EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Flebogamma DIF

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

Flebogamma DIF

Administrative information:

Trade name of the medicinal product:	Flebogamma DIF 0.5 g/10ml Flebogamma DIF 2.5 g/50 ml Flebogamma DIF 5 g/100ml Flebogamma DIF 10 g/200 ml Flebogamma DIF 20 g/400ml Flebogamma DIF 5 g/50 ml Flebogamma DIF 10g/100ml Flebogamma DIF 20g/200 ml
INN (or common name) of the active substance(s):	Human normal immunoglobulin(IV IG) 50 or 100 mg/ml
Manufacturer of the finished product	Instituto Grifols, S.A., Poligono Levante, c/Can Guasch, 2, 08150 Parets del Vallès, Barcelona, Spain.
Marketing Authorization holder	Instituto Grifols, S.A., Can Guasch, 2. Parets del Vallès, 08150 Barcelona Spain
Applied Indication(s):	treatment of: -Primary immunodeficiency syndromes (PID) with impaired antibody production -Secondary immunodeficiencies (SID), - Primary immune thrombocytopenia (ITP), -Guillain Barré syndrome - Kawasaki disease (in conjunction with acetylsalicylic acid) - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

	- Multifocal motor neuropathy (MMN)
Pharmaceutical form(s) and strength(s):	Solution for IV infusion
Route of administration	intravenous (IV) administration
Approved pack	-**for 2.5g/50ml:** **-for 5g/50ml:** Carton box containing one colorless glass (type II) bottle of 50ml solution closed with stelmi 6422GS chlorobutyl rubber stopper, alloyed aluminium cap with plastic top and plastic shrink band that guarantee the intactness of packaging + insert leaflet -**for 0.5g/10ml:** Carton box containing one colorless glass (type II) vial of 10ml solution closed with stelmi 6422GS chlorobutyl rubber stopper, alloyed aluminium cap with plastic top and plastic shrink band that guarantee the intactness of packaging + insert leaflet **-for 10 g /100 ml:** **-for 5 g /100 ml** Carton box containing one colorless glass (type II) bottle of 100ml solution closed with stelmi 6422GS chlorobutyl rubber stopper, alloyed aluminium cap with plastic top and plastic shrink band that guarantee the intactness of packaging + insert leaflet **-for 10 g /200 ml:** **-for 20 g /200 ml:** **-for 20 g /400 ml:**

	Carton box containing one colorless glass (type II) bottle of 200 ml solution closed with stelmi 6422GS chlorobutyl rubber stopper, alloyed aluminium cap with plastic top and plastic shrink band that guarantee the intactness of packaging + insert leaflet

List of abbreviations:

EMA	European medicines Agency
CTD	Common Technical Document
AI	Active ingredient
EU	European union
WFI	Water for injection
OSD	organic solvent detergent
DEAE	Diethylaminoethyl
DIF	dual inactivation and filtration
IgG	immunoglobulin G
PID	Primary immuno deficiencies
IgA	immunoglobulin A
AIDS	acquired immunodeficiency syndrome
IVIg	intravenous Immune globulin
IGIV3I GRIFOLS	Name of flebogamma in clinical trials
PK	Pharmacokinetic
PD	pharmacodynamic
ITP	Primary immune thrombocytopenia
ITT	Intention to treat
AEs	Adverse events
HFI	hereditary fructose intolerance
SID	Secondary immunodeficiencies

CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
MMN	Multifocal motor neuropathy
SmPC	Summary of product characteristics

Dossier initial submission and evaluation process:

- The product was submitted for registration via reliance level I.
- The dossier evaluation by the registration administration units was started on 22.11.2022 after providing all the required documents (EMA detailed unredacted assessment report & List of variations and assessment of each along with Full CTD for the product)

1. **General introduction about the product including brief description of the AI, its mode of action and indications**:

-Flebogamma DIF is a sterile solution, intended for intravenous administration, which has as active ingredient human normal immunoglobulin obtained from human plasma following a fractionation process based on the Cohn method.
-Flebogamma DIF is obtained from a suspension of Fraction II+III by precipitation with PEG 4% and DEAE ion-exchange chromatography before an acid pH treatment, a pasteurisation and a treatment with organic solvent detergent (OSD). Afterwards, the OSD and aggregates are eliminated by tangential flow filtration. To increase the product virus safety margin against enveloped and nonenveloped viruses, a nanofiltration is included at the end of the production process.
-Flebogamma DIF is a high purity human immunoglobulin G (IgG) solution having a broad spectrum of antibodies against various infectious agents.
-Flebogamma DIF retains the biological functions of endogenous immunoglobulin and has low anticomplementary activity.
-The main action of IgG in the case of immunodeficiency is replacement of functionally deficient immunoglobulins. In the case of immune-mediated diseases like Primary thrombocytopenia, the mechanism of action is less well understood. Several mechanisms have been postulated, such as reticuloendothelial blockade, an increase in T suppressor cells or natural killer cells, and a decrease in antibody synthesis.
-Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range.

2. **Quality aspects:**

- **Manufacturer(s):**

Instituto Grifols, S.A., Barcelona, Spain, is responsible for the whole manufacturing process, i.e. from plasma starting material to the labelling, packaging, quality control testing and batch release of the finished product.

- **Stability**

-Based on available stability data,

- **Drug substance:**
  - **Approved shelf life**: Fraction II+III: **36 months**
    UFI and UFII: **7 days**
  - **Approved Storage Conditions**: Fraction II+III**: ≤ -20ºC**
    UFI and UFII**: 5±3ºC**
- **Drug product:**
  - **Required Shelf Life:** 2 years
  - **Approved Storage Conditions:** Do not store above 30ºC. Do not freeze.

3. Non-clinical aspect:

-The first use of purified human immunoglobulin G is for treatment of Primary immuno deficiencies (PID) disorders which are characterized by increased susceptibility to recurrent infections, secondary to the underlying defects in humoral and/or cell-mediated immunity. To date, more than 100 different PID syndromes have been reported in the literature. The best described of these include X-linked a gamma-globulinemia, common variable immune deficiency disease, selective IgA deficiency, severe combined immune deficiency, chronic granulomatous disease, Wiskott Aldrich syndrome, X-linked hyper IgM syndrome, DiGeorge syndrome, IgG subclass deficiency, ataxia telangiectasia, leukocyte adhesion deficiency, and complement deficiencies.
-IVIG is also used in secondary immunodeficiencies such as those occurring in patients with multiple myeloma and B-cell chronic lymphocytic leukemia, acquired

immunodeficiency syndrome (AIDS) or in patients undergoing bone marrow transplantation.

-Flebogamma DIF is made like Flebogamma, another medicine containing human normal IgG, with some additional steps in the purification of the product from human plasma (addition of a solvent-detergent treatment and sequential nanofiltration as additional viral elimination steps for Flebogamma DIF), hence, The new manufacturing process results in an intact IgG molecule with complete functional activity.

-**Therefore,** the preclinical program was focused on toxicological safety considerations, to discard any potential adverse effect related to the production process, which is specific of Flebogamma DIF

-The dosage of IVIG is already well defined. **Therefore,** the toxicity study was carried out at levels equal or higher than the equivalent human dosage.

-The Flebogamma DIF used as test article in the nonclinical studies presented is **IGIV3I.** The toxicity studies were performed with IGIV3I 5% but they are fully supportive for IGIV3I 10%, since the total doses and the infusion rates employed were higher than those employed for infusion in humans.

-The results of the acute toxicity studies showed **no mortality**, neither in mice nor rats, although these studies were performed at dose levels equal or higher than the maximum dose used in humans and the infusion rate was 6 to 30 times higher than the maximum rates recommended for humans.

-No relevant adverse effects could be confirmed either affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behavior of treated mice and rats.

-The non-clinical development of Flebogamma DIF is overall acceptable

4. Clinical aspect:

- **Clinical Pharmacology (PK/PD):**

***Flebogamma10%**

-Overall, the patterns observed in the PK behavior for total IgG levels, IgG subclass levels, and the IgG antibody levels to specified antigens were similar to the previous 5% formulation. For total IgG, the estimated half-life is around 34 and 37 days for 21-day infusion schedule and 28-day infusion schedule, respectively.

-Moreover, trough total IgG and IgG subclass concentrations were maintained throughout the treatment period with IGIV3I 10%, as evidenced by both the relatively small changes in these parameters observed over the course of the study and the absence of any patients with decreases from screening or first infusion in trough total IgG that were higher than 50%.

These trough levels are considered protective for patients with immunodeficiencies, as all the individual values are well above 400 mg/dl, being the mean value much higher than 600 mg/dl. In summary, the results obtained with IGIV3I 10% show a PK profile similar to IGIV3I 5%, Flebogamma and other IVIG products. In addition, IgG trough levels are comparable to those after previous treatments and well above the minimum considered protective level.
-Flebogamma DIF contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Flebogamma DIF 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.
-This is proved for Flebogamma DIF 50 mg/ml in the study IG201 and for Flebogamma DIF 100 mg/ml in the study IG304

- **Clinical Efficacy conclusions**

***Flebogamma10%**

-As the efficacy of IGIV3I 10% has been demonstrated in PID syndromes at standard doses it can be expected that the product will be efficacious in replacement therapy in secondary immunodeficiencies in patients who suffer from severe or recurrent infections.
-The efficacy results from open-label, Study IG0601 demonstrated that IGIV3I 10%, was efficacious in treating both adult and pediatric subjects with chronic ITP.
The results study IG0601 were supported by Study IG202 Extension ,the study results indicated that the primary efficacy endpoint of the study was achieved.
The clinical effect of IGIV3I 10% also was evident in high rate of regression of hemorrhage/bleeding (83.3%).

-Overall, the efficacy results demonstrated that IGIV3I 10%, administered for a total dose of 2 g/kg, was effective in treating both adult and pediatric subjects with chronic ITP.
The efficacy of IGIV3I 10% was demonstrated by robust response in platelet count and clinical improvements in regression of hemorrhage/bleeding.

- **Safety Conclusions**

-When comparing potentially related AEs by MedDRA SOC and Preferred Term (ITT) in study 304 with the AEs observed in study IG 201 study (Flebogamma DIF 5%) which had a similar patient population and size, the following aspects were noted:

In Study 304 45 patients (98%) experienced 719 AEs, compared to Study 201 with Flebogamma DIF 5% where 94% experiencing 595 AEs . Thirty-eight patients (83%) experienced 309 AEs that were possibly related to Flebogamma DIF 10%, which is more than those experienced under Flebogamma DIF 5% (31 patients (67%) experienced 107 potentially related AEs). A >5% difference between the two products (Flebogamma DIF 10% vs. Flebogamma DIF 5%) for the percentage of patients with related AEs was observed for tachycardia (22% vs. 2%), chest discomfort or pain (6.5% vs. 0), pyrexia (33% vs 17%), rigors (37% vs. 9%), body temperature increased (8.7% vs 0%), back pain (17% vs 4%), myalgia (17% vs 4%), headache (52% vs 22%) and hypotension (25% vs 4%). Injection site reaction (6.5% vs 13%) and urticaria (0 vs 6.5%) were the only AEs found in more patients treated with Flebogamma DIF 5%. Of the 601 infusions administered, 48% were associated with a treatment-related AE that occurred during an infusion or within 72 hours after its completion.

-When comparing Flebogamma DIF 100 mg/ml with Flebogamma DIF 50 mg/ml a four-fold increase in the total number of treatmentrelated AEs that occurred during an infusion or within 72 hours. Furthermore, more patients received pre-medication for side-effects in the Flebogamma DIF 100 mg/ml study (21/46) compared to Flebogamma DIF 50 mg/ml (14/46). The total number of adverse events after pre-medication was 86 vs. 16 for Flebogamma DIF 10% and 5%, respectively

-The company has therefore proposed lower infusion rates for the SPC and have set increments at which to evaluate the state of the patient and his/her tolerance of a given infusion rate. If tolerated, the maximum infusion rate possible is 0.08 ml/kg/min, if patients experience adverse reactions, the maximum rate would be 0.04 ml/kg/min, which is lower than for Flebogamma DIF 5% (0.1 ml/kg/min) and for the other centralized 10%-IVIG-products where the maximum infusion rate is 0.12 - 0.13 ml/kg/min.

-The increase in AE frequency is likely to be related to the increased infusion rate. Appropriate guidance on lowering the infusion rate in case of AEs has therefore should been included in the SmPC.

-Flebogammma is contraindicated In babies and young children (aged 0 - 2 years),as hereditary fructose intolerance (HFI) may not yet be diagnosed and may be fatal, thus, they must not receive this medicinal product

-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 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.

In conclusion the overall benefit/risk of Flebogamma 100 mg/ml is favorable in the treatment of - Primary immunodeficiency syndromes (PID) with impaired antibody production - Secondary immunodeficiencies (SID), Primary immune thrombocytopenia (ITP), Guillain Barré syndrome - Kawasaki disease (in conjunction with acetylsalicylic acid) - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) - Multifocal motor neuropathy (MMN)

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/flebogammadif-epar-assessment-report_en.pdf