Flebogamma DIF

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0077/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a	09/10/2023	30/10/2023	SmPC, Annex II and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	new specification parameter to the specification with its corresponding test method				
IG/1673	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	02/10/2023	n/a		
IG/1602	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	13/03/2023	n/a		
WS/2366	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	12/01/2023	n/a		
IG/1578	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	29/11/2022	n/a		
IG/1563	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	05/10/2022	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IG/1536	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	13/07/2022	n/a		
IB/0071	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	05/07/2022	n/a		
IG/1500/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/03/2022	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2022	30/10/2023	Labelling and PL	

II/0067	to include a new kit Bio-Rad Monolisa Anti-HBs PLUS (BioRad reference 72566) used to determine the Anti-HBs antibodies in the analytical method (IG_MA-000196C_ING v10) performed at the Quality Control Laboratory of Instituto Grifols, S.A. B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	02/09/2021	n/a		to include a new kit Bio-Rad Monolisa Anti-HBs PLUS (BioRad reference 72566) used to determine the Anti-HBs antibodies in the analytical method (IG_MA-000196C_ING v10) performed at the Quality Control Laboratory of Instituto Grifols, S.A.
IG/1402	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	09/06/2021	n/a		
PSUSA/1633/202005	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2021	n/a		PRAC Recommendation - maintenance
IG/1328	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/01/2021	n/a		
IG/1298	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	08/10/2020	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IG/1252	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	11/05/2020	n/a		
IG/1188	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	05/12/2019	n/a		
IG/1161	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	08/10/2019	n/a		
II/0059/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	31/07/2019	SmPC and PL	The SmPC of Flebogamma DIF 50 mg/ml and 100 mg/ml are updated in line with the EMA core SmPC guideline for human normal immunoglobulin for intravenous administration. The main changes concern the wording of SID and the addition of MMN and CIDP therapeutic indications. Results from study IG0601 are in accordance with efficacy results from other IVIGs and in line with information already contained in Flebogamma DIF SmPC. The safety results did not raise any new ADRs; the frequency and

					severity reflect similar patterns to those seen with other IVIGs. The table on adverse drug reactions of the SmPC for both strengths is revised based on all completed studies previously submitted. Overall, the source of the safety database is from clinical trials and post-authorisation safety studies in a total of 128 patients exposed to Flebogamma DIF 50 mg/ml (with a total of 1318 infusions) and in a total of 160 patients exposed to Flebogamma DIF 100 mg/ml (with a total of 915 infusions). The update for Flebogamma DIF 100 mg/ml includes also final results for study IG0601. The RMP is updated to add MMN and CIDP indications and to conform to the Guideline on GVP Module V rev.2. The list of safety concerns is revised to add lupus-like syndrome as an important potential risk to remove hereditary fructose intolerance and use in paediatric population under 2 years old from the important potential risk and the missing information, respectively.
IG/1048	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/03/2019	n/a		
IAIN/0058	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	31/07/2019	SmPC	
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/10/2018	31/07/2019	PL	

IG/0937	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/05/2018	n/a		
IA/0055	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/04/2018	n/a		
IA/0053	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	26/02/2018	n/a		
IG/0902	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/02/2018	n/a		
PSUSA/1633/ 201705	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	11/01/2018	n/a		PRAC Recommendation - maintenance
N/0051	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/06/2017	31/07/2019	PL	
IAIN/0050	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	15/06/2017	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
R/0048	Renewal of the marketing authorisation.	23/02/2017	24/04/2017	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Flebogamma DIF in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0049	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	09/02/2017	n/a		
PSUSA/1633/ 201605	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	12/01/2017	n/a		PRAC Recommendation - maintenance
IAIN/0046	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/06/2016	n/a		
IB/0045	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	16/05/2016	n/a		
IAIN/0044	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/04/2016	n/a		

PSUSA/1633/ 201505	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0043	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	12/12/2016	SmPC and PL	
IAIN/0041	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	03/07/2015	n/a		
IAIN/0040	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	23/04/2015	n/a		
IA/0039	B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	15/04/2015	n/a		
PSUSA/1633/ 201405	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2015	n/a		PRAC Recommendation - maintenance
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2014	08/07/2015	PL	

II/0037/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	20/11/2014	n/a		
II/0032	Update of sections 4.4, 4.8, and 5.1 to include the final results obtained from the clinical trials IG0705 and IG0601 in the paediatric population. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	08/07/2015	SmPC and PL	In this variation the company added information on different rates of side effects in children when compared to adults based on results from two clinical studies to the product information. In addition, the company recommended that vital signs (body temperature, blood pressure, heart rate and respiratory rate) should be observed during the infusion of Flebogamma DIF in children and adolescents.
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/06/2014	04/07/2014	PL	
II/0030	Submission of the final clinical study report for study IG 0202 to address CHMP request from the renewal R-17 CHMP. The study (IG0202) is a multi-center, prospective, open-label, clinical trial to assess the safety and the efficacy of intravenous immune globulin (IGIV3I Grifols 10%) in patients with	22/05/2014	n/a		Within a prospective, open-label, uncontrolled, multi-centre study in 18 (ITT population) adult patients with chronic immune thrombocytopenic purpura (ITP) efficacy on rise in platelet count and regression of haemorrhages of Flebogamma DIF10% has been generally confirmed. The safety data was comparable to the previously known safety

	immune thrombocytopenic purpura. No changes to the product information are proposed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				profile of the product in the treatment for ITP.
IAIN/0033	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/05/2014	n/a		
IAIN/0031	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/02/2014	n/a		
PSUSA/1633/201305	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0026/G	This was an application for a group of variations. Introduction of an alternative stopper. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the	18/12/2013	n/a		

	container or closure (immediate packaging) - Sterile medicinal products				
IAIN/0029	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	05/12/2013	n/a		
IAIN/0027	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/08/2013	n/a		
IAIN/0025	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	01/07/2013	n/a		
IAIN/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2013	04/07/2014	Annex II	
IAIN/0023/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or	24/01/2013	n/a		

	amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
IA/0022	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	09/11/2012	n/a		
IB/0021	B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP	08/10/2012	n/a		
II/0019	Submitted data to support Ph. Eur monograph compliance on procoagulant activity B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	20/09/2012	20/09/2012		
R/0017	Renewal of the marketing authorisation.	21/06/2012	30/08/2012		Based on review of date available since granting of the Marketing Authorisation, the CHMP confirmed that the benefit-risk balance for this product remained positive. However, the CHMP recommended that an additional renewal is requested in 5 years, due to limited post-marketing experience and the need to further monitor the safety profile. In addition, during this procedure, the SmPC has been updated to better address the potential risks related to presence of an excipient sorbitol (regarding use

					in patients for whom inherited fructose intolerance cannot be excluded).
IAIN/0020	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	17/07/2012	n/a		
IAIN/0018	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/03/2012	n/a		
IB/0016	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	15/03/2012	30/08/2012	SmPC, Labelling and PL	Update of the SmPC to implement the changes to reflect the new Guideline on core SmPC for human normal immunogobulin for intravenous administration (EMA/CHMP/BPWP/94038/2007 rev.3). The MAH also harmonised the SmPC wording for the two approved strenghts, updated the contact details for Germany, France and Croatia in the list of local representatives in the PL, and made minor linguitistic amendments in various languages thoughout the PI.
IAIN/0015	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	29/11/2011	n/a		
IB/0014	B.II.d.1.z - Change in the specification parameters	12/08/2011	n/a		

	and/or limits of the finished product - Other variation				
IA/0013/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	04/07/2011	n/a		
IA/0012	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/03/2011	n/a		
X/0006	Annex I_2.(c) Change or addition of a new strength/potency	23/09/2010	13/12/2010	SmPC, Labelling and PL	
IA/0011	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/11/2010	n/a		

IA/0010	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	02/09/2010	n/a	SmPC, Labelling and PL	
II/0009	Addition of a manufacturing site for part of the manufacturing process of the finished product. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	22/07/2010	11/08/2010		
IA/0008	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/05/2010	n/a		
IA/0007	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	14/04/2010	n/a		
II/0005	Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	24/07/2009	SmPC and PL	
2PMF/0004	Inclusion of the updated or amended Plasma Master File (Grifols EMEA/H/PMF/000002/04) in the marketing authorisation dossier	20/02/2009	n/a		

MF/0003	2PMF (2nd step of PMF certification procedure)	26/06/2008	n/a		
MF/0002	2PMF (2nd step of PMF certification procedure)	30/04/2008	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/03/2008	n/a	Labelling	