Ondexxya

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
II/0044	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to update the safety and efficacy information based on the final results from study 18-513 (ANNEXA-I), listed as a specific obligation in the Annex II; this is a phase 4 randomised controlled trial to investigate the efficacy and safety of	19/06/2025		SmPC, Annex II, Labelling and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	andexanet alfa versus usual care in patients with acute intracranial haemorrhage taking apixaban, rivaroxaban or edoxaban. The Annex II and Package Leaflet are updated accordingly. The updated RMP version 4.0, succession number 2.0 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI and to bring it in line with the latest QRD template version 10.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0049	Renewal of the marketing authorisation.	30/01/2025	04/04/2025		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the re-newal of the conditional MA for Ondexxya, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0046/G	This was an application for a group of variations. 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	27/03/2025	n/a		B.I.b.2.d (Type II) - To replace the current Generation 1 process specific method for Host Cell Protein (HCP) for release testing of Ondexxya (andexanet alfa) active substance with a Generation 2 process specific polyclonal antibody assay (Gen 2 HCP assay). This type II variation is to fulfil a Quality Recommendation (PAM, REC002 from iMAA).

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				B.I.b.1.b (Type IB) - To tighten the release and shelf-life active substance specification limits for HCP from ≤ 10.0 µg HCP/mg protein to ≤ 6.9 µg HCP/mg protein.
PSUSA/10764 /202404	Periodic Safety Update EU Single assessment - andexanet alfa	28/11/2024	n/a		PRAC Recommendation - maintenance
IB/0048/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile)	17/09/2024	n/a		
PSUSA/10764 /202310	Periodic Safety Update EU Single assessment - andexanet alfa	16/05/2024	n/a		PRAC Recommendation - maintenance
R/0041	Renewal of the marketing authorisation.	25/01/2024	11/03/2024		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ondexxya, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0043/G	This was an application for a group of variations.	18/12/2023	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0042	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	11/12/2023	11/03/2024	SmPC and PL	
PSUSA/10764 /202304	Periodic Safety Update EU Single assessment - andexanet alfa	30/11/2023	n/a		PRAC Recommendation - maintenance
II/0033	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2023	08/06/2023	SmPC, Annex II and PL	The SmPC and package leaflet were updated based on results of a PK and PK/PD Analysis aiming at confirming the approved posology to fulfil Specific Obligations (SOB) 001 and 003. This is a PK and PK/PD Analysis of Intravenously Administered Andexanet after dosing to steady state with a factor Xa inhibitor, rivaroxaban or apixaban, in healthy subjects and patients who have acute major bleeding. The posology should in general be maintained, but SmPC and package leaflet were updated to reflect that no evidence-based recommendation for andexanet treatment for "unknown" DOAC treatment-modality is available from clinical data or M&S. For more information, please refer to the Summary of

					Product Characteristics.
IB/0039	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	30/05/2023	11/03/2024	SmPC, Labelling and PL	
PSUSA/10764 /202210	Periodic Safety Update EU Single assessment - andexanet alfa	12/05/2023	n/a		PRAC Recommendation - maintenance
R/0034	Renewal of the marketing authorisation.	23/02/2023	24/04/2023		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ondexxya, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0038/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/03/2023	n/a		
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2023	24/04/2023	SmPC, Labelling and PL	

IAIN/0037	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/02/2023	24/04/2023	Annex II and PL	
PSUSA/10764 /202204	Periodic Safety Update EU Single assessment - andexanet alfa	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0029/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.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	04/07/2022	n/a		
T/0031	Transfer of Marketing Authorisation	29/04/2022	07/06/2022	SmPC, Labelling and PL	
IB/0030/G	This was an application for a group of variations. 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	12/05/2022	n/a		

	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 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
R/0025	Renewal of the marketing authorisation.	27/01/2022	29/04/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ondexxya, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0022/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the final study report from study 14-505 (ANNEXA-4). This is a prospective, open-label study	22/04/2022	07/06/2022	SmPC, Annex II and PL	The recommended dose regimen of Ondexxya is based on the dose of the direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) the patient is taking at the time of anticoagulation reversal, as well as on the time since the patient's last dose of the direct factor Xa (FXa) inhibitor

	of andexanet alfa in patients receiving a factor Xa inhibitor who have acute major bleeding to confirm safety and efficacy in patients with acute major bleeds. The package leaflet was updated accordingly. In addition, the marketing authorisation holder took the opportunity to implement editorial changes in the SmPC and PL. The Annex II (SOBs) has been updated. The revised RMP version 2.5 has also been submitted. Change to the summary of pharmacovigilance system due to change in QPPV. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(apixaban or rivaroxaban). Measurement of baseline anti-FXa-level should support the clinical decision of starting treatment (if level is available in an acceptable timely frame). For more information, please refer to the Summary of Product Characteristics.
IB/0028/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	14/03/2022	n/a		

IB/0026	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	17/12/2021	n/a		
PSUSA/10764 /202104	Periodic Safety Update EU Single assessment - andexanet alfa	02/12/2021	n/a		PRAC Recommendation - maintenance
IB/0024/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	11/10/2021	n/a		

	or addition) for the AS or a starting material/intermediate				
II/0020/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	07/10/2021	n/a		
II/0003	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/09/2021	29/04/2022	Annex II	
PSUSA/10764 /202010	Periodic Safety Update EU Single assessment - andexanet alfa	10/06/2021	n/a		PRAC Recommendation - maintenance
II/0009/G	This was an application for a group of variations. 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	20/05/2021	29/04/2022	SmPC, Annex II and PL	
IAIN/0021	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/04/2021	n/a		

IB/0019	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	31/03/2021	n/a		
R/0015	Renewal of the marketing authorisation.	10/12/2020	19/02/2021		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ondexxya, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IAIN/0018	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	09/02/2021	29/04/2022	Annex II and PL	
T/0016	Transfer of Marketing Authorisation	19/11/2020	07/01/2021	SmPC, Labelling and PL	
PSUSA/10764 /202004	Periodic Safety Update EU Single assessment - andexanet alfa	26/11/2020	n/a		PRAC Recommendation - maintenance
II/0011	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/10/2020	16/11/2020	SmPC and PL	

II/0012/G	This was an application for a group of variations. 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 B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.b.4 - Stability of FP - Extension of the shelf life of the finished product - Based on extrapolation of stability data not in accordance with ICH/VICH guidelines	03/09/2020	16/11/2020	SmPC	
IB/0013	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/06/2020	16/11/2020	SmPC	
PSUSA/10764 /201910	Periodic Safety Update EU Single assessment - andexanet alfa	14/05/2020	n/a		PRAC Recommendation - maintenance
II/0007	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	17/04/2020	n/a		
IB/0006/G	This was an application for a group of variations.	06/04/2020	n/a		

	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) 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				
R/0004	Renewal of the marketing authorisation.	30/01/2020	01/04/2020	Annex II	
IB/0005	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	16/12/2019	n/a		
II/0002	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/12/2019	01/04/2020	SmPC and Annex II	
IAIN/0001	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	05/07/2019	01/04/2020	Annex II and PL	