Obizur

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/0064	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	28/11/2024		SmPC	
IB/0062	B.I.b.2.a - Change in test procedure for AS or	10/10/2024	n/a		

[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).

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IA/0061/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	12/09/2024	n/a		
IA/0060/G	This was an application for a group of variations. 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.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	05/09/2024	n/a		
IB/0059	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/09/2024	n/a		
S/0056	8th annual re-assessment	25/07/2024	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation

					of Obizur should be maintained.
IB/0057	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	20/03/2024	n/a		
IA/0058	A.7 - Administrative change - Deletion of manufacturing sites	19/03/2024	n/a		
IA/0055	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	09/10/2023	n/a		
IB/0054	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/07/2023	n/a		
PSUSA/10458 /202211	Periodic Safety Update EU Single assessment - susoctocog alfa	08/06/2023	n/a		PRAC Recommendation - maintenance
S/0050	7th annual re-assessment	30/03/2023	26/05/2023	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Obizur should be maintained.
IA/0053	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	25/04/2023	n/a		
IB/0052	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	15/03/2023	n/a		

	of the AS				
II/0049	Submission of the final report for study 241501 listed as a category 2 study in the RMP in order to fulfil SOB/001.4. This is a prospective and retrospective, non-interventional post-authorisation safety study (PASS) to evaluate the safety and effectiveness of Obizur in real-life practice. The RMP version 6.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/02/2023	n/a		Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.No'
II/0047/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	27/10/2022	n/a		
IB/0048/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New	20/09/2022	n/a		

	storage site of MCB and/or WCB				
S/0044	6th annual re-assessment. The efficacy and safety data collected as part of the specific obligation for Obizur during the period covered by this annual re-assessment confirmed its positive benefit-risk balance in the approved indication.	22/04/2022	20/06/2022	SmPC	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Obizur should be varied. Section 4.2 of the SmPC has been updated with the following information: "If testing of anti-rpFVIII antibodies is negative at baseline, a dose lower than the recommended 200 U/kg may be used as the initial treatment dose. Clinical response should be closely monitored as dosing below 200 U/kg has been associated with a lack of efficacy (see section 4.4)."
PSUSA/10458 /202111	Periodic Safety Update EU Single assessment - susoctocog alfa	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0042	Submission of the final report from OBIZUR study 241502. This is a Phase 3, multicenter, single-arm, open-label study of the efficacy and safety of B-Domain deleted recombinant porcine factor VIII (BAX 802) in subjects with congenital hemophilia A with factor VIII inhibitors undergoing surgical or other invasive procedures. Changes to the Product Information were implemented at the request of the CHMP, in particular a contraindication was added for Congenital Haemophilia A with Inhibitors. In addition minor template changes were made to the Product Information. C.I.13 - Other variations not specifically covered	24/02/2022	28/03/2022	SmPC, Annex II, Labelling and PL	SmPC new text The results of the CHAWI study in patients with congenital haemophilia A with FVIII inhibitors (CHAWI) were presented in the SmPC, and in particular a new contra-indication 'Congenital Haemophilia A with Inhibitors (CHAWI) (see section 5.1)' was added to section 4.3.

	elsewhere in this Annex which involve the submission of studies to the competent authority				
IAIN/0046/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites 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)	28/02/2022	20/06/2022	Annex II and PL	
II/0043	Submission of the final report from US PASS 241302 study, EUPAS register Number EUPAS36659, listed as a category 3 study in the RMP. This is a post-marketing non-interventional safety evaluation of Obizur in the treatment of bleeding episodes for patients with acquired hemophilia A (AHA).The primary objective is to determine the incidence of therapy-related serious adverse events (SAEs) in patients with AHA who are prescribed and treated with OBIZUR in routine clinical practice. The RMP version 5.0 has also been submitted and endorsed. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/01/2022	n/a		

PSUSA/10458 /202105	Periodic Safety Update EU Single assessment - susoctocog alfa	02/12/2021	n/a		PRAC Recommendation - maintenance
PSUSA/10458 /202011	Periodic Safety Update EU Single assessment - susoctocog alfa	24/06/2021	20/08/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10458/202011.
IB/0036/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	26/03/2021	20/08/2021	SmPC, Annex II and PL	
S/0039	5th annual re-assessment. The efficacy and safety data collected as part of the specific obligation for Obizur during the period covered by this annual re-assessment confirmed its positive benefit-risk balance in the approved indication	25/03/2021	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Obizur should be maintained
IB/0038	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	02/03/2021	n/a		
IB/0037	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/01/2021	n/a		
PSUSA/10458	Periodic Safety Update EU Single assessment -	26/11/2020	n/a		PRAC Recommendation - maintenance

/202005	susoctocog alfa				
R/0033	Renewal of the marketing authorisation.	17/09/2020	16/11/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Obizur in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds: Safety issues identified with Obizur warrant additional evaluations and analyses conducted in a second renewal: Lack of drug effect Summary tabulation cumulatively lists 108 serious adverse reactions. Leading SOC at the PT level is SOC "General and administration site disorders" with 30 SARs, 18 referring to PTs related to drug effect decreased/drug ineffective/ Condition aggravated and thus accounting for 60 % of the serious adverse event PTs reported in this SOC. In "cumulative all" events (including non-serious) 25 out of 46 events in SOC "General disorders" refer to lack of drug effect-PTs which is 54 % of all PTs in this SOC. In view of the committees lack of drug effect therefore represents a prominent concern for Obizur. Based on the limited information available on case level many cases might be associated with dosing other than the recommended dose in the SmPC despite the additional risk minimisation measures. While a minority of patients only receive the currently recommended dose of 200 IU there seem to be a high number of 'lack of drug effect' cases of which the majority (68%) is associated with under dosing. Furthermore, it seems that that under dose may be also associated with occurrence of anamnestic reaction leading

					to the aggravation of the underlying condition. Anamnestic reaction Thirty-nine (39) serious adverse events were reported through clinical trials for Susoctocog alfa. SOC Immune system disorders is presenting with two SAEs, one thereof referring to anamnestic and one to anaphylactic reaction. Furthermore, during the current renewal interval SUSAR 'anamnestic reaction' was reported in the clinical trial CHAWI (study in patients with congenital haemophilia A with inhibitors undergoing surgical or other invasive procedures; 241502). Out of the eight subjects included in the trial six developed new inhibitors (anti-rpFVIII or FVIII) or experienced an increase in their previously known FVIII inhibitors. The committees recommended that anamnestic reaction be explicitly included in the safety concerns for the product as a separate identified risk. The MAH will communicate the risk of 'lack of efficacy' and in particular the risk of anamnestic reaction associated with under dosing by an update of the educational material in due time following this renewal.
II/0030	Update of the sections 4.4 and 4.8 of SmPC to add information on anamnestic reaction and to list it with the frequency very common. The Package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/09/2020	16/11/2020	SmPC	The variation expanded information on Obizur adverse events by adding that anamnestic reactions with rise in human factor VIII and/or porcine factor VIII inhibitors have also been reported in patients treated with Obizur. These anamnestic rises may result in lack of response to OBIZUR. Furthermore, anamnestic reaction was included in the ADR table with the frequency 'very common'.

					For more information, please refer to the Summary of Product Characteristics.
II/0034	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	03/09/2020	n/a		
S/0028	Annual re-assessment.	25/06/2020	n/a		
PSUSA/10458 /201911	Periodic Safety Update EU Single assessment - susoctocog alfa	11/06/2020	n/a		PRAC Recommendation - maintenance
IB/0032	B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	30/04/2020	n/a		
II/0027	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	30/04/2020	n/a		
IA/0029	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	18/12/2019	16/11/2020	Annex II	
PSUSA/10458 /201905	Periodic Safety Update EU Single assessment - susoctocog alfa	28/11/2019	n/a		PRAC Recommendation - maintenance

PSUSA/10458 /201811	Periodic Safety Update EU Single assessment - susoctocog alfa	14/06/2019	n/a		PRAC Recommendation - maintenance
S/0023	3rd annual re-assessment	26/04/2019	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Obizur should be maintained.
II/0022/G	This was an application for a group of variations. 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 B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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	14/02/2019	n/a		

	biol/immunol method 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.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.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products				
IA/0024	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	06/12/2018	n/a		
PSUSA/10458 /201805	Periodic Safety Update EU Single assessment - susoctocog alfa	29/11/2018	n/a		PRAC Recommendation - maintenance
II/0021	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	15/11/2018	n/a		

PSUSA/10458 /201711	Periodic Safety Update EU Single assessment - susoctocog alfa	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0019	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/03/2018	n/a		
S/0016	2nd annual re-assessment.	22/02/2018	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Obizur should be maintained.
IA/0017/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	14/12/2017	n/a		
PSUSA/10458 /201705	Periodic Safety Update EU Single assessment - susoctocog alfa	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0015	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	31/10/2017	n/a		

IB/0013	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	02/08/2017	n/a		
PSUSA/10458 /201611	Periodic Safety Update EU Single assessment - susoctocog alfa	09/06/2017	n/a		PRAC Recommendation - maintenance
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/06/2017	16/11/2020	Labelling and PL	
IB/0011	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	01/03/2017	n/a		
S/0006	Annual re-assessment.	23/02/2017	n/a		
IB/0008	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	22/02/2017	16/05/2017	SmPC and PL	
IB/0009	To harmonize the One Stage Coagulation Assay for determining the potency of Obizur finished product (sample preparation and instrument maintenance) between Ipsen and the Baxalta Milford facility. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/12/2016	n/a		

IB/0007	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	14/12/2016	n/a		
PSUSA/10458 /201605	Periodic Safety Update EU Single assessment - susoctocog alfa	01/12/2016	n/a		PRAC Recommendation - maintenance
II/0005	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	29/09/2016	n/a		
IA/0002	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	03/06/2016	n/a		
IA/0001/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	21/04/2016	16/05/2017	SmPC and Annex II	

	specification limits				