Truberzi

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
IAIN/0013	A.1 - Administrative change - Change in the name and/or address of the MAH	12/02/2020		SmPC, Labelling and PL	
II/0009/G	This was an application for a group of variations. Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information based on	19/09/2019	24/10/2019	SmPC and PL	PK study ELX-PK-01 confirmed the renal excretion route as a minor elimination pathway of eluxadoline. In participants with end stage renal disease (ESRD) not yet on dialysis, exposure of eluxadoline was significantly increased (4.2-

[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).

	results from PK study ELX-PK-01 listed as a category 3 study in the RMP; this is a Single-dose, Open-label, Pharmacokinetic study of Eluxadoline in Healthy Subjects with normal Renal Function and Patients with Renal Impairment. Accordingly the RMP was updated to remove use in patients with renal impairment as missing information. Update of sections 4.4 and 4.8 of the SmPC following Company Core Data Sheet (CCDS) update based on review of clinical safety data and post- marketing safety data. Section 4.3 has been updated to add clarification in line with section 4.4. and Section 5.1 has been updated to add Pharmacotherapeutic Group and ATC code. The RMP version 3.1 has also been submitted. The Package Leaflet is updated accordingly. In addition, the MAH also took the opportunity to change "eluxadoline" to "Truberzi" when referring to the medicinal product throughout the SmPC. Furthermore the MAH took the opportunity to update the list of local representatives in the PI. 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				fold) compared with matched, healthy participants with normal renal function. However eluxadoline is acting locally in the gastrointestinal tract and the observed plasma concentrations in patients with ESRD were still very low, and in the same range as observed in several larger studies in healthy volunteers and thus unlikely to be of clinical significance. Accordingly it was added to the SmPC that no dose adjustment is necessary based on renal function Based on review of clinical safety data and post- marketing safety data hypersensitivity was added to 4.8 of the SmPC with a frequency of "not known". Furthermore it was added to 4.4 of the SmPC that most of the reported cases of serious sphincter of Oddi spasm occurred within a week of starting treatment with eluxadoline and some developed symptoms after one to two doses. The restriction to wait for 4 days before the intake of eluxadoline is stopped in case of severe constipation was deleted from the SmPC and precautionary statements to avoid concomitant drugs that may cause constipation was added to the to increase the safety of administration. Further editorial changes were made to other parts of the product information (please refer to the SmPC for further details).

PSUSA/10528 /201903	Periodic Safety Update EU Single assessment - eluxadoline	03/10/2019	n/a		PRAC Recommendation - maintenance
PSUSA/10528 /201809	Periodic Safety Update EU Single assessment - eluxadoline	11/04/2019	n/a		PRAC Recommendation - maintenance
IB/0010	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/03/2019	n/a		
PSUSA/10528 /201803	Periodic Safety Update EU Single assessment - eluxadoline	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0005/G	This was an application for a group of variations. Update of sections 4.5 and 5.2 of the SmPC in order to update the drug interaction information based on the final report from study 3030-102-002: a single-center, non-randomized, open-label, single-sequence study to evaluate the effect of eluxadoline on the single-dose pharmacokinetics of midazolam in healthy subjects, listed as a category 3 study in the RMP. The package leaflet was updated accordingly. Submission of the final report from study ELX-PH-08: in vitro evaluation of eluxadoline as an inducer of cytochrome P450 (CYP) 1A2 and 3A4 expression in cultured human hepatocytes, listed as a category 3 study in the RMP. Following the assessment of EMEA/H/C/PSUSA/00010528/201703, the RMP was updated to version 2.1 to update the existing important identified risk "SO spasm" to "SO spasm (Sphincter of Oddi dysfunction, SOD)" and include	06/09/2018	09/08/2019	SmPC and PL	

	pancreatitis as a new important identified risk. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10528 /201709	Periodic Safety Update EU Single assessment - eluxadoline	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0006/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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	06/04/2018	n/a		

	changes to an approved test procedure 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information				
PSUSA/10528 /201703	Periodic Safety Update EU Single assessment - eluxadoline	12/10/2017	08/12/2017	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10528/201703.
IB/0002/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished	31/01/2017	08/12/2017	SmPC, Labelling and PL	

	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				
T/0001	Transfer of Marketing Authorisation	17/11/2016	05/12/2016	SmPC, Labelling and PL	