Dovprela

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
IA/0021	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/09/2024		SmPC	
II/0019/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to	16/05/2024	28/06/2024	SmPC and PL	For consistency and clarity, the wording of the indication section in the SmPC was updated to avoid conflicting information with respect to updated definitions for drug-

[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).

	new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				resistant TB from World Health Organization (WHO). Section 5.1 was also updated to specify the resistance profile of the patient populations studied in the ZeNix and NixTB clinical trials.
II/0020	updatindg addresses/names of manufacturers; updating raw material specifications, in-process tests and limits for the intermediate and finally extending the retest period of the active substance. B.I.z - Quality change - Active substance - Other variation	11/04/2024	n/a		
PSUSA/10863 /202308	Periodic Safety Update EU Single assessment - pretomanid	07/03/2024	n/a		PRAC Recommendation - maintenance
II/0013	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2023	15/11/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Dovprela-H-C-005167-II-0013'
PSUSA/10863 /202302	Periodic Safety Update EU Single assessment - pretomanid	28/09/2023	n/a		PRAC Recommendation - maintenance
R/0015	Renewal of the marketing authorisation.	26/04/2023	23/06/2023		
IB/0017	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)	09/06/2023	04/10/2023	SmPC	
PSUSA/10863 /202208	Periodic Safety Update EU Single assessment - pretomanid	16/03/2023	n/a		PRAC Recommendation - maintenance

IB/0014/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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	22/02/2023	23/06/2023	SmPC, Annex II and PL	
PSUSA/10863 /202202	Periodic Safety Update EU Single assessment - pretomanid	29/09/2022	n/a		PRAC Recommendation - maintenance

R/0010	Renewal of the marketing authorisation.	22/04/2022	14/06/2022	PL	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 Dovprela, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10863 /202108	Periodic Safety Update EU Single assessment - pretomanid	10/03/2022	n/a		PRAC Recommendation - maintenance
II/0008	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	13/01/2022	14/06/2022	Annex II	
PSUSA/10863 /202102	Periodic Safety Update EU Single assessment - pretomanid	30/09/2021	n/a		PRAC Recommendation - maintenance
II/0004/G	This was an application for a group of variations. Grouped application including three type II variations under category C.I.4. Update of sections 4.5 and 5.3 of the SmPC based on data from three non-clinical studies: - Assessment of pretomanid as an inhibitor of human OCT2-, OATP1B3-, BCRP-, and P-gp mediated transport;	22/07/2021	14/06/2022	SmPC	SmPC new text "4.5 Interaction with other medicinal products and other forms of interaction Effects of pretomanid on other medicinal products […] Effect on CYP2C8, 2C9 and 2C19 substrates In vitro studies show that pretomanid is an inducer of CYP2C8 while the studies are inconclusive regarding the

	- In vitro evaluation of induction/inhibition of CYP 2C8, 2C9, and 2C19 in human hepatocytes; - A 24-Month Oral (Gavage) Carcinogenicity Study in Rats. 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				potential of pretomanid to induce CYP2C9 and 2C19. In vivo induction cannot be excluded as no clinical studies have been performed. If pretomanid is co-administered with substrates of CYP2C8, 2C9 and 2C19, e.g., paclitaxel, warfarin, mephenytoin, prescribers and their patients should be observant for potentially reduced efficacy of these substrates. Effect on OAT3, OATP1B3, P-gp and BCRP substrates Pretomanid is an inhibitor of the OAT3 transporter in vitro, which could result in increased concentrations of OAT3 substrate medicinal products clinically and may increase the risk of adverse reactions of these medicines. If pretomanid is co-administered with OAT3 substrate medicinal products (e.g., methotrexate, benzylpenicillin, indomethacin, ciprofloxacin), monitoring for OAT3 substrate drug-related adverse reactions should be performed and dosage reductions for OAT3 substrate medicinal product should be considered, if needed (see section 4.4). In vitro studies indicate that pretomanid is an inhibitor of BCRP, OATP1B3 and P-gp. No clinical studies have been performed to investigate these interactions. Therefore, it cannot be excluded that co administration of pretomanid with sensitive OATP1B3 substrates (e.g., valsartan, statins), BCRP substrates (e.g. rosuvastatin, prazosin, glyburide, sulfasalazine) and P-gp substrates (e.g. digoxin, dabigatran etexilate, verapamil) may increase their exposure. If pretomanid is co-administered with substrates of OATP1B3, BCRP or P-gp, monitoring for drug-related adverse reactions to the co-administered medicinal product should be performed

					5.3 Preclinical safety data […] In addition, in a 2-year carcinogenicity study in rats, pretomanid resulted in an increased incidence of cataracts at 10 mg/kg/day, resulting in an exposure in the same range as at the MRHD. The clinical relevance of this finding is unknown. […] In a 2-year study in rats, an increased incidence of Leydig cell adenomas was observed at a dose of 10 mg/kg/day. The observation is likely of limited relevance to humans." For more information, please refer to the Summary of Product Characteristics.
R/0005	Renewal of the marketing authorisation.	22/04/2021	17/06/2021		
IAIN/0006/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites	17/03/2021	17/06/2021	Annex II and PL	
IB/0003	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	08/02/2021	17/06/2021	SmPC	
T/0002	Transfer of Marketing Authorisation	20/11/2020	14/01/2021	SmPC,	

				Labelling and PL	
IAIN/0001	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	13/11/2020	11/01/2021	SmPC, Labelling and PL	