ATryn

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/0038	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	20/11/2018		SmPC and PL	
II/0033/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	19/07/2018		Annex II	

[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).

	manufacturer of a novel excipient 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.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.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 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.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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.d.1.b.3 - Stability of AS - Change in the storage				

	conditions - Change in storage conditions of the AS				
IAIN/0034	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	29/06/2018		Annex II and PL	
PSUSA/224/201707	Periodic Safety Update EU Single assessment - antithrombin alpha	08/02/2018	n/a		PRAC Recommendation - maintenance
S/0030	10th annual re-assessment	14/12/2017	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 ATryn should be maintained.
T/0031	Transfer of Marketing Authorisation	23/10/2017	16/11/2017	SmPC, Labelling and PL	
II/0027	Introduction of the first version of the RMP following request in 6th Annual Re-assessment EMEA/H/C/000587/S/0021 and second renewal EMEA/H/C/000587/R/0024. The product information has been updated accordingly to list the risk minimisation measures prior commercialisation of ATryn in each member state. In addition, the due date for the submission of the specific obligation reflected in section E of Annex II of the PI to extend the indication to the peri-partum period has been extended from 31st March 2017 to 31st March 2020.	23/02/2017	16/11/2017	Annex II	This variation intended to introduce the first version of the Risk Management Plan for this medicinal product. The compulsory character of RMPs as a requirement to marketing authorisation was only applicable for products submitting a marketing authorisation application after 21 July 2012. However, the marketing authorisation holder took the opportunity to introduce a risk management plan for this medicinal product. As a consequence, Annex II of the product information has been updated in accordance to the current QRD template to list risk minimisation measures in section D. In addition, the due date for the submission of the specific obligation reflected in section E of Annex II of the PI to

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				extend the indication to the peri-partum period has been extended from 31st March 2017 to 31st March 2020.
PSUSA/224/201607	Periodic Safety Update EU Single assessment - antithrombin alpha	09/02/2017	n/a		PRAC Recommendation - maintenance
S/0028	Annual re-assessment.	15/12/2016	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 ATryn should be maintained.
R/0024	Renewal of the marketing authorisation.	26/05/2016	15/07/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Atryn in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation under exceptional circumstances with unlimited validity.
S/0026	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 ATryn should be maintained.	26/05/2016	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 ATryn should be maintained.

PSUSA/224/201507	Periodic Safety Update EU Single assessment - antithrombin alpha	17/03/2016	n/a		PRAC Recommendation - maintenance
S/0021	6th Annual Re-assessment	25/06/2015	08/09/2015	Annex II	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 Atryn should be varied. Specifically, the due dates for the Specific Obligations have been revised as follows: SOB 001 is now due on 31/03/ 2016 and SOB 002 is due on 31/03/2018.
IAIN/0023	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	21/07/2015	n/a		
PSUSA/224/201407	Periodic Safety Update EU Single assessment - antithrombin alpha	10/04/2015	n/a		PRAC Recommendation - maintenance
S/0020	5th Annual Re-assessment	25/07/2013	04/10/2013	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
IAIN/0019/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV C.I.9.c - Changes to an existing pharmacovigilance	22/11/2012	n/a		

	system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities				
II/0015/G	This was an application for a group of variations. - Change in the name of the manufacturer of the active substance from Lonza Hopkinton Inc. to Lonza Biologics Inc. - Change in the name of the contract laboratory responsible for mycoplasma testing. - Change in the site for storage of the source material. - Changes to the manufacturing process of the active substance. - Changes to the in-process controls. - Changes to the active substance specifications. - Introduction of new in-house reference standards. - Changes to the container, storage conditions and shelf life of the active substance. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	21/06/2012	29/10/2012	Annex II	

	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.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.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile) 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.b.2 - Stability of AS - Change in the storage conditions - Change in storage conditions of biological/immunological ASs, when the stability studies have not been performed in accordance with a currently approved stability protocol A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the				

	AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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				
II/0014/G	This was an application for a group of variations. - Change in site responsible for labelling and secondary packaging. - Change in site responsible for batch release from LEO Pharma A/S, Ballerup, Denmark to MedImmune Pharma BV, Lagelandseweg 78, 6545 CG Nijmegen, The Netherlands. - Changes to the manufacturing process of the finished product. - Changes to the specifications for the finished product. - Changes in provider of the bromobutyl rubber stopper. - Extension of the shelf life of the finished product from 36 months to 48 months. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/06/2012	29/10/2012	SmPC, Annex II and PL	

	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing 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 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 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.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)				
S/0013	4th Annual Re-assessment	15/12/2011	02/03/2012	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable.
R/0012	Renewal of the marketing authorisation.	19/05/2011	05/08/2011	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of ATryn continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of this medicinal product continues to be favourable. The CHMP

					recommends the renewal of the Marketing Authorisation for ATryn, subject to the conditions and obligations as laid down in Annex II to the Opinion as well as the commitments of the Marketing Authorisation Holder as laid down in his Letter of Undertaking (see Attachment 4 of this Assessment Report). The Marketing Authorisation should remain under exceptional circumstances. The CHMP is however of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required. The MAH was requested to submit yearly PSURs unless otherwise specified by the CHMP
S/0011	Annual re-assessment.	18/02/2010	17/06/2010		
T/0010	Transfer of Marketing Authorisation	13/07/2009	23/07/2009	SmPC, Labelling and PL	The Marketing Authorisation for ATryn has been transferred from LEO Pharma A/S to GTC Biotherapeutics UK Limited.
S/0009	Annual re-assessment.	22/01/2009	06/03/2009	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that no amendments of Annex I and III are necessary however, an amendment of Annex II of the Commission Decision is adopted. The marketing authorisation remains under exceptional circumstances.
S/0007	Annual re-assessment.	13/12/2007	18/02/2008	Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, recommended that an amendment of Annex II of the Commission Decision is necessary and that the marketing

					authorisation remains under exceptional circumstances.
IA/0008	IA_28_Change in any part of primary packaging material not in contact with finished product	23/11/2007	n/a		
IA/0006	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	03/10/2007	n/a		
II/0002	Update of or change(s) to the pharmaceutical documentation Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	20/09/2007	25/09/2007		
IA/0005	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	01/08/2007	n/a	Annex II	
IA/0004	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	01/08/2007	n/a	Annex II and PL	
IB/0003	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	25/07/2007	n/a	SmPC	
T/0001	Transfer of Marketing Authorisation	26/11/2006	18/12/2006	SmPC, Annex II, Labelling and PL	The Marketing Authorisation for ATryn has been transferred from Genzyme Europe B.V. to LEO Pharma A/S.