LIVMARLI

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/0003/G	This was an application for a group of variations. Grouped variation consisting of: Extension of indication to include treatment of Progressive Familial Intrahepatic Cholestasis (PFIC) in patients 3 months of age and older for LIVMARLI, based on results from studies MRX-502, LUM001-501, MRX-503, MRX-800 and MRX-801; MRX-502 is an international, multicenter, randomized, double-blind, placebo-controlled, parallel group Phase 3 study that evaluated the efficacy and safety of	30/05/2024	28/06/2024	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Livmarli-EMEA/H/C/005857/II/0003/G'

[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).

	maralixibat in PFIC participants aged >12 months to <18 years on a proposed dosage of up to 600 µg/kg BID over 6 months. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Annex II are updated in accordance. Version 4.1 of the RMP is agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes to the labelling. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
PSUSA/11032 /202309	Periodic Safety Update EU Single assessment - maralixibat	25/04/2024	20/06/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/11032/202309.
S/0012	1st annual re-assessment.	25/04/2024	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 LIVMARLI should be maintained.
II/0008/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	14/03/2024	n/a		

	specification parameter to the specification with its corresponding test method 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.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP 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.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.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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-				

	significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier				
IA/0013	B.II.b.4.b - Change in the batch size (including batch size ranges) of the finished product - Downscaling down to 10-fold	25/01/2024	n/a		
II/0009	Update of section 5.3 of the SmPC in order to update preclinical safety information based on final results from study MRX-NC-006, listed as a category 3 study in the RMP. This is a 104-week oral gavage carcinogenicity study of maralixibat in Sprague Dawley Rats performed to evaluate the toxicity and carcinogenic potential of maralixibat. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2024	20/06/2024	SmPC	Administration of maralixibat to rats resulted in no increases in tumour incidences in the final data of the presented study. Based on the negative outcome of the rat carcinogenicity study and the overall weight of evidence, no carcinogenic risk is anticipated for patients and chapter 5.3 SmPC has been updated accordingly. In addition, the detailed information in 5.3 of the SmPC that no effects on fertility were observed I female rats was deleted as not considered helpful for the prescriber.
IB/0010	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	07/12/2023	20/06/2024	SmPC, Labelling and PL	
IB/0007	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/11/2023	n/a		

PSUSA/11032 /202303	Periodic Safety Update EU Single assessment - maralixibat	26/10/2023	n/a		PRAC Recommendation - maintenance
IAIN/0006	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	04/07/2023	20/06/2024	Annex II	
II/0002	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	15/06/2023	n/a		
IA/0004/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) B.II.f.1.e - Stability of FP - Change to an approved stability protocol	01/06/2023	n/a		
II/0001/G	This was an application for a group of variations. 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.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)	12/05/2023	20/06/2024	SmPC	The SmPC section 6.3 has been updated as follows: Shelf-life (30 months)