Hizentra

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/0133	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	06/01/2022	n/a		
II/0129	Extension of indication to expand the approved secondary immunodeficiencies (SID) indications to any symptomatic SID in accordance with the	14/10/2021	15/11/2021	SmPC and PL	Please refer to Scientific Discussion 'EMEA/H/C/002127/II/0129'

[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).

	Guideline on core SmPC for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94038/ 2007 Rev 5; CHMP, 2018). As a consequence, sections 4.1 and 4.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.6 of the RMP has been accepted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0131/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	05/10/2021	n/a		
II/0128	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/09/2021	n/a		
IG/1429	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	20/08/2021	n/a		

	do not affect the properties of the FP				
IB/0130	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	21/07/2021	n/a		
IB/0127/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	25/03/2021	n/a		
II/0122	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	25/03/2021	n/a		
IB/0125	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/03/2021	n/a		
IG/1356	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	16/02/2021	n/a		
IB/0124/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation	02/02/2021	n/a		

	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 B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised				
PSUSA/1633/ 202005	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2021	n/a		PRAC Recommendation - maintenance
II/0119/G	This was an application for a group of variations. B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	14/01/2021	n/a		
IB/0123	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	22/12/2020	n/a		
II/0117	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	22/10/2020	n/a		
II/0116	B.I.a.2.c - Changes in the manufacturing process of	17/09/2020	n/a		

	the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol				
IB/0120/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	31/08/2020	n/a		
II/0111/G	This was an application for a group of variations. B.II.e.5.c - To add a presentation - 20 ml pre-filled syringe - for the sterile parenteral, biological, immunological medicinal product Hizentra 200 mg/ml solution for subcutaneous injection in pre-filled syringe. New pack size for single syringe (EU/1/11/687/01XX). B.II.e.4.c - A change in the dimensions of the immediate packaging of the finished sterile medicinal product - to add a new, larger 20 ml pre-filled syringe. B.II.e.5.a.1 - To add a new pack-size for the 20 ml pre-filled syringe in a cardboard box for Hizentra within the range of currently approved pack sizes	23/07/2020	15/11/2021	SmPC, Labelling and PL	The SmPC section has been updated as follows: Addition of 20mL pre-filled syringe presentation in Section 1 of the SmPC. The instruction for appropriate selection of way of infusion (device-assisted or manual push infusion) in case of home-treatment is updated in Section 4.2 of the SmPC to indicate that the selection should be based on patient´s individual situation and preferences. The PL has been updated accordingly.

	(EU/1/11/687/0XX - 10 syringes). Furthermore, the PI is being brought in line with the latest QRD template version 10.1. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products				
IG/1269	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	15/07/2020	n/a		
II/0112/G	This was an application for a group of variations. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.2.z - Changes in the manufacturing process of	14/05/2020	n/a		

	the AS - Other variation				
IB/0115	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	04/05/2020	n/a		
IB/0114	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	27/03/2020	n/a		
IG/1209	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	25/02/2020	n/a		
II/0110/G	This was an application for a group of variations. Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to include the number of PID patients, to include prescriber information and tolerability information for manual push infusion, to update prescriber information on device-assisted infusion and to include safety information, based on final results from study IgPro20_4004, an open-label study to evaluate the safety and tolerability of higher infusion parameters of Hizentra infused manually or with pump assistance in PID patients. Update of sections 4.2 and 4.8 of the SmPC in order to update the number of PID patients and to include safety information based on final results from study IgPro_4005, a phase 4, open-label, single-sequence,	12/12/2019	15/11/2021	SmPC, Annex II and PL	In study IgPro20_4004 (HILO), the primary endpoint on the percentage of subjects responding to a higher infusion parameter was met for the 3 cohorts (manual push technique: n=16, pump-assisted flow rate administration: n=18, and pump-assisted infusion volumes administration n=15). The majority of the 49 PID patients (>60%) increased their volumes of up to 50 mL and flow rates up to 100 mL/h per injection site via pump as well as flow rates of up to 120 mL/h via manual push. These increases were well tolerated and IgG levels were maintained at the same level at the end of study compared to baseline. No new safety concerns were identified from this study. A total of 25 PID patients, including 15 paediatric patients, participated in Study IgPro20_4005. No new safety concerns were identified from this study.

	crossover study to investigate the tolerability, safety and efficacy of biweekly Hizentra dosing in PID patients. Section 4.8 of the SmPC is further updated to present the adverse drug reactions frequency per infusion. The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the list of local representative in the Package Leaflet, to make some editorial updates in sections 4.2, 5.1 and 5.2 of the SmPC and to bring the PI in line with the latest QRD template version 10.1. 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				
IB/0109	B.II.z - Quality change - Finished product - Other variation	25/09/2019	n/a		
IB/0108	B.I.z - Quality change - Active substance - Other variation	20/08/2019	n/a		
IB/0106	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/08/2019	n/a		

IB/0107	B.I.a.z - Change in manufacture of the AS - Other variation	19/06/2019	n/a		
N/0105	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/06/2019	13/01/2020	PL	
IB/0103	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	10/04/2019	n/a		
IG/1074	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	01/04/2019	n/a		
II/0102	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/01/2019	13/01/2020	SmPC and PL	
N/0101	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/01/2019	13/01/2020	PL	
II/0097/G	This was an application for a group of variations. Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to reflect the final results from the study IgPro20_3004: Multi-centre, open-label extension study to investigate the long-term safety and efficacy of IgPro20 in maintenance treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in subjects completing Study IgPro20_3003. The	15/11/2018	11/01/2019	SmPC, Labelling and PL	A phase 3, multicenter, 48-week open-label extension study enrolled 82 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients from the PATH study. The extension study investigated the long-term safety and efficacy of Hizentra maintenance therapy in the two weekly doses, 0.2 g/kg and 0.4 g/kg bw. Due to the study design, the same subject could receive both doses during the study; 72 subjects received doses of 0.4 g/kg and 73 subjects received doses of 0.2 g/kg during the efficacy

	Package Leaflet is updated accordingly. Update of sections 4.2, 5.1 and 5.2 of the SmPC with the total number of patients with primary immunodeficiency (PID) based on the data from 7 previously submitted clinical trials in PID patients. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes in the PI and to bring the Labelling in line with the latest QRD template version 10. 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				evaluation period. The mean efficacy evaluation period was 125.8 days (range: 1-330) in the 0.2 g/kg, and 196.1 days (range: 1-330) in the 0.4 g/kg bw group. Patients who completed the pivotal PATH study without relapse on 0.4 g/kg bw dose and initially received this dose in the extension study had a relapse rate of 5.6 % (1/18 patients). For all patients who received 0.4 g/kg bw in the PATH extension study, 9.7 % (7/72 patients) had a relapse. Patients who completed the PATH study without relapse on 0.2 g/kg bw dose and initially received this dose in the extension study had a relapse rate of 50 % (3/6 patients). For all patients who received 0.2 g/kg bw in the extension study, 47.9 % (35/73 patients) had a relapse. Down-titrating patients in the extension study who completed the PATH study on either dose from 0.4 g/kg to 0.2 g/kg bw dose was possible in 67.9 % of subjects (19/28 patients) without occurrence of relapse; all of the 9 relapsers recovered within 4 weeks after treatment with 0.4 g/kg bw dose. Grip strength, MRC sum score, and R-ODS centile score remained stable as compared to baseline for patients who never had a relapse in the extension study. Safety results showed the typical adverse events (AE) profile of SCIGs (mainly local reactions, mainly mild). No new signals were observed. There was no indication of increased AEs/ infusion in the higher dose (0.4 g/kg) group. The safety and effectiveness of Hizentra have been established in paediatric subjects 2 to 18 years of age. Hizentra was evaluated in 54 paediatric subjects with PID 2 to <12 years of age and in 45 paediatric subjects 12 to <18 years of age. There were no differences in the pharmacokinetics, safety and efficacy profiles as compared

					with adult subjects. No paediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. No overall differences in safety or efficacy were observed between PID subjects >65 years and PID subjects 18 to 65 years of age. In the clinical studies Hizentra was evaluated in 9 patients with PID >65 years of age and no specific dose adjustments were necessary to achieve the desired serum IgG levels. No overall differences in safety or efficacy were observed between CIDP subjects >65 years and CIDP subjects 18 to 65 years of age. In the clinical studies with CIDP patients, 61 subjects >65 years of age were treated with Hizentra and no specific dose adjustments were necessary to achieve the desired clinical outcome.
IB/0099	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	11/12/2018	n/a		
IB/0100	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	31/10/2018	n/a		
IB/0098	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/09/2018	n/a		
IB/0096	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	31/08/2018	n/a		

IB/0095	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	06/07/2018	n/a		
IB/0094	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	16/05/2018	n/a		
II/0093/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.II.z - Quality change - Finished product - Other variation	19/04/2018	n/a		
II/0087	Extension of indication to include immunomodulatory therapy in adults, children and adolescents (0-18 years), for the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. Section 4.7 of the SmPC was updated to bring it in line with the latest QRD template. The Package Leaflet is updated in accordance. The RMP is updated (finally agreed version 4.2). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	25/01/2018	05/03/2018	SmPC and PL	Please refer to the Scientific Discussion of Hizentra EMEA/H/C/002127/II/0087.

	modification of an approved one				
II/0091	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	15/02/2018	n/a		
IG/0885	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	29/01/2018	n/a		
PSUSA/1633/ 201705	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	11/01/2018	n/a		PRAC Recommendation - maintenance
II/0089	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	30/11/2017	n/a		
II/0086	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	19/10/2017	n/a		
II/0074/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	14/09/2017	30/01/2018	SmPC, Labelling and PL	

	site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products				
IB/0088	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	19/07/2017	n/a		
IA/0084/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.a - Change in supplier of packaging	15/05/2017	n/a		

	components or devices (when mentioned in the dossier) - Deletion of a supplier				
IB/0085	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/05/2017	n/a		
IB/0083	B.I.a.z - Change in manufacture of the AS - Other variation	08/05/2017	n/a		
II/0075	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	05/05/2017	n/a		
IB/0082	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	27/04/2017	n/a		
IB/0079	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/04/2017	n/a		
IG/0788	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	12/04/2017	n/a		
IA/0080/G	This was an application for a group of variations.	05/04/2017	n/a		

	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation				
IB/0076	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/02/2017	30/01/2018	SmPC and PL	
IG/0757	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	26/01/2017	n/a		
PSUSA/1633/201605	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	12/01/2017	n/a		PRAC Recommendation - maintenance
IB/0072	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	22/12/2016	n/a		
II/0070	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	10/11/2016	n/a		

N/0073	Update of the package leaflet with revised contact details of the local representatives for Cyprus, Estonia, Greece, Latvia and Lithuania. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/10/2016	30/01/2018	PL	
IB/0071	B.V.a.1.z - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Other variation	30/09/2016	n/a		
II/0068	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	15/09/2016	n/a		
II/0062	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	21/07/2016	n/a		
II/0061	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	14/07/2016	n/a		

IB/0067	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	21/06/2016	n/a		
IAIN/0066	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	31/05/2016	n/a		
IB/0064	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	12/05/2016	n/a		
II/0060	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	12/05/2016	n/a		
IAIN/0063	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	04/05/2016	n/a		
IG/0676/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	27/04/2016	n/a		

	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 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				
II/0058	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	18/02/2016	n/a		
R/0054	Renewal of the marketing authorisation.	17/12/2015	18/02/2016	SmPC	Based on the review of the available information the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Hizentra continues to be favourable. The CHMP considered that the Marketing Authorisation could be granted with unlimited validity. The CHMP recommended amendments to the Annexes I and

					IIIB to align the product information with the latest QRD template version 9.1. These changes do not affect the benefit-risk balance of the product, which remains positive.
PSUSA/1633/ 201505	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0056	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	17/12/2015	n/a		
IB/0057	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/10/2015	n/a		
II/0053	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	17/09/2015	n/a		
II/0049	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/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	23/07/2015	n/a		

IAIN/0052	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	19/05/2015	n/a		
IAIN/0051	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	13/05/2015	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/05/2015	30/01/2018	PL	
II/0047	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	26/03/2015	n/a		
IB/0048	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	09/02/2015	n/a		
PSUSA/1633/ 201405	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2015	n/a		PRAC Recommendation - maintenance
IB/0046	B.II.d.1.c - Change in the specification parameters	23/12/2014	n/a		

	and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method				
II/0042	Changes to the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	18/12/2014	n/a		
IA/0045	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	21/11/2014	n/a		
II/0040	Update of section 5.2 of the SmPC in order to include additional information on the dosing regimens. The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	16/12/2014	SmPC and PL	Simulations by empirical Population Pharmacokinetic models suggest that comparable IgG exposure levels (AUC0-14days, Cmin 14days) may be obtained if Hizentra is administered subcutaneously every two weeks using double the weekly dose during maintenance therapy. These simulations further suggest that comparable serum IgG trough levels can be achieved when the weekly maintenance dose of Hizentra is administered in proportional amounts more frequently than once a week (e.g. 2 times per week, 3 times per week, 5 times per week or daily). Simulation of 2-3 missed daily doses resulted in a median serum IgG level decrease of≤4% compared to consistent daily dosing. By replacing the missed doses when daily

					dosing was resumed, the median concentration profile recovered within 2 to 3 days. However, if missed doses were not replaced when dosing was resumed, it took up to 5-6 weeks for the IgG trough levels to return to steady-state.
II/0041	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	25/09/2014	n/a		
IA/0043	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	19/08/2014	n/a		
II/0038	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	22/05/2014	n/a		
IB/0036	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	15/04/2014	n/a		
N/0039	To update the contact details of the local representatives and to revise the statement on Aseptic Meningitis Syndrome in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/03/2014	16/12/2014	PL	

IAIN/0037	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	17/02/2014	n/a		
PSUSA/1633/ 201305	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0027/G	This was an application for a group of variations. Update of section 4.4 and 4.8 of the SmPC to include safety information on Aseptic Meningitis and Thromboembolic events derived from previous P46-013 and PSUR assessment. Update of section 4.8 of the SmPC following post marketing analysis to include Anaphylactic reaction, Tremor and Burning Sensation. The PL is updated accordingly. Section 4.3 of the SmPC has also been clarified to further specify the type of Hyperprolinemia (Type I and II). Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and the SmPC guideline. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications	18/12/2013	16/12/2014	SmPC, Labelling and PL	Following assessments of P46-013, previous PSURs and post marketing data, the MAH has implemented in the product information safety information regarding Aseptic Meningitis Syndrome, Thromboembolic Events, Anaphylactic Reaction, Tremor and Burning Sensation. Moreover Section 4.3 of the SmPC regarding Hyperprolinemia has been clarified to further specify the type of Hyperprolinemia (i.e. type I and II). The CHMP endorses the changes to the product information and the risk minimisation measures proposed by the MAH.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0031	Submission of the relevant validation data to demonstrate that the manufacturing process is in accordance with the revision of the Ph. Eur. Monograph on human normal immunoglobulin (0338). B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	21/11/2013	n/a		
II/0024	Update of section 5.2 to revise the Pharmacokinetics information in order to include alternative frequency for the dosing regimen during maintenance therapy. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/10/2013	18/12/2013	SmPC and PL	MAH has provided a pharmacometric modelling evaluation of a possible administration of Hizentra every two weeks using double the weekly dose during maintenance therapy elaborating data deriving from previous clinical studies. Assessment of the model and the results obtained during the simulations indicate that the modelling and simulation (M&S) has some limitations which may partially affect the full credibility of the model applied. Nevertheless despite the shortcomings in the modelling and simulation exercise, the practical aspect of individual tailoring of dosage and dose intervals, is central and has to be kept in mind. It is indeed understood that the clinical context provides reassurance that dosing every two weeks is likely to result in similar trough levels to dosing weekly. This make the focus on M&S used as the only basis for the SmPC statement the only objection in the discussion, because it does not acknowledge the underlying uncertainties of the method. For this reason, the CHMP suggested to make a

					direct reference to the limitations/uncertainties of this modelling approach in the SmPC. The final agreed wording is indeed encompassing this issue and the procedure is considered acceptable.
II/0032	Changes to the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	19/09/2013	n/a		
II/0030	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	19/09/2013	n/a		
IA/0033	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	13/08/2013	18/12/2013	SmPC, Labelling and PL	
N/0029	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2013	18/12/2013	PL	Update of the list of local representatives for Bulgaria and Czech Republic.
IAIN/0034	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/07/2013	n/a		
II/0026	Changes to the manufacturing process of the active	25/07/2013	n/a		

	substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol				
II/0025	Change to finished product specification. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	27/06/2013	n/a		
IAIN/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/06/2013	18/12/2013	Annex II	
II/0019	Change in the manufacturing procedure of the active substance during purification process. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	25/04/2013	n/a		
II/0018	Change in the manufacturing procedure of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	21/03/2013	n/a		

II/0022	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	21/02/2013	n/a		
II/0021	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	21/02/2013	n/a		
IAIN/0023	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	31/01/2013	n/a		
II/0020/G	This was an application for a group of variations. To introduce an additional 50mL filling size for IgPro20 in packs of 1 and 10 vials B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within	17/01/2013	18/12/2013	SmPC, Labelling and PL	

	the range of the currently approved pack sizes B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products				
II/0016	Changes in the manufacturing process of the drug substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	18/10/2012	n/a		
IB/0017	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the currently approved batch size	21/09/2012	n/a		
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	30/05/2012	n/a		
IA/0014	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	30/04/2012	n/a		
N/0013	The MAH relocated the IgA deficiency warning and	28/02/2012	22/05/2012	PL	The MAH relocated the IgA deficiency warning and deleted

	deleted one of two identical sodium statements and updated the name of the local representative for Romania in the package leaflets for all the language versions. The MAH also took the opportunity to correct a spelling error in the English package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				one of two identical sodium statements and updated the name of the local representative for Romania in the package leaflets for all the language versions. The MAH also took the opportunity to correct a spelling error in the English package leaflet.
N/0012	Implementation of changes following a 'User Testing' in the Package Leaflet. The MAH also took the opportunity to amend the local representatives contact details for Ireland and the United Kingdom in the Package Leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/01/2012	22/05/2012	PL	Implementation of changes following a 'User Testing' in the Package Leaflet. The MAH also took the opportunity to amend the local representatives contact details for Ireland and the United Kingdom in the Package Leaflet.
II/0009	Change in the manufacturing process of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	15/12/2011	15/12/2011		
II/0007	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	17/11/2011	17/11/2011		

	biological/immunological medicinal products				
II/0005	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	17/11/2011	17/11/2011		
IB/0010	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	09/11/2011	n/a		
IA/0011	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	08/11/2011	n/a		
IB/0008	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/10/2011	n/a	SmPC, Annex II, Labelling and PL	To extend the shelf life of the finished product from 24 to 30 months based on real time data. The MAH also took the opportunity to make changes in the Product information, which require linguistic review.
II/0004	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	22/09/2011	22/09/2011		
IA/0006	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	07/09/2011	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0001	Change in batch size of Hizentra bulk active substance. B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	21/07/2011	21/07/2011		
IA/0003	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	31/05/2011	n/a		
IA/0002/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 B.V.a.1.d - PMF - Inclusion of a new, updated or	30/05/2011	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				