Flebogamma® DIF

Human Normal Immunoglobulin (IVIg)

50 mg/ml | 100 mg/ml

Be DIFferent

- Demonstrated **tolerability and proven efficacy** in both immune replacement and autoimmune disease.[1,2]
- **Each patient is different:** Flebogamma® DIF is available in 50mg/mL and 100mg/mL concentrations, allowing you to choose the best product to meet each patient's individual needs.
- **An outstanding safety record over 20 years**, with almost 100 million grams of Flebogamma®/Flebogamma® DIF administered to patients worldwide.[3]

GRIFOLS

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50 mg/ml **100** mg/ml

Distributed in Ireland by:
Caragen Ltd
No. 7 Regus, The Gables,
Torquay Road, Foxrock,
Dublin D18 A2N7, IRELAND

Tel: +353 1 566 2609
Fax: +353 1 686 4969
Email: info@caragen.com
Web: www.caragen.com

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Instituto Grifols, S.A.
Can Guasc, 2 08150 Parets del Vallès, Barcelona - ESPAÑA Tel. (34) 935 710 100
www.grifols.com

GRIFOLS

ABBREVIATED PRESCRIBING INFORMATION

Flebogamma® DIF 50mg/mL & 100mg/mL solution for infusion

Abbreviated Prescribing Information

Flebogamma® DIF 50mg/mL & 100mg/mL solution for infusion

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Therapeutic indications: Flebogamma® DIF is indicated for: Replacement therapy in adults, children & adolescents (2-18 years) in: Primary immunodeficiency syndromes with impaired antibody production; hypogammaglobulinaemia & recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia & recurrent bacterial infections in plateau-phase multiple myeloma patients who failed to respond to pneumococcal immunisation; hypogammaglobulinaemia in patients after allogenic haematopoietic stem cell transplantation (HSCT); congenital AIDS with recurrent bacterial infections. Immunomodulation in adults, children & adolescents (2-18 years) in: Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count; Guillain Barré Syndrome; Kawasaki disease.

Presentation: The solution is clear, or slightly opalescent and is colourless, or pale yellow. Flebogamma® DIF is isotonic, with an osmolality from 240 to 370 mOsm/kg. Flebogamma® DIF is supplied in 50ml, 100ml, 200ml solution in a vial (type II glass) with stopper (chloro-butyl rubber). Not all pack sizes may be marketed.

Dosage: In replacement therapy the dose may need to be individualised for each patient dependent on the pharmacokinetic and clinical response. The following dose regimens are given as a guideline. ***Replacement therapy in primary immunodeficiency syndromes:*** The dose should achieve a trough level of IgG (measured before the next infusion) of at least 5 - 6g/l. Three to six months are required after the initiation of therapy for equilibration to occur. The recommended starting dose is 0.4 - 0.8g/kg followed by at least 0.2g/kg/month every three to four weeks. The dose interval when steady state has been reached varies from 3 – 4 weeks. Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels. ***Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed; hypogammaglobulinaemia & recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation; congenital AIDS with recurrent bacterial infections:*** The recommended dose is 0.2 - 0.4g/kg every three to four weeks. ***Hypogammaglobulinaemia in patients after allogenic haematopoietic stem cell transplantation:*** The recommended dose is 0.2-0.4 g/kg every three to four weeks. The trough levels should be maintained above 5g/L. ***Primary Immune Thrombocytopenia:*** For the treatment of an acute episode, 0.8 - 1g/kg on day one, which may be repeated once within 3 days, or 0.4g/kg daily for two to five days. The treatment can be repeated if relapse occurs. ***Guillain Barré syndrome:*** 0.4g/kg/day for 5 days. ***Kawasaki disease:*** 1.6 - 2g/kg should be administered in divided doses over two to five days or 2g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.

Method of administration: Flebogamma® DIF 50mg/ml should be infused intravenously at an initial rate of 0.01 - 0.02ml/kg/min for the first thirty minutes. If well tolerated, the rate of administration may gradually be increased to a maximum of 0.1ml/kg/min. Flebogamma® DIF 100mg/ml should be infused intravenously at an initial rate of 0.01ml/kg/min for the first thirty minutes. If tolerated, advance to 0.02 ml/kg/min for the second 30 minutes. Again, if tolerated, advance to 0.04 ml/kg/min for the third 30 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 0.08ml/kg/min.

Contra-Indications: The product is contraindicated in children aged 0-2 years (see Special warnings & Precautions). Hypersensitivity to any of the components. Hypersensitivity to human immunoglobulins, especially when the patient has antibodies against IgA. Fructose intolerance.

Special warnings and Precautions: 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 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® DIF. In case of inadvertent application and suspicion of hereditary 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. Certain severe adverse drug reactions may be related to the rate of infusion. The recommended infusion rate given in the SmPC must be closely followed. Patients must be closely monitored and carefully observed for any symptoms throughout the infusion period. It is recommended to monitor vital signs when administering Flebogamma DIF to paediatric patients. 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. Caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events (see SmPC for further details). 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, hypovolaemia, overweight, concomitant nephrotoxic medicinal products or age over 65. IVIG administration requires adequate hydration prior to infusion, monitoring of urine output and serum creatinine levels and avoidance of concomitant use of loop diuretics. In case of adverse reaction, either the rate of administration must be reduced or the infusion stopped. Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines and may result in transient misleading positive results in serological testing. Use with caution in pregnant women and breast-feeding mothers. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. Overdose may lead to fluid overload and hyper viscosity, particularly in patients at risk, including elderly patients or patients with renal impairment. Information on overdose in children has not been established with Flebogamma® DIF. However, as in adult population, overdose may lead to fluid overload and hyperviscosity as with any other intravenous immunoglobulins.

Undesirable Effects: The most reported post-marketing ADRs received since the product was authorised for both concentrations were chest pain, flushing, blood pressure increased and decreased, malaise, dyspnoea, nausea, vomiting, pyrexia, back pain, headache and chills. 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 syndrome, 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. For further information including safety regarding transmissible agents see the SmPC. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance.

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

Pharmaceutical Precautions: Flebogamma® DIF should not be stored above 30ºC. The contents must not be frozen. Flebogamma®DIF may be stored for 2 years under these conditions. 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. **Legal Category:** POM

Marketing Authorisation Number: EU/1/07/404/001-005 50mg/mL & EU/1/07/404/006-008 100mg/mL **Marketing Authorisation Holder:** Instituto Grifols S.A, Can Guasc 2, Parets del Vallès, 08150 Barcelona, Spain. **API last revised:** June 2016

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Information about adverse event reporting can be found at www.hpra.ie. You can report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 676 4971; Fax: +353 1 676 2517 or E-mail:medsafety@hpra.ie or medical@athlone-laboratories.com

For a full copy of the SPC or additional information please contact **Caragen**: Caragen Ltd. No. 7 Regus, The Gables, Torquay Road, Foxrock, Dublin D18 A2N7, IRELAND Tel: +353 1 566 2609 Fax: +353 1 686 4969 Email: info@caragen.com Web: www.caragen.com

Each patient is different: Flebogamma® DIF is available in in 5% and 10% concentrations, allowing you to choose the best product to meet each patient's individual needs.

High purity, functional **integrity**, and **osmolality** within the physiological range[7]

- **Osmolality, sodium, sugar and IgA content can affect the clinical tolerability in your patients. Choose the right product based on your patients' needs:**

  - **Hyperosmolar solutions**, administered intravenously may cause fluid shifts leading to haemodynamic changes, thromboembolic incidents, or renal complications[5]
  - **Low sodium preparations** may make Flebogamma® DIF appropriate for patients with restricted sodium intake; higher incidences of adverse events and thromboembolic complications may be seen with increased salt concentrations[6]
  - **Sugar content** has been associated with adverse events, especially renal failure or insufficiency; up to 90% of the IVIG-associated renal adverse events have been linked to sucrose-containing preparations[6]
  - **Patients with selective IgA deficiency** and the ability to produce antibodies may be at risk for developing IgE- or IgG-type anti-IgA antibodies[6,7]

Risk factors considerations[6]

	IVIG product characteristics				
Patient risk factors	Sugar content	Sodium content	Osmolality	Volume load	IgA
Cardiac impairment		✓	✓	✓	
Renal dysfunction	✓	✓	✓	✓	
Anti-IgA antibodies					✓
Thromboembolic risk		✓	✓	✓	
(Pre) Diabetes	✓				
Elderly	✓	✓	✓	✓	
Neonates/pediatrics		✓	✓	✓	

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1 Berger M, *et al.* A multicenter, prospective, open label, historically controlled clinical trial to evaluate efficacy and safety in primary immunodeficiency diseases (PID) patients of Flebogamma® 5% DIF, the next generation of Flebogamma®. *J Clin Immunol.* 2007;**27**(6):628-33.
2 Berger M, Pinciaro PJ, Althaus A, *et al.* Efficacy, pharmacokinetics, safety, and tolerability of Flebogamma® 10% DIF, a high-purity human intravenous immunoglobulin, in primary immunodeficiency. *J Clin Immunol.* 2010;**30**(2):321-9.
3 Data on file. Instituto Grifols, S.A.
4 Flebogamma® DIF Summary of product characteristics.
5 Shah S. Pharmacy considerations for the use of IGIV therapy. *Am J Health Syst Pharm.* 2005;**62**(16 Suppl 3):S5-11.
6 Adapted from *International Immunopharmacology*, Vol 6, Gelfand EW, Differences between IGIV products: impact on clinical outcome, 592-599, (2006).
7 NIH consensus conference. Intravenous immunoglobulin. Prevention and treatment of disease. *JAMA.* 1990;264(24):3189-93.

Each patient is different: Flebogamma® DIF is available in in 5% and 10% concentrations, allowing you to choose the best product to meet each patient's individual needs.

Sucrose-free, very **low levels of IgA** and **sodium,** and **no preservatives**[8]

- **Flebogamma® DIF** is a **highly purified IVIG with high functional integrity of the IgG molecule**[3] suitable for your patients as:
  - It is **preservative-free**[8]
  - Its **osmolality is within the physiological range** (240-350 mOsm/kg)[4]
  - It contains **trace amounts of sodium** (<3.2 mmol/L)[8]
  - It uses **sorbitol as stabilizer** (no sucrose, no maltose and no glucose), a polyol that plays a physiologically protective role as an organic osmolyte in the kidneys, which translates into a lower risk of acute renal failure[9]
  - It contains **trace amounts of IgA** (<0.003 mg/mL)*, being one of the lowest concentrations of IgA in the IVIG market[3]

Sorbitol stabilization provides physiological osmolality, **minimizing potential renal complications** seen with sucrose and maltose formulations[9]

A more careful matching of patient risk factors with the attributes or deficiencies of a given product becomes important [6]

Flebogamma® DIF is a highly purified IVIG with trace amounts of IgA and sodium and stabilized with sorbitol, making it suitable for patients with certain risk factors[6-10]

8 Siegel J. Immune globulins: therapeutic, pharmaceutical, cost and administration considerations. Pharmacy Practice News. Special Edition, Educational Reviews. January 2014.
9 Ochs HD, Siegel J. Stabilizers used in intravenous immunoglobulin products: a comparative review. Pharmacy Practice News. Special Reports. August 2010.
10 Jorquera JI. Flebogamma® 5% DIF development: rationale for a new option in intravenous immunoglobulin therapy. Clin Exp Immunol. 2009;157 Suppl 1:17-21.
11 Gürcan H.M *et al.* Information for healthcare providers on general features of IVIG with emphasis on differences between commercially available products. *Autoimmunity reviews* 2010; **9**(8):553-559

*Mean values: Flebogamma® 5% DIF (50 mg/mL), n=156. Flebogamma® 10% DIF (100 mg/mL), n=85.

Each patient is different: Flebogamma® DIF is available in in 5% and 10% concentrations, allowing you to choose the best product to meet each patient's individual needs.

Flebogamma® DIF is convenient for:

Your patients:

Patient risk factors and certain clinical conditions should be considered when selecting which concentration of IVIG to use[6]

5% concentration

- It may be an appropriate choice for patients who have certain frequent adverse reactions to infusions of IVIG[11]
- It may be suitable also for patients who would benefit from additional fluid[11]

10% concentration

- It can be infused in a lower volume being able to meet the needs of patients at risk of volume overload, including patients with heart failure or renal dysfunction[6]

Your clinical practice:

- Ready-to-use liquid
- Storable at room temperature for the entire two-year shelf life*
  (Can also be stored at 2-8°C with no change in stability)

Flebogamma® DIF
Human Normal Immunoglobulin (IVIg)
50 mg/ml 100 mg/ml

*≤ 30°C