European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR FLEBOGAMMADIF

International Nonproprietary Name:
human normal immunoglobulin

Procedure No. EMEA/H/C/000781

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Instituto Grifols S.A. submitted on 05 September 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Flebogammadif, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 29 March 2006. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Licensing status:
Flebogammadif (Flebogamma 5% DIF) has been given a Marketing Authorisation in US on 21 December 2006.
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: **Manfred Haase** Co-Rapporteur: **Concepción Prieto Yerro**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 05 September 2006.
- The procedure started on 27 September 2006.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 December 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 December 2007. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 22-25 January 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 January 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 April 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 25 May 2007.
- During the meeting on 18-21 June 2007, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Flebogammadif on 21 June 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 June 2007.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Problem statement

The first use of purified human immunoglobulin G (IgG) for treatment of PID was described by Bruton, and involved the administration of intermediate purity IgG by subcutaneous injection. Subsequent investigators reported treatment primarily administered by intramuscular injection. In the early 1980s, highly purified, lyophilized preparations of IgG for intravenous administration (IVIg) were developed by a number of manufacturers. These highly purified IVIg products are now the standard of care for treatment of primary immuno deficiencies (PID), offering the possibilities of higher and more effective dosing than intramuscular administration.

PID disorders result in 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 agammaglobulinemia, 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.

Therapeutic options for the treatment of infections in PID include standard antibiotic treatment and intravenous administration of IgG. Therapeutic options for treatment of PID are transplantation of bone marrow-derived stem cells, and recently, gene therapy.

IVIg also has been used in the treatment of 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.

IVIg also has been used in the treatment of Idiopathic thrombocytopenic purpura (ITP). Therapeutic options for the treatment of ITP mainly include intravenous immunoglobulins, oral corticosteroids, anti D-immunoglobulins and splenectomy. In addition to its use in therapy for PID and ITP IVIg products are also effective in the management of immune mediated disorders such as Kawasaki syndrome, and Guillain Barré syndrome.

The main mechanism of action of immunoglobulin in the case of immunodeficiency is replacement of functionally deficient immunoglobulins. In the case of immune-mediated diseases like ITP, 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.
Since the early 1980s, highly purified preparations of IgG for intravenous administration (IVIg) were developed by a number of manufacturers whereas the first products consisted of so-called modified products (modification of the Fc-part of the IgG to allow intravenous administration). Nowadays non-modified, so-called native IVIgs are the standard of care for the replacement therapy of patients with primary immunodeficiency and they are part of the therapy regimen of the other indications mentioned before.

About the product

Flebogammadif is a plasma-derived product consisting of a highly purified preparation of human IgG manufactured by Instituto Grifols, S.A., which shares formulation characteristics, as well as identical biochemical and stability profiles, with Flebogamma®, the forerunner product. The main differences between the processes are the addition of a solvent-detergent treatment and sequential nanofiltration through filters with pore sizes of 35 nm and 20 nm as extra viral elimination steps in addition to pasteurization, already performed in Flebogamma.

Flebogamadif is a sterile 5% solution (referred to in the assessment as IVIg Grifols). 97% of the protein is gamma globulin with a normal subclass distribution. The new manufacturing process results in an intact IgG molecule with complete functional activity. The final product contains trace amounts of IgA. D-sorbitol is used as a stabiliser.
For further details see the assessment of the Quality Part related to the characterisation studies encompassing the biological characteristics of the product such as molecular size distribution, distribution of subclasses and antibody specificity and potency, as well as the biological activities

Pharmacological classification
Human Normal Immunoglobulin G
ATC code: J06B A02

Indications and posology

Therapeutic indications
Indications applied for:

1. 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 (CLL) with severe secondary hypogammaglobulinemia and recurrent infections
Children with congenital AIDS and recurrent infections

2. 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
   - Kawasaki disease

3. Allogeneic bone marrow transplantation

Posology and method of administration

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	on day 1, possibly repeated once within 3 days
	0.4 g/kg/d	for 2 - 5 days
Guillain Barré syndrome	0.4 g/kg/d	for 3 - 7 days
Kawasaki disease	1.6 - 2 g/kg or	in several doses for 2 - 5 days in association with acetylsalicylic acid

	2 g/kg	in one dose in association with acetylsalicylic acid
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

Flebogammadif 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.

The development programme/Compliance with CHMP Guidance/Scientific Advice

This is a new centralised application for marketing authorisation of a Human Normal Immunoglobulin for Intravenous Administration. It is a complete and independent application under article 8.3(i) of Directive 2001/83/EC as amended, with a known active substance. The forerunner product Flebogamma/Alphaglobin, is currently authorised in Argentina, Chile, Hong Kong, Japan, Mexico, Peru, CZ, ES, DE, GB, IE, IT.
The submission is in CTD format.
The global clinical program for the evaluation of Flebogammadif comprises 2 studies. The study design, choice of endpoints and statistical evaluation in the two clinical trials (Study IG 201 in primary immunodeficiency patients (PID) and Study IG 202 in Immune Thrombocytopenic Purpura patients (ITP)) are considered adequate and fulfil the requirements stipulated in the relevant Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (CPMP/BPWG/388/95 rev.2). According to this Note for Guidance, marketing authorisation for IVIg will be granted for the indications in the core SPC based on efficacy data from studies in primary immunodeficiency syndromes and idiopathic thrombocytopenic purpura without the requirement for separate studies in all other established indications. The indications follow the wording of the indications listed in the core SPC (CPMP/BPWG/859/95 rev. 1).

No paediatric development is planned. Adolescents were included in the clinical trials. IVIgs are routinely used in children and adolescents and separate trials are not specifically required according to the relevant CHMP Guidance.

No formal scientific advice was obtained from CHMP.

2.2 Quality aspects

- Introduction

Flebogammadif is a sterile 5% 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.

- Drug Substance

Flebogammadif is a sterile solution, which has as active ingredient human normal immunoglobulin obtained from human plasma following a fractionation process based on the Cohn method. From this purification process, the isolated active ingredient is not obtained but the final product is obtained directly. Due to the continuous manufacturing process of Human normal immunoglobulin, Grifols prior to the final formulation steps, no distinct intermediate Drug Substance stage can be defined.
Instituto Grifols, S.A. (Barcelona, Spain) is responsible for the entire manufacturing process, starting. from plasma through labeling, packaging, quality control testing and batch release of the finished product.

- Control of Materials

The human plasma used for the manufacture of Flebogammadif originates from the USA. It complies with the requirements of the Ph. Eur. Monograph *Human Plasma for Fractionation*, and with the Note for Guidance on Plasma-Derived Medicinal Products (CPMP/BWP/269/95 rev. 3). It is described in the Plasma Master File of Instituto Grifols S.A. This PMF is certified by EMEA.
In the manufacturing process of Flebogammadif no other material of human origin is used.
Controls of the other incoming raw materials are performed. For the specific viral removal step the Planova 35N and Planova 20N filter units were presented in detail.

- Drug Product

Flebogammadif is a sterile 5% 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.
The only active ingredient of Flebogammadif is human normal immunoglobulin (97% gammaglobulin; pH 5 - 6) and the excipient used is D-sorbitol which acts as stabiliser. Water for injection is used as solvent.
The vials consists of type II glass vials/bottles and chloro-butyl-rubber stoppers which meet the requirements of the Ph. Eur. These containers have filling capacities of 10 ml, 50 ml, 100 ml, 200 ml and 400 ml. Overfilling of each size ensures that the nominal amount of product can be drawn from the vial.

- Formulation Development

Several saccharides were studied as stabilising substances in order to establish the optimum conditions during heat treatment of IVIg solutions at 60 ºC for 10 hours. The results showed that sorbitol and sucrose were the most appropriate stabilisers.

- Physicochemical and Biological properties: Characterisation studies

A complete characterisation study of the final product identity indicates that the immunoglobulin purity of this product is higher than 99% and IgG subclasses are distributed in a physiological pattern. A broad spectrum of functional antibodies against various infectious agents is detectable. Finally, the Fc fragment integrity is demonstrated, expressed as functionality after antigen binding. The IgA content and anti-complementary activity are very low as well as other contaminants studied.
Instituto Grifols, S.A. has performed characterisation studies of different process intermediates as well as of the final product.

- Manufacturing Process Development (Process Validation and Product Characterisation)

Instituto Grifols, S.A. has developed a production process to extract IgG from Fraction II+III of the Cohn fractionation considering the purification process previously used for Flebogamma. The purification process includes the use of PEG as precipitation agent in several steps and the use of DEAE resins for the reduction of potential impurities. Additionally to the pasteurisation step already included in Flebogamma, the process includes other specific viral inactivation steps: solvent-detergent treatment and sequential nanofiltration.
For the production consistency and the reproducibility 11 lots have been studied (IVIg3I Grifols 5%: Consistency of the production process. 3 processes include Planova 35N nanofiltration and 3 processes include Planova 35N followed by Planova 20N nanofiltration. The product yield and purification degree in the adjusted bulk solution as well as in the different steps of the process can be considered acceptable and reproducible. The combined action of 4% PEG precipitation and of ion-exchange chromatography allows obtaining a product with an appropriate degree of purity. According to the composition of the filtered product, it has been demonstrated that nanofiltered batches (through Planova 35N and through Planova 35N + Planova 20N) and non-nanofiltered batches present the same behaviour.
In order to validate the changes in the facility, a consistency study has also been performed with conformance industrial lots of Flebogammadif obtained in the new manufacturing plant of the P1 building. The results obtained show that the product yield and its purification degree in the 5% adjusted final bulk, as well as in the different steps of the process, can be considered optimum and reproducible.

In the study report submitted by the applicant, three production scales: preparative, industrial (lots at clinical scale) and industrial (conformance lots) were compared, with regard to materials, equipment, specific process conditions and final product. Data submitted demonstrated that different working scales (preparative, clinical and conformance production scale) have equivalence in the most significant parameters of the process and in the composition of the product in the different steps. The preparative scale shows higher values on impurities e.g. PEG, Tween-80, ACA, polymers than the other scales.

- Development of Container Closure System and Microbiological Attributes

The containers/closure system used as packaging material for Flebogammadif product is a Type II glass material with butyl-rubber stopper in accordance with the Ph. Eur. requirements. The stability studies support the compatibility of the final IVIg formulation and dosage form with the container/closure system.

- Microbiological Attributes

Flebogammadif is a sterile-filtered preparation to prevent degradation in its final formulation intended for intravenous use. The final liquid formulation at 5% of protein content is filtered through a sterile filter of nominal pore size of 0.22 µm as a microorganism-retaining filter. The sterile bulk solution is stored at 5 ± 3 ºC in a closed system to prevent microbiological contamination. The sterile final bulk solution undergoes a second final sterile filtration prior to aseptic filling process into sterile glass type II containers and stoppers. This further sterile filtration is performed as close as possible to the filling point. All the operations are validated and performed in accordance with the current Good Manufacturing Practices (GMPs) for sterile medicinal products.

- Batch Formula

The ranges of batch size are indicated. A batch can be produced from either 3850±250l of plasma or from 7700±500 l of plasma.

- Manufacture

Flebogammadif is obtained from Fraction II+III of fresh plasma fractionation with ethanol (obtained in Instituto Grifols, Parets del Vallès, Barcelona, Spain). The fraction II+III can be stored at ≤-20°C for ≤3 years.
The extraction of the immunoglobulin from the above mentioned Fraction II+III till the final product is well described in the dossier
Immunoglobulin is extracted from Fraction II+III and the other part of globulins is precipitated with polyethylene glycol (PEG) in the presence of an inorganic adsorbent (bentonite). The resulting material is purified by an ion exchange resin column, which essentially adsorbs those proteins accompanying immunoglobulin G, the column effluent is diafiltered and concentrated and brought to appropriate conditions to perform the virus inactivation steps. The product bulk is filtered and prepared for the specific steps of virus inactivation by incubation at acid pH, performing the pasteurisation in the presence of sorbitol and, finally, chemical treatment with tri-n-butyl phosphate and polysorbate-80 (organic solvent and detergent). The product is precipitated with PEG-4000 and the precipitate is retained on a tangential flow filtration membrane (TFF) and washed to eliminate the organic solvent and detergent (OSD). This precipitate is then dissolved in order to precipitate subsequently the high molecular weight aggregates, which are also retained on a TFF membrane. The filtrate obtained is concentrated and diafiltered against sorbitol solution for protein concentration adjustment before the nanofiltration. It is nanofiltered and then concentrated by ultrafiltration to the required protein concentration of 5%. The adjusted product is clarified by depth and sterile filtrations and aseptically filled into appropriate glass vials or flasks. After incubation, the final product is subjected to visual inspection.

- Control of Critical Steps and Intermediates

Critical steps of the manufacturing process are identified. Tests and acceptance criteria are established to ensure that the process is controlled.
Microorganism count and viral markers are analysed in the cryoprecipitate supernatant and in Fraction II+III. The determination of immunoglobulin purity allows concluding that the precipitation of Fraction II+III has been performed correctly. Microbial load is also controlled in the clarified 4%

PEG-4000 filtrate, the intermediate bulk solution, the TFF IVIg filtrate (before and after adjustments and concentration) and in the nanofiltered bulk solution (after concentration and adjustment). The correct addition of TnBP and polysorbate 80 in the viral inactivation treatment by OSD is evaluated by analysis of the two components of this step. The determination of optical density at 280 nm before and after the pasteurisation step is performed in order to confirm that the addition of sorbitol solution (stabiliser) before pasteurisation has been performed correctly. In order to control the post-washing of the nanofiltration step by Planova 35N and Planova 20N, an $O.D._{280\ nm}$ determination before and after this step is included.
The sterility test in adjusted bulk solution controls that the sterile filtration has been correctly performed.

- Process Validation and Evaluation

The critical operations like DEAE sepharose column, heat treatment, solvent detergent treatment and aseptic filling were validated. Process consistency and data supporting the consistency have been satisfactorily submitted.

- Control of Excipients

The excipient used is D-sorbitol which acts as stabiliser, which complies with Ph Eur.

- Control of Drug Product

The applicant states that Flebogammadif complies with the Ph. Eur. monograph "Human Normal Immunoglobulin for Intravenous Administration" and will always be adapted to the edition in force. The analytical procedures and validation studies are acceptable.
The results of the analysis of 6 batches analysis certificates were provided, they passed the final release specification for Flebogammadif. The used standards were listed. The working reference standards were calibrated against the primary reference standard.

- Container Closure System

The packaging material in contact with the product consists of type II glass vials/bottles and chloro-butyl-rubber stoppers which comply with the specifications of the Ph. Eur. In order to support that the packaging components of Flebogammadif are compatible with the product, a stability report is provided. The samples used in the stability study are stored in inverted position in order to keep the solution in contact with the stoppers as "worst case" storage conditions.

- Stability

The presented stability program is acceptable. Selected test-parameters and acceptance criteria are suitable to demonstrate product stability. The results of the stability study with IVIg3I GRIFOLS 5% 10 ml, 50 ml, 100 ml, 200 ml and 400 ml support a shelf-life of 24 months at 5ºC or at 30 ºC of Flebogammadif, all selected parameters are still in the specified ranges. During the storage and transport temperature shifts should be avoided and the product should be transported and stored under a defined constant temperature in order to avoid quality loss in the product. In their responses to the LoQ, the applicant has submitted a proposal for a stability study protocol including repeated temperature shifts within the range 5-30 ºC, which is reasonable. Furthermore, the applicant has agreed to commit to submit the results of the repeated temperature shifts proposed on an ongoing basis after the authorisation of the product. If the results of this study reveal that repeated temperature shifts lead to quality loss in the product, the SPC should be adapted according to the data obtained with the submission of a variation application.

- Stability of in-process intermediates

The intermediate storage studied were Fraction II+III stored between -20 ºC and -30 ºC for 36 months and UF-I / UF-II stored at 5 ± 3 ºC for 30 days. The presented stability studies for the intermediates fraction II+III and Ultrafiltrate I / II are acceptable.

- Facilities and Equipment

Acceptable description of the facility, the product flow, material flow and personnel flow was provided. The preparation, cleaning and sterilisation of the equipments are described. The prevention of cross contamination is outlined. Floor plans for all facilities are provided.

- Adventitious Agents Safety Evaluation

Flebogammadif is produced from human plasma. The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Plasma is collected in USA and single donations are screened by an adequate testing program for viral infections (Anti HIV, HBs-Ag, Anti-HCV, ALT). Further manufacturing pools are tested by NAT for HIV-RNA, HCV-RNA, HBV-DNA, and B19-DNA (limit: less than 10^4 IU per ml). Donors with an increased risk for sporadic or variant Creutzfeldt-Jakob-Disease are excluded. The donor selection and plasma donation testing strategy for viral markers is considered adequate. Testing of source materials has been assessed at PMF certification.

The immunoglobulins are purified by Cold-Ethanol Fractionation and PEG precipitation steps and chromatographic steps. Effective reduction of a broad variety of enveloped and non-enveloped viruses and animal TSE agents at one PEG-precipitation/depth filtration step has been demonstrated.
Additionally three dedicated steps for virus inactivation/removal have been introduced into the manufacturing steps. (1) Pasteurisation is performed at 60°C for 10h. Effective inactivation of enveloped viruses as well as of non-enveloped viruses has been shown. Effective inactivation included porcine parvovirus (PPV) which is known as a rather heat-resistant model virus. (2) Enveloped viruses are efficiently inactivated during a conventional solvent detergent treatment. (3) The product is processed through two serially-coupled nanofilters with average pore sizes of 35nm and 20nm. The 20nm-filter has been demonstrated to remove effectively the small non-enveloped model virus PPV. It is, therefore, reasonable to postulate a similar or higher reduction capacity for the larger enveloped viruses such as HIV, HCV, HBV and most non-enveloped viruses including Hepatitis A virus. The combination of 4 production steps with complementary mechanisms for virus inactivation or virus removal (precipitation, heating, SD-treatment, nanofiltration), results in a very high overall reduction capacity for both enveloped and non-enveloped viruses.
Seven production steps (Precipitation of Fraction I, Fraction II+III suspension, 4% PEG precipitation, Low pH incubation, pasteurization, SD-treatment, nanofiltration) have been validated for their capacity to inactivate/remove viruses. . The selection of process steps is considered sufficient. The virus studies are of good quality and comply with the requirements of Guideline CPMP/BWP/268/95. Adequate controls (cytotoxicity, interference) have been performed and complete study reports including raw data have been submitted. The virus reducing capacity of the studied process steps has been submitted in the dossier and discussed in detail.

The reduction factors from the investigated production steps are summarised in Tab. SV.1.

Tab. SV1. Virus reduction factors from production steps

Step/Virus	HIV	HBV	HCV	WNV	HAV	B19V
Fraction I precipitation	(1.32)[a]		2.78 WNV	2.78 WNV		
Fraction II+II precipitation	(1.48)[a]			(<1)[c] WNV		
4% PEG Precipitation	≥6.10	≥5.92 PRV	≥5.78 (BVDV)	≥5.78 BVDV	≥6.41 EMCV	6.35 PPV
pH 4 treatment (4h 37°C)	2.47	(≥5.32)[b] PRV	(0.46)[c] BVDV	(0.46)[c] BVDV	(1.36)[e] EMCV	
Pasteurisation	≥5.64	≥6.33 IBR	≥6.49 BVDV	5.41 WNV	≥5.56 EMCV	4.08 PPV
SD-Treatment	≥4.61	≥6.95 PRV	≥6.14 BVDV	≥5.59 WNV		
Planova 20N Nanofiltration.	4.61[d] PPV	4.61[d] PPV	4.61[d] PPV	4.61[d] PPV	4.61[d] PPV	4.61[d] PPV
Global reduction factor	**≥23.43**	**≥23.81**	**≥25.80**	**≥24.17**	**≥16.58**	**15.04**

[a] Log reduction factors are not summarised because a similar mechanism (low pH) may be underlying HIV inactivation at these steps and pH4 treatment.
[b]: The reduction factor from PRV is not considered for HBV because it in unknown whether PRV would reflect HBV
[c]: Log reduction factors below 1 are not summarised
[d]: Reduction factors from PPV-experiments are considered applicable to larger viruses
[e] Reduction factor from EMCV at low pH treatment is not considered representative for reduction of HAV

A risk assessment according to new chapter 6 of Guideline CPMP/BWP/269/95 concerning HIV, HBV, and HCV has been provided.

The capacity of the production process to inactivate/remove enveloped viruses widely exceeds the potential maximum input of virus genomes in the plasma pool. Non-enveloped model viruses reflecting HAV and Parvovirus B19 are efficiently reduced at least by 3 production steps (4% PEG precipitation, pasteurisation, nanofiltration). Therefore, it can be concluded that the product is safe with respect to HIV, HBV, and HCV, HAV and Parvovirus B19. Further safety with respect to West Nile Virus has been demonstrated according to CPMP-position statement on WNV and Plasma-derived medicinal products (CPMP/BWP/3752/03).
In summary, a high safety margin with respect to HIV, HBV, HCV, HAV, and parvovirus B19 has been convincingly demonstrated.

This information has been included in the SPC, section 4.4. with the following recommended text:
"The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV, HAV and Parvovirus B19."

Discussion on chemical, pharmaceutical and biological aspects
The issues primarily identified during the evaluation of the dossier had been resolved by the applicant with the responses to the List of questions.
As follow up measure, the applicant will submit the results of the stability study (protocol including repeated temperature shifts within the range 5-30 ºC) on an ongoing basis. If the results of this study reveal that repeated temperature shifts lead to quality loss in the product, the SPC should be adapted according to the data obtained with the submission of a variation application.

The marketing authorisation application for Flebogammadif is recommended for approval based on quality grounds.

2.3 Non-clinical aspects

Introduction

Flebogammadif is a highly purified human immunoglobulin G (IgG) solution, intended for intravenous administration (IVIg 5%). The active ingredient is obtained from human plasma following a fractionation process based on the Cohn method. Flebogammadif retains the biological functions of endogenous immunoglobulin, contains a broad spectrum of antibodies against various infectious agents and has low anti-complementary activity.

The product can be defined as belonging to a well known and characterized biological product family. Flebogammadif complies with all the pharmacopoeial requirements (European Pharmacopoeia monograph 01/2006:0918).

The pharmacology and pharmacokinetics of the product are supported by specific studies conducted by the former Grifols' associate Green Cross Corporation (now Benesis) with Venoglobulin-IH (an IVIg obtained with the same production process as Flebogamma) in rats and rabbits, comparing some of the results to Venoglobulin-I (lyophilized human normal immunoglobulin, not submitted to heat treatment). Since Flebogamma is a human normal immunoglobulin having characteristics equivalent to those of Venoglobulin-IH and is obtained by the same manufacturing process, the results of the toxicological and pharmacological studies carried out on Venoglobulin-IH are applicable to Flebogamma. The main differences between the manufacturing processes for Flebogamma and Flebogammadif are the addition of a solvent-detergent treatment and sequential nanofiltration through pore sizes of 35 nm and 20 nm as additional viral elimination steps for Flebogammadif.

Pharmacology

- Primary pharmacodynamics

Preclinical studies were conducted by the former Green Cross Corporation. These studies were performed on Venoglobulin-IH (liquid heated intravenous human immunoglobulin) as compared to Venoglobulin-I (non-heated lyophilized intravenous human immunoglobulin).

- Both immunoglobulins administered at the doses tested protected significantly against experimental thrombocytopenia
- The survival rate of mice infected with *St. pneumoniae* proved to be significantly dose-dependent.
- The efficacy of Venoglobulin-IH in mice infected with *Ps. aeruginosa* increased with the dose tested.
- The efficacy of Venoglobulin-IH is significantly dose-dependent for *Ps. aeruginosa* infections in granulocytopenic mice.
- Antibody titres of Venoglobulin-IH to bacteria, protozoa and viruses are equivalent to those of Venoglobulin-I, indicating once again no reduction of the aforementioned antibody titre by heat treatment of the liquid immunoglobulin
- Venoglobulin-IH and Venoglobulin-I present equivalent effects on the bactericidal and phagocytosis activities of the PMNs.

- Safety pharmacology

The core battery of safety studies was included in the toxicological studies:
Study CD01/7955T: "Acute intravenous toxicity study in mice, by infusion. Determination of maximum non-lethal dose and minimum lethal dose".
Study CIFA 001/02: "Study of the acute toxicity of the product new gammaglobulin intravenous 5% Grifols for intravenous route in the mouse".
Study CD01/7624T: "Acute intravenous toxicity study in rats, by infusion. Determination of maximum non-lethal dose and minimum lethal dose".
Study CIFA 002/02: "Study of the acute toxicity of the product new gammaglobulin intravenous 5% Grifols for intravenous route in rat".

The absence of mortality in the toxicological preclinical studies and the lack of any confirmed relevant adverse sign affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour of the treated mice and rats, supports the safety of Flebogammadif for clinical trials in humans.

Functional index of potential toxicity on the cardiovascular, respiratory, and central nervous systems were incorporated in the design of the toxicity studies **CIFA 001/02** and **CIFA 002/02** and the results have not raised any concern. However, comparative anaphylactoid and thrombogenic potential have not been assessed. Data obtained during preclinical and clinical testing do not indicate increased anaphylactoid or thrombogenic potential of this product when compared to other IVIgs currently in clinical use.
In order to avoid potential complications, the product should be injected slowly, carefully monitoring for any symptoms, as described in the SPC (section 4.4).

Pharmacokinetics

A pharmacokinetic study has been carried out by the former "The Green Cross Corporation (Benesis)" to study the pharmacokinetics of Venoglobulin-IH in rats and rabbits, comparing some of the results to Venoglobulin-I.

Following the administration of radiolabelled Venoglobulin-IH, plasma levels of radioactivity in male rats and male rabbits decreased biphasically, showing a rapid phase with half-life values of $T_{1/2}\alpha$ = 12.4 h in rats and $T_{1/2}\alpha$ = 6.0 h in rabbits, and a slow phase with half-life values of $T_{1/2}\beta$ = 10.3 days in rats and $T_{1/2}\beta$ = 3.5 days in rabbits. The administration of repeated doses for 5 days in male rats

increased the values of $T_{1/2}\alpha$ to 20.4 hours and $T_{1/2}\beta$ to 10.7 days.

Approximately 12% of the dose administered to pregnant rats on the 19th day of gestation was found in the foetus on the following day.

The maximum level of radioactivity in the mothers' milk was found 6 hours following administration.

In general, there was no accumulation of radioactivity in the tissues of the rats examined. Most of the radioactivity was excreted into the urine (approximately 70% in both rats and rabbits). 2.5% and 3.6% in rats and rabbits, respectively, was excreted into the faeces.

Due to the fact that some differences are observed between the two animal species studied, the patient should be monitored and carefully observed for a certain period of time after administration, as stated in the SPC, section 4.4.

Toxicology

- Single dose toxicity

Four studies were provided.
Study CD01/7955T: "Acute intravenous toxicity study in mice, by infusion. Determination of maximum non-lethal dose and minimum lethal dose".
Results: The LD_{50} of Flebogammadif, when administered intravenously to CD-1 mice proved to be greater than 2500 mg/kg.
Clinical signs, like piloerection or palpebral ptosis and ataxia were detected. No relevant adverse effects were detected affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour.

Study CIFA 001/02: "Study of the acute toxicity of the product new gammaglobulin intravenous 5% Grifols for intravenous route in the mouse".
Results: The LD_{50} of Flebogammadif, when administered intravenously to Swiss mice proved to be greater than 2500 mg/kg. Only minor signs were observed, like piloerection and a slight increase of the respiratory rate in a treated female (which normalized in 30 minutes). No relevant adverse effects were detected affecting respiratory, circulatory, renal, autonomic and central nervous systems, somatomotor activity and behaviour.

Study CD01/7624T: "Acute intravenous toxicity study in rats, by infusion. Determination of maximum non-lethal dose and minimum lethal dose".
Results: The LD_{50} of Flebogammadif, when administered intravenously to Sprague Dawley rats proved to be greater than 2500 mg/kg. During the first phase of the study, ataxia was observed for 5 minutes after administration in all the animals from the control group and in all but one animal from the treated group. No further clinical signs were detected in any animal during the first phase of the study.
Following the infusion of the highest dose, a short term ataxia was also detected in all animals, both from the treated and from the control group. The maximum duration of this sign was 90 minutes in both groups. Therefore the differences between the two groups are hardly evaluable, especially taking into account that the animals had to be placed in an immobilisation device during infusion.
Four (1 male and 3 females) out of 14 animals treated with the highest dose (combining both phases of the study) showed "reddish urine" up to 90 minutes to 3 hours immediately after treatment.
No macroscopic alterations were recorded in the necropsies carried out on the animals belonging to the highest dose, second phase of the study, with the exception of calicilar dilatation in both kidneys in one male from the control group and slight calicilar dilatation in the right hand side kidney of one of the treated females. Furthermore, no differences were detected in kidney weights between the treated and control group. No histopathological renal alteration was detected related to the treatment.

Study CIFA 002/02: "Study of the acute toxicity of the product new gammaglobulin intravenous 5% Grifols for intravenous route in rat".

Results: 10 treated animals (5 male, 5 female) received a continuous infusion of 2500 mg in a volume of 50 ml/kg with an infusion rate of 0.1 ml/min and were followed for 14 days.
The administration of a volume of 50 ml/kg bw in rats, with an administration rate of 0.1 ml/min implies an increase of between 70 to 80% of the blood volume in a time ranging between 1 and 2 hours. This increase in blood volume can produce arterial hypertension, which could be the cause of renal alterations – hematuria, proteinuria and slight pathomorphologic changes – as observed in both treated and control animals. The results obtained are considered to be equivalent to that obtained for other intravenous immunoglobulins.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose toxicity studies were not performed since administration of Flebogammadif to animals can be expected to initiate the immunological response, which would interfere with the toxicity evaluation. (CPMP/ICH/302/95).

- Other toxicity studies

Reproductive, developmental, genotoxicity, carcinogenicity, or local tolerance studies were not performed due to the nature of Flebogammadif, which is a naturally expressed human protein (CPMP/ICH/302/95).

Ecotoxicity/environmental risk assessment

Flebogammadif is a product made of naturally expressed human proteins and therefore it is unlikely to result in significant risk for the environment. According to the Guideline EMEA/CHMP/SWP/4447/00 on the environmental risk assessment of medicinal products for human use, the lack of an ERA is acceptable for this product. This product is not considered to be a risk to the environment.

2.4 Clinical aspects

Introduction

The studies were performed to support the following indications:

4. 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 (CLL) with severe secondary hypogammaglobulinemia and recurrent infections
   Children with congenital AIDS and recurrent infections

5. 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
   - Kawasaki disease

6. Allogeneic bone marrow transplantation

The indications are in line with the requirements laid down in the note for guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (CPMP/BPWG/388/95 rev. 1).

Two studies were performed to evaluate PK, efficacy and safety of the product: **Study IG 201** (**PK, Efficacy and Safety)** and **Study IG 202 (Efficacy and Safety)**

GCP

The studies were conducted according to the Guidelines on GCP (CHMP/ICH/135/95) and the ethical principles conveyed by the Declaration of Helsinki.
The trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The study, performed in the USA, was prospective, open-label, uncontrolled, multi-centre in 46 primary immunodeficiency patients (PID) patients enrolled between Nov-2002 and May-2004.
Forty six (46) patients were enrolled and 41 patients finished the study. The duration of the treatment was 12 months. Inclusion and exclusion criteria were according to the NfG for intravenous immunoglobulins (CPMP/BPWG/388/95 rev 1). Patients were treated following either a 21-day or a 28-day infusion schedule.
Trough IgG levels were determined in all patients included in this trial. Other standard PK parameters (Cmax, Tmax, t1/2 and AUC for total IgG, subclass IgG, and antibodies to selected specific antigens) were measured in a subgroup of 20 patients with PID. Mean trough IgG level ranged from 822.2 to 895.2 mg/dl for 21-day infusion schedule patients and from 779.3 to 1180.0 mg/dl for 28-day infusion schedule patients. These levels are above those required in the Note for Guidance on normal human immunoglobulin (CPMP/BPWG/388/95 rev 1).

Half-life, AUC, Cmax and Tmax were performed in a subset of 20 patients, most of them on a 28-day infusion schedule. Samples were taken at Infusion 5 in patients previously treated and documenting trough levels for the previous two infusions.

The median serum half-life for total IgG was 28 and 33 days for the 21 and 28 day dosing schedule, respectively. For IgG subclasses the median serum half-life ranged from 24 to 33 days. The median AUC levels for the total IgG were 30423.4 and 32484.5, the median Cmax levels were 1965 mg/dl and 2010 mg/dl, respectively for both dosing schedules.

The results obtained in the study are in keeping with those reported in the literature and with other studies using similar products, also complying with the current standards requested by the Guideline CPMP/BPWG/388/95-rev. 1 for PID patients.

Pharmacodynamics

Not applicable. PD studies are not requested by the relevant Guideline. The text of the core SPC under 5.1 Pharmacodynamic properties has been adopted:

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 donations. 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 efficacy

- Main Studies

Study IG 201 – Primary Immunodeficiency (PID)
Study IG201 was a multicentre, non-controlled trial to determine the clinical efficacy, pharmacokinetics and safety of Flebogammadif and was performed in the USA.
IgG trough levels were examined in all patients. In a subset of Study IG 201 in 20 PID patients the following PK parameters were analysed: Cmax, Tmax, elimination rate constant (λz), AUC from time 0 to the time of the last post-dose quantifiable serum concentration (AUC(0-last)), AUC from time 0 to infinity (AUC(0-inf)), t1/2, CL, and Vd.

METHODS

Study participants and treatments
Forty-six patients (children and adults with primary immunodeficiency - PID) were enrolled and treated with Flebogammadif at a dose of 300-600 mg/kg every 21-28 days (mean total dose: 451 mg/kg for 21-day patients and 448 mg/kg for 28-day patients). They were followed for 1 year and received a total of 709 infusions.

Outcomes/Endpoints and Results

The primary efficacy endpoint was the number of serious bacterial infections, based on the criterion for efficacy of ≤1 serious bacterial infection/patient/year for bacterial pneumonia, bacteraemia or sepsis, osteomyelitis/septic arthritis, visceral abscesses and bacterial or meningitis.
The estimated infection rate is 0.021 serious bacterial infections/PID patient/year, with a 98% confidence interval of 0.001-0.112. This rate satisfies the predefined efficacy criterion of ≤1 serious bacterial infection/patient/year for the primary endpoint. There were no other infections documented by positive radiograph or fever.

The secondary efficacy endpoints were:
-Days off school/work
Approximately half the patients missed at least one day of work/school. There is a large difference between mean and median values of number of days missed due to outlying values of some patients (mean 12.95 and median 0.4 [0.0-226.6]).
-Infectious episodes
Seventy two percent (72%) of patients had at least 1 infectious episode, with a mean number of infectious episodes of 2.1, (median: 2.0 with a range 0-8). The median annual infection rate was 1.7 infections/patient/year (0.00-8.32).
-Stay in hospital and visits to physician or emergency room
Four patients had a mean of nearly one day of stay in hospital and 63% paid a mean of 4.4 visits to the physician or emergency room.
-Antibiotic use
Seventy six (76) % and 4% of patients received oral or parenteral antibiotic use at least 1 day, respectively. Twenty one patients (46%) received fluoroquinolones, 16 patients (35%) received combinations of penicillins, including beta-lactamase inhibitors and 13 patients (28%) received imidazole and triazole derivatives. “Other” antibiotics, including topical use, were administered to 35% of the patients. The data on use and duration of oral antibiotics (both prophylactic and therapeutic) showed a large divergence between the mean and the median due to outlying values of some patients being treated for longer times. Approx. 40% of the patients were treated with prophylactic oral antibiotics and two-thirds received therapeutic oral antibiotics.

In general the data for the primary and secondary endpoints collected from the 46 PID patients in Study IG 201 are in keeping with data from similar products and with those reported in the recent literature.

Study IG 202 – Immune thrombocytopenic purpura (ITP)

Study IG202, performed in Spain, UK and Russia, was a prospective, open-label, uncontrolled, multi-centre trial to determine the clinical efficacy and safety of IVIg Grifols in 20 adult patients with acute phase, chronic ITP.

METHODS

Study participants and treatments

The patients received IVIg treatment for 5 consecutive days at a dose of 0.4 g/kg/day. The patients received a total of 97 infusions and were followed for 3 months after the first infusion. The study design complies with the current standards requested by the Guideline (CPMP/BPWG/388/95 rev. 1).
Most patients were adults with a long history of chronic ITP so can be considered representative of the target population. The platelet count was collected on D1, D2, D3, D4, D5, D10, D14, D21, 1m, 3m.
The administration of booster doses or changes in treatment (including corticoids and platelet concentrates) were not allowed in the protocol

Outcomes/Endpoints and Results

The primary efficacy endpoint was the response to therapy, defined as a platelet count to > 50 x 10^9/l at any time during the study period. This endpoint is consistent with the requirements of the current CPMP Guideline on IVIg (CPMP/BPWG/388/95 rev. 1).
The primary endpoint of Study IG 202 (a platelet increase to ≥50 x 10^9/L within the study period and not receiving alternative treatment) was reached in either 12/19 PP patients (63%) or in 14/19 (73%) depending on the rigidity of methodology. The latter value is approximately in accordance with response rates in the literature of 75- 79%, the former value would be at the decidedly lower end of response rates in the literature.

The secondary efficacy endpoints were:

-time to a platelet count of >50x10^9/l and duration of response.

The mean platelet count was >50 x 10^9/l by day 3 and was maintained over 50 x 10^9/l until Day 14. The highest mean platelet count (Day 5) was 129 x 10^9/L (range from 21.00 x 10^9/l to 914.00 x 10^9/l). However, due to some unusually high outlying values in particular of patient 0101 (Day 5: 798 x10^9/l, Day 10 914x10^9/l) the median values which describe the central tendency of the data are considered more robust. The median platelet count in responders was raised to 64 x 10^9/l at Day 5; this is low (also compared to other products) and does not reach normal platelet levels. This platelet level corresponds more to values obtained in modified IVIg products. The lower platelet count is commented on in the SPC, section 5.1.

The duration of response (mean > 14.3 days, median > 7 days) was estimated from the first measurement that the subject had a platelet count greater than or equal to 50,000 /µl to the last measurement that the subject had still a platelet count over that level. Performing new calculations with less stringent criteria, slightly better results were obtained, namely 12.5 days median duration in 12 responders or 11.5 days in 14 responders.
This less stringent criteria is acceptable and has been adopted for other products. In the recent literature (Bierling, P. & Godeau, B. Intravenous immunoglobulin and ITP: 22 years on. Vox Sanguinis 86 (1), 8-14. 2004) mean duration of response has been described as lasting 18 days after 2g/kg of IVIg.

-regression of haemorrhages during the first 10 or 14 days of observation.
A total of 18 patients (95% PP and 90% ITT) had a regression of bleedings on Day 10 and 89% and 85% (PP and ITT respectively on day 14.). Overall the mean time to regression was 7.4 days, the median being 5 days, that is considered acceptable.

A comparison with the literature was made. The study most comparable to the current one (by Varga (2006)) showed better values especially for the parameters median platelet count (163 x 10^9/L) and response duration (25 days). Other studies showed better response rates particularly due to a different choice of patient population.
In this current study the overall response rate and median platelet count remain low. In order to alert the treating physician, the SPC, section 5.1, reflects these results.

According to the current NfG (CPMP/BPWG/859/95 rev.1), indications for use in Guillain Barré syndrome, Kawasaki disease and allogeneic bone marrow transplantation can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes and in patients with ITP is established.

Clinical safety

In both clinical trials the majority of patients reported AEs, that in nearly all cases were classified as mild or moderate. Most of these adverse events are well-known and are covered in section 4.8 of the SPC (e.g., pyrexia, headache, hypotension or allergic reactions.)

Safety Results of PID Study IG 201

- Patients exposure

IVIg31 GRIFOLS 5% was given by intravenous infusion at a dose of 300- 600 mg/kg. A total of 706 infusion were administered to 46 patients.

- Adverse events

Forty three (43) patients (94%) experienced 595 AEs. Of the 706 infusions administered, 10% were associated with an AE related to Flebogammadif that occurred during the infusion or within 72 hours after infusion completion. Thirty-one patients (67%) experienced 107 potentially related AEs. Most AEs were mild to moderate in intensity.

Seven (7) patients (15%) experienced 8 AEs that were severe in intensity. No patient died, 1 patient withdrew from the study because of an AE (hyperkeratosis) that was considered not to be related to study drug, and 3 patients experienced 6 SAEs that were also considered not related to study drug.

The most common AEs were sinusitis, pyrexia, headache, upper respiratory tract infection, wheezing or asthma aggravated, diarrhoea, pharyngitis, injection site reaction, arthralgia, and nasal congestion. Numerous infections (i.e sinusitis NOS, upper respiratory tract infection NOS, asthma, combined bronchitis, diarrhoea NOS, pharyngitis) were reported as AEs with an overall frequency of 43% (20/46). In some other studies these kinds of infections were more rigidly defined as a secondary endpoint, however, the frequency rate in the current study seems to be acceptable. The most common treatment-related AEs were headache, pyrexia, injection site reaction, diarrhoea, rigors, and urticaria.

- Laboratory findings

The laboratory measures obtained in this study were within normal ranges for the majority of patients. Five patients (11%) experienced 11 clinically significant abnormalities of AST, 3 patients (7%) experienced 6 clinically significant abnormalities of ALT, and 2 patients each (4%) experienced 2 clinically significant LDH and serum creatinine abnormalities. No patients experienced clinically significant abnormalities of bilirubin.
Seven patients had positive Coombs' test results after baseline.

Safety Results of ITP Study IG 202

- Patients exposure

Twenty patients were treated with Flebogammadif as an intravenous infusion at doses of 400 mg/kg/day over 5 days.

- Adverse events

Sixteen patients (80%) experienced a total of 85 AEs, whereby 39/85 AEs were bleeding adverse events related to the patient disease. Six of these bleeding AEs occurred during or after infusions and 33 bleeding episodes were reported during the follow up. No patient required a platelet or red cell transfusion.

The most frequent AEs were petechiae, headache, pyrexia and epistaxis. Two serious AEs were reported for one patient (ganglionar tuberculosis and fever) but were not related to the study drug. There is no obvious temporal relationship with the study medication (approximately 12 weeks after the last infusion and the patient was likely immunocompromised at the time of the infection). For one patient the 3rd infusion had to be stopped because of high fever.
Of 21 AEs potentially related to study drug (headache, fever, hypertension, decreased systolic blood pressure, hypotension, bradycardia, thrombocythaemia, blood pressure fluctuation and weakness) 16 events were of mild intensity and 5 events were of moderate intensity, only one AEs was classified as severe (tuberculosis) and was not related.
Of the 97 infusions administered, 18% (17 infusions) were associated with at least one AE suspected to be related to IVIg3I Grifols. Thirty-two percent of the infusions (31 infusions) were associated with at least one AE, 6% with at least one bleeding AE and 29% with at least one non-bleeding AE.

- Laboratory findings

Although Coomb's testing was only included in the lab panel performed at recruitment and not performed during the study, there were only some minor deviations for the parameters haemoglobin, bilirubin and LDH, and thus no clinically relevant signs for haemolysis.
No relevant abnormalities for vital signs and physical examinations were observed in both clinical trials.

With respect to viral safety, viral and prion clearance studies have been satisfactorily validated in line with the current guidelines. No seroconversion was observed in clinical studies IG201 and IG202. This has been properly described in sections 4.4. and 4.8. according to the guideline on Warning on transmissible agents in SPC and Package leaflet for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The Pharmacovigilance system described mainly fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The MAA submitted a risk management plan.

Summary of the risk management plan for Flebogammadif

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Reactions related to the rate of infusion such as headache, chills, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure, moderate low back pain and cutaneous reaction	Routine pharmacovigilance	• Infusion rate recommendations given under section 4.2 of the SPC • Listed as ADR in section 4.8 of the SPC • Warning in section 4.4 of the SPC informing that certain adverse drug reactions may be related to the rate of infusion and that the recommended rate of infusion must be closely followed Close monitoring of the patients is recommended throughout the infusion period and in case of adverse reaction, either the rate of administration must be reduced or the infusion stopped.
True hypersensitivity reactions, anaphylactic or anaphylactoid reaction	Routine pharmacovigilance	• Contraindication in cases of IgA deficiency, when the patient has antibodies against IgA (section 4.3 of the SPC) • Warning in section 4.4 of the SPC with recommendation to first inject the product slowly at an initial rate of 0.01 - 0.02 ml/kg/min; and to carefully monitored the patients throughout the infusion period, at least 20 minutes after and for the first hour after the first infusion in 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 • In case of shock standard medical treatment for shock should be implemented , • Listed as ADR in section 4.8 of the SPC
Aseptic meningitis	Routine pharmacovigilance	• Listed as ADR in section 4.8 of the SPC
Haemolytic anaemia/haemolysis	Routine pharmacovigilance	• Listed as ADR in section 4.8 of the SPC
Thromboembolic events such as myocardial infarction, stroke,	Routine pharmacovigilance	• Listed as ADR in section 4.8 of the SPC • Warning in section 4.4 of the

pulmonary embolism and deep vein thromboses		SPC informing that caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events. In patients at risk the product should be administered at the minimum rate of infusion and dose practicable
Acute renal failure or increase in serum creatinine	Routine pharmacovigilance	• Listed as ADR in section 4.8 of the SPC • Warning in section 4.4 of the SPC informing about the risk factors identified and recommending in patients at risk, the minimum rate of infusion and dose practicable , the monitoring of urine output and serum creatinine levels and avoidance of concomitant use of loop diuretics. In case of renal impairment, IVIg discontinuation should be considered.
Reactions due to fructose hereditary intolerance	Routine pharmacovigilance	• Warning in section 4.4 of the SPC: In case of fructose hereditary intolerance this product should not be used
Transmission of infective agents such as viruses, emerging viruses, other not identified infective agents or pathogens	Routine pharmacovigilance	• Listed as ADR in section 4.8 of the SPC • Warning in section 4.4 of the SPC recommending that the name and batch number of the product used are always recorded
Impairment in the efficacy of the live attenuated virus vaccines	Routine pharmacovigilance	• Information is included in section 4.5 of the SPC recommending an interval of 3 months before vaccination with live attenuated virus vaccines and that patients receiving measles vaccine should have their antibody status checked
Interference with serological testing	Routine pharmacovigilance	• Information is included in section 4.5 of the SPC. It is stated that passively transferred antibodies may result in misleading positive results in serological testing including the antiglobulin test (Coomb's test).
Lack of experience in children under 10 year old	• Routine pharmacovigilance As it is expected that the product is used in paediatric populations with congenital AIDS, Kawasaki	

	disease or other diseases, the periodic safety update reports will include data of adverse drug reactions reported in this newly exposed population. That data will be specifically monitored and discussed in the PSURs.	

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

Based on the submitted data, the marketing authorisation application for Flebogammadif is recommended for approval based on quality grounds.

Non-clinical pharmacology and toxicology

Overall, the non-clinical studies show that the non clinical pharmacology and toxicology profile of Flebogammadif does not raise any particular concern.
The product can be defined as belonging to a well known and characterized biological product family and therefore, according to the general principles outlined in the Note for Guidance ICH S6 on preclinical safety evaluation of biotechnology-derived pharmaceuticals, "biopharmaceuticals that are structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive toxicity testing". Repeat dose toxicity studies were not performed since administration of Flebogammadif to animals can be expected to initiate the immunological response, which would interfere with the toxicity evaluation. Reproductive, developmental, genotoxicity, carcinogenicity, or local tolerance studies were not performed due to the nature of Flebogammadif, which is a naturally expressed human protein. Moreover, at this stage of development the preclinical findings are superseded by the clinical data.
Regarding this aspect, the SPC, section 5.3, states: "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."

Efficacy

The correct patient population (primary immunodeficiency syndromes (PID), and patients with idiopathic thrombocytopenic purpura (ITP),) was included in the studies. The doses administered to the PID patients were adequate to maintain protective IgG trough levels. In the PID population relevant, serious bacterial infections matched the predefined efficacy criteria of ≤1 serious bacterial infection/patient/year. Data on use of antibiotics shows that most patients received antibiotics, mainly by oral route. This appears consistent with data from other studies.

For the ITP population doses as laid down in the core SPC were administered. For approx. 60% of the study population platelet levels were raised > 50 x 10^9/L and were maintained at this level for 14 days.
In general the values obtained in the ITP study for the number of responders, the platelet levels and response duration were slightly below those cited in the recent literature. Nevertheless, the CHMP can accept these results on the basis that ITP response to IVIg can vary considerably and that any given selection of 20 patients could be at the lower end of the expected range.
The median platelet count did not reach normal values. This is stated in the SPC, section 5.1.

Safety

The safety profile is in accordance with that expected from non-clinical studies and known class effects. The adverse events reported in the clinical trials are described in the section 4.8 of the SPC. Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment
Benefit

Flebogammadif is a sterile 5% 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.

The claimed indications are: a) Replacement therapy in primary immunodeficiency syndromes, myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and children with congenital AIDS and recurrent infections; and b) Immunomodulation in 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, Kawasaki disease and c) Allogeneic bone marrow transplantation. These indications are listed in the core SPC for IVIg (CPMP/BPWG/859/95 rev.1).

The quality part of the dossier is well documented regarding the biological and pharmaceutical aspects of the product. Flebogammadif complies with the Eur. Ph. Monograph "Human Normal Immunoglobulin for Intravenous Administration". Stability studies support the applied shelf life of the product.

With respect to clinical efficacy, two clinical trials were performed, one (Study IG201) for *replacement therapy* in patients with Primary Immunodeficiency Disease (PID) and another (Study IG202) for *immuomodulation* in patients with Idiopathic Thrombocytopenic Purpura (ITP). According to the NfG for the clinical investigation of IVIg (CPMP/BPWG/388/95 rev.1), demonstration of efficacy in PID would apply to all types of primary immunodeficiencies due to deficiency of functional IgG.

Furthermore, according to the current NfG (CPMP/BPWG/859/95 rev.1):

- indications for replacement therapy in myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections, and replacement therapy in children with congenital AIDS and recurrent infections can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes has been established.
- indications for use in Guillain Barré syndrome, Kawasaki disease and allogeneic bone marrow transplantation can be accepted without specific clinical trial data provided that efficacy in patients with primary immunodeficiency syndromes and in patients with ITP is established.

In general, the results for the clinical pharmacokinetics, efficacy and safety obtained from both clinical studies are in line with those reported in the literature and in other studies with similar products. They also fully comply with the current standards requested by the European Note for Guidance for the clinical investigation of IVIg (CPMP/BPWG/388/95 rev. 1).

Risks

The evaluation of the non-clinical studies shows that the toxicity profile of Flebogammadif does not raise any particular concern and therefore is not seen as an issue precluding a positive benefit/risk assessment, especially considering that the product can be defined as belonging to a well known and characterized biological product family and therefore, according to the general principles outlined in the Note for Guidance ICH S6 on preclinical safety evaluation of biotechnology-derived

pharmaceuticals, this product, that is "… structurally and pharmacologically comparable to a product for which there is wide experience in clinical practice may need less extensive toxicity testing"
No new clinical safety issues could be discerned from the submitted data; the adverse reactions to IVIgs are well known and have been described as a tabulated overview in in the SPC, section 4.8.

With respect to viral safety, viral and prion clearance studies have been satisfactorily validated in line with the current guidelines. No seroconversion was observed in clinical studies IG201 and IG202. This has been properly described in sections 4.4. and 4.8 of the SPC, according to the guideline "Warning on transmissible agents in SPC and Package leaflet for plasma-derived medicinal products" (CPMP/BPWG/BWP/561/03).

Benfit/Risk balance

The overall B/R of Flebogammadif is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Flebogammadif in the treatment of:

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 (CLL) 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 Barré syndrome
− Kawasaki disease

Allogeneic Bone Marrow Transplantation

was favourable and therefore recommended the granting of the marketing authorization.