLOBULIN (IVIg)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet

What is in this leaflet:
1. What Flebogamma 5% DIF is and what it is used for
2. What you need to know before you use Flebogamma 5% DIF
3. How to use Flebogamma 5% DIF
4. Possible side effects
5. How to store Flebogamma 5% DIF
6. Contents of the pack and other information

1. WHAT FLEBOGAMMA 5% DIF IS AND WHAT IT IS USED FOR

What Flebogamma 5% DIF is
Flebogamma 5% DIF contains human normal immunoglobulin. This medicine belongs to the group of medicines called intravenous immunoglobulins. These are used to treat conditions where the body's defence system against disease is not working properly.

What Flebogamma 5% DIF is used for

Treatment of adults, children and adolescents (2-18 years) who do not have sufficient antibodies (replacement therapy). There are five groups:
- Patients with Primary Immunodeficiency Syndromes (PID), an inborn lack of antibodies.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) and recurrent bacterial infections in patients with chronic lymphocytic leukaemia (cancer of the blood where too many white blood cells are produced), in whom prophylactic antibiotics have failed.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) and recurrent bacterial infections in myeloma (tumour composed of cells derived from the bone marrow) patients who failed to respond to pneumococcal immunisation.
- Hypogammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) in patients after a stem cell transplantation (allogeneic haematopoietic stem cell transplantation), when you are given stem cells from another person.
- Children and adolescents with the Acquired Immune Deficiency Syndrome (AIDS), it can be used to prevent troublesome infections.

Treatment of adults, children and adolescents (2-18 years) with certain autoimmune disorders (immunomodulation). There are three groups:
- Primary immune thrombocytopenia (ITP), a condition where the number of platelets in the blood stream is greatly reduced. Platelets form an important part of the clotting process and a reduction in their numbers may cause unwanted bleeding and bruising. The product is also used in patients at high risk of bleeding or prior to surgery to correct the platelet count.
- Guillain Barré syndrome, where the immune system damages the nerves and hinders them from working properly.
- Kawasaki disease, an illness in children where the blood vessels (arteries) in the body become enlarged.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE FLEBOGAMMA 5% DIF

Do not use Flebogamma 5% DIF
- If you are allergic to human normal immunoglobulin or any of the other ingredients of this medicine (listed in section 6).
- If you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.
- If you have fructose intolerance, a quite rare genetic condition where the enzyme for breaking down fructose is not produced. In babies and young children (aged 0-2 years) hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they must not receive this medicine (see special warnings about excipients at the end of this section).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Flebogamma 5% DIF.
Certain side effects may occur more frequently:
- in case of high rate of infusion.
- if you have hypo- or agammaglobulinaemia (a condition implying low immunoglobulin levels in your blood) with or without IgA deficiency.
- if you are having Flebogamma 5% DIF for the first time, or it has been switched from an alternative human normal immunoglobulin (IVIg) product, or it is a long time since your last infusion (e.g. several weeks). You will be watched carefully until an hour after the infusion to detect potential side effects.

Allergic reactions are rare. It may happen particularly if you do not have enough immunoglobulins of the type IgA in your blood or have developed antibodies to IgA.

Patients with pre-existing risk factors
Please tell your doctor if you have any other condition and/or illness, as caution is required in patients with pre-existing risk factors for thrombotic events. In particular, tell your doctor if you have:
- diabetes
- high blood pressure
- history of vascular disease or thrombosis
- overweight
- blood volume decrease
- diseases which increase blood viscosity
- age over 65

Patients with a kidney problem
If you have a kidney problem, your doctor should consider whether to stop treatment since cases of acute renal failure have been reported in patients receiving IVIg therapy, generally in patients with risk factors.
Tell your doctor, even when any of the above-mentioned circumstances had happened to you in the past.

Effects on blood tests

After receiving Flebogamma 5% DIF, the results of certain blood tests (serological tests) may be interfered for a certain time. If you have a blood test after receiving Flebogamma 5% DIF, please tell the analyst or your doctor that you have been given this medicine.

Special safety warning

Flebogamma 5% DIF is made from human plasma. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A and parvovirus B19 viruses.

Immunoglobulins have not been associated with hepatitis A or parvovirus B19 infections possibly because the antibodies against these infections, which are contained in the product, are protective.

It is strongly recommended that every time you receive a dose of Flebogamma 5% DIF, the name and batch number of the product are recorded in order to maintain a record of the batches used.

Other medicines and Flebogamma 5% DIF

- Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.
- Effects on vaccines: Flebogamma 5% DIF may reduce the effectiveness of certain types of vaccines (live attenuated virus vaccines). In case of rubella, mumps and varicella a period of up to 3 months should elapse after receiving this medicine and before receiving these vaccines. In case of measles, the period is up to 1 year.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Patients may experience reactions (for example dizziness or nausea) during treatment, which might affect the ability to drive and use machines.

Flebogamma 5% DIF contains sorbitol

This medicine contains 50 mg of sorbitol per ml. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

In persons more than 2 years old with problems to tolerate fructose, a spontaneous reaction for fructose-containing foods develops which may have the following symptoms: vomiting, gastro-intestinal disorders, apathy, height and weight retardation. Therefore, patients should be examined for the symptoms of Hereditary Fructose Intolerance prior to receiving Flebogamma 5% DIF.

3. HOW TO USE FLEBOGAMMA 5% DIF

Flebogamma 5% DIF is given by injection into your veins (intravenous administration). It may be self-administered if you have been fully trained by hospital staff. You must make up the infusion in exactly the way you have been shown in order to stop germs getting in. You must never self-administer it alone; a responsible adult must be always present.

The dose that you will be given will depend on your illness and body weight and will be worked out by your doctor (please see section "Instructions for healthcare professionals" given at the end of this leaflet).

At the beginning of your infusion you will receive Flebogamma 5% DIF at a slow rate (0.01-0.02 ml/kg/min). Depending on how comfortable you feel, your doctor may then gradually increase the infusion rate (up to 0.1 ml/kg/min).

Use in children

The dose in children is not considered to be different to that of adults as it will be given depending on the illness and body weight of the children.

If you use more Flebogamma 5% DIF than you should

If you get more Flebogamma 5% DIF than you should, your body may take on too much fluid. This could particularly happen when you are a patient at risk, e.g. an elderly patient or a patient having problems with your kidneys. Tell your doctor immediately.

If you forget to use Flebogamma 5% DIF

Tell your doctor or pharmacist immediately and follow his/her instructions.
You must not be given a double dose to make up for a forgotten dose.
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In rare and isolated cases, the following side effects have been reported with immunoglobulin preparations. **Tell your doctor if any of the following side effects happen during or after the infusion:**

- A sudden fall in blood pressure and, in isolated cases, anaphylactic shock (which symptoms or signs are rash, hypotension, palpitation, wheezing, coughing, sneezing and difficulty breathing among others), even if you have shown no hypersensitivity to previous administration.
- Cases of temporary meningitis (which symptoms or signs are headache, fear or intolerance of light, stiff neck).
- Cases of temporary reduction in the number of the red cells in the blood (reversible haemolytic anaemia/haemolysis).
- Cases of transient cutaneous reactions (side effects on your skin).
- Increase in serum creatinine level (a test which measures your kidney function) and/or acute renal failure (which symptoms or signs are low back pain, fatigue, decrease in the amount of urine).
- Thromboembolic reactions such as myocardial infarction (tight band around the chest with feeling like your heart is beating too fast), stroke (muscle weakness in the face, arm, or leg, trouble speaking or understanding others who are speaking), pulmonary embolism (shortness of breath, chest pain and fatigue), deep vein thromboses (pain and swelling in an extremity).

Other side effects:

Common (may affect up to 1 in 10 people):

- headache
- injection site reaction
- fever (body temperature increased)

Uncommon (may affect up to 1 in 100 people):

- Coombs test positive
- dizziness (motion sickness)
- blood pressure increased or decreased
- bronchitis
- cough
- wheezing
- abdominal pain (including abdominal pain upper)
- diarrhoea
- vomiting
- nausea
- urticaria
- pruritus (itching)
- rash (eruption of the skin)
- dermatitis contact
- back pain
- myalgia
- arthralgia (joint pain)
- muscle cramp
- rigors (cold shivering sensation)
- asthenia
- pain
- infusion site inflammation
- injection site reaction (including injection site oedema, pruritus, swelling and pain)
- migration of an implant

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

To report any side effect(s):

- The National Pharmacovigilance and Drug Safety Centre (NPC)
  Fax: +966-11-205-7662
  Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
  Toll free phone: 8002490000
  E-mail: npc.drug@sfda.gov.sa
  Website: www.sfda.gov.sa/npc

5. HOW TO STORE FLEBOGAMMA 5% DIF

Keep this medicine out of the reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label and carton after Exp.

Do not store above 30 ºC. Do not freeze.

The solution should be clear or slightly opalescent. Do not use this medicine if you notice that the solution is cloudy or has deposits.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Flebogamma 5% DIF contains

- The active substance is human normal immunoglobulin (IVIg). One ml contains 50 mg of human normal immunoglobulin, of which at least 97% is 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
  The percentage of IgG subclasses is approximately 66.6% IgG_1, 28.5% IgG_2, 2.7% IgG_3 and 2.2% IgG_4. It contains trace amounts of IgA (lower than 50 micrograms/ml).
- The other ingredients are sorbitol and water for injections (see section 2 for further information about ingredients).

What Flebogamma 5% DIF looks like and contents of the pack

Flebogamma 5% DIF is a solution for infusion. The solution is clear or slightly opalescent and colourless or pale yellow.
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 of 1 vial.
Not all sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last revised in 02/2017