TAKHZYRO

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/0040	Update of section 4.2, 4.4 and 5.1 of the SmPC in order to replace the information related to the use of lanadelumab in HAE patients with normal C1-INH activity, based on results from studies CASPIAN (SHP643-303) and CASPIAN OLE (TAK-743-3001). CASPIAN (SHP643-303) is a Phase 3, multicenter,	25/04/2025		SmPC, Labelling and PL	SmPC new text Section 4.2 Consideration should be given to discontinuing treatment in patients with HAE with normal C1 esterase inhibitor (nC1 INH) who have shown insufficient reduction in attacks after 3

[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).

	randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of lanadelumab for prevention against acute attacks of NONHISTAMINERGIC ANGIOEDEMA with Normal C1 Inhibitor (C1-INH); and CASPIAN OLE (TAK-743-3001) is an open-label study to evaluate the long term safety and efficacy of lanadelumab for prevention against acute attacks of Nonhistaminergic Angioedema with Normal C1-Inhibitor (C1-INH). The RMP version 4.0 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				months of treatment (see section 4.4 and 5.1). Section 4.4 There is limited clinical data on the use of lanadelumab in HAE patients with normal C1 INH (see section 5.1). Patients with HAE nC1 INH having mutations that are not associated with the kallikrein kinin system (KKS) pathway are not expected to respond to TAKHZYRO. It is recommended to perform genetic testing, if available, according to the current HAE guidelines and to discontinue the treatment if clinical response is not observed (see section 4.2 and 5.1). For more information, please refer to the Summary of Product Characteristics.
II/0043/G	This was an application for a group of variations. 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.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.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets,	13/02/2025		SmPC, Labelling and PL	As a result of this group of variations, sections 1, 2, 4.2, 4.4, 5.1, 6.3, 6.4, 6.5, 6.6 and 8 of the SmPC are being updated to reflect the new 300 mg solution for injection in pre-filled pen presentations, and new separate Labelling and Package Leaflet are added.

	ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging				
IB/0045/G	This was an application for a group of variations. 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 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	14/01/2025	n/a		
IB/0044	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/01/2025	n/a		
IB/0042	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/07/2024	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2024		Labelling and PL	

PSUSA/10743 /202308	Periodic Safety Update EU Single assessment - lanadelumab	07/03/2024	n/a		PRAC Recommendation - maintenance
IB/0039/G	This was an application for a group of variations. B.II.e.7.z. - Change in supplier of packaging components or devices (when mentioned in the dossier) - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	14/12/2023	n/a		
X/0034/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2023	15/11/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion "TAKHZYRO EMEA/H/C/004806/X/0034/G".
IB/0036/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 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.z - Changes in the manufacturing process of the AS - Other variation	21/09/2023	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
R/0035	Renewal of the marketing authorisation.	22/06/2023	11/08/2023	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 TAKHZYRO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
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	07/08/2023	n/a		
PSUSA/10743 /202208	Periodic Safety Update EU Single assessment - lanadelumab	16/03/2023	n/a		PRAC Recommendation - maintenance
IAIN/0032/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.1 - Administrative change - Change in the name and/or address of the MAH	13/10/2022	11/08/2023	SmPC, Annex II, Labelling and PL	
IB/0031	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/08/2022	29/09/2022	SmPC and PL	
II/0030/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	21/07/2022	n/a		

	material/intermediate/reagent - Tightening of specification limits 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 B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method				
IB/0029	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	30/03/2022	n/a		
PSUSA/10743 /202108	Periodic Safety Update EU Single assessment - lanadelumab	10/03/2022	n/a		PRAC Recommendation - maintenance
IB/0028	B.II.e.z - Change in container closure system of the Finished Product - Other variation	15/02/2022	n/a		
IA/0027/G	This was an application for a group of variations. 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) A.5.b - Administrative change - Change in the name	24/01/2022	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
II/0022	Update the SmPC sections 4.8 and 5.1 to reflect the result of study DX-2930-04 (HELP Study Extension: an open-label study to evaluate the long-term safety and efficacy of DX-2930 for prevention against acute attacks of Hereditary Angioedema (HAE)). In addition, the MAH is taking the opportunity to include a refrigeration statement for the multi-pack pre-filled syringe in the SmPC and pre-filled syringe PIL in section 6.4. The Risk Management Plan is also updated to version 2.2 following the completion of study DX-2930-04 and according to GVP Module V Rev 2 Integrated RMP template. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/12/2021	29/09/2022	SmPC and PL	The main scope of this variation is to update sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) to reflect the results of Long-term safety and efficacy, pharmacokinetics (PK), and impact on health-related quality of life (HRQoL) of TAKHZYRO for prophylaxis to prevent HAE attacks obtained in an open-label uncontrolled HELP study extension. Safety data available from the HELP study extension are consistent with the safety data from the HELP study. A total of 212 adult and adolescent (≥ 12 years) subjects with symptomatic type I or II HAE received at least one dose of lanadelumab 300 mg q2wks in this study, including 109 subjects who entered as rollover subjects from the HELP study. Rollover subjects, regardless of randomisation group in the HELP Study, received a single dose of lanadelumab 300 mg at study entry and did not receive additional treatment until the occurrence of an HAE attack. After the first HAE attack, all subjects received open-label treatment with lanadelumab 300 mg q2wks. The study also included 103 new or non-rollover subjects (including 19 subjects from Phase1b study) who had a historical baseline attack rate of ≥1 attack per 12 weeks. The non-rollover subjects received lanadelumab 300 mg q2wks at study entry. Subjects were allowed to initiate self administration after receiving the first 2 doses from a health care professional in clinic and completing appropriate training. The majority of subjects (173/212; 81.6%) who were treated in this study completed at least 30 months of

					treatment (either as a rollover or non-rollover subjects). The mean (SD) time in the HELP study extension was 29.6 (8.20) months. The majority of subjects self-administered lanadelumab (60.6% of 8,018 injections). There was a sustained reduction in attack rates compared to baseline during the HELP study extension, with a similar response to TAKHZYRO observed in both rollover (92.4%) and non-rollover groups (82.0%) and an overall reduction rate of 87.4%. Though the magnitude of the attack rate reduction in the HELP study limited the potential for further reductions in the HELP extension study, mean attack rates for the rollover subjects decreased further at the time of the final analysis and ranged from 0.08 to 0.26 attacks per month. In addition, the mean (SD) percentage of attack-free days was 97.7 (6.0)% and the mean (SD) duration of the attack-free period was 415.0 (346.1) days. The proportion of patients with a maximum attack-free period of 6 months or more or 12 months or more was 81.8% and 68.9%, respectively. Furthermore, section 6.4 is updated to inform patients of precautions to storage. Patients are adviced that when one pre-filled syringe from a multi-pack is removed from refrigeration, the remaining pre-filled syringes should return to the refrigerator until future use when needed. For more information, please refer to the Summary of Product Characteristics.
IA/0025/G	This was an application for a group of variations. B.II.e.z - Change in container closure system of the Finished Product - Other variation A.4 - Administrative change - Change in the name	22/11/2021	n/a		

	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.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol				
IAIN/0026	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	16/11/2021	29/09/2022	Annex II and PL	
II/0021/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.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 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.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	14/10/2021	29/09/2022	Annex II	

	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.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.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				
T/0023	Transfer of Marketing Authorisation	10/09/2021	29/09/2021	SmPC, Labelling and PL	
PSUSA/10743 /202008	Periodic Safety Update EU Single assessment - lanadelumab	11/03/2021	n/a		PRAC Recommendation - maintenance
IB/0019	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/11/2020	n/a		
IA/0018	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/11/2020	n/a		
IA/0017	B.II.e.7.b - Change in supplier of packaging	05/11/2020	n/a		

	components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
PSUSA/10743 /202002	Periodic Safety Update EU Single assessment - lanadelumab	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0016	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	24/07/2020	19/02/2021	SmPC and PL	
II/0014/G	This was an application for a group of variations. 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.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	25/06/2020	n/a		
II/0012/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.1.a - Replacement or addition of a	07/05/2020	19/02/2021	SmPC, Annex II, Labelling and PL	

	manufacturing site for the FP - Secondary packaging site 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.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.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.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 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.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				
PSUSA/10743 /201908	Periodic Safety Update EU Single assessment - lanadelumab	12/03/2020	n/a		PRAC Recommendation - maintenance
IB/0013	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	05/03/2020	19/02/2021	SmPC	
IB/0009	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	19/12/2019	n/a		
IB/0007	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	18/12/2019	n/a		
IAIN/0011	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	02/12/2019	n/a		
IAIN/0010	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/11/2019	n/a		
IB/0008	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of	22/11/2019	n/a		

	the AS				
IB/0005	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	21/11/2019	n/a		
PSUSA/10743 /201902	Periodic Safety Update EU Single assessment - lanadelumab	05/09/2019	n/a		PRAC Recommendation - maintenance
IA/0004/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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	14/06/2019	n/a		
IA/0003	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	23/05/2019	n/a		
IB/0001/G	This was an application for a group of variations. 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.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	14/03/2019	09/03/2020	SmPC, Labelling and PL	