Dapivirine Vaginal Ring 25 mg

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
PSUV/0019	Periodic Safety Update	01/09/2022	n/a		PRAC Recommendation - maintenance
II/0015/G	This was an application for a group of variations. Submission of the four addenda from studies IPM 032, MTN-025, IPM 007 and MTN-015 listed as	01/09/2022	n/a		The Scientific Opinion Holder (SOH) has submitted four addenda for studies IPM 032, MTN-025, IPM 007 and MTN-015, concerning the results of retrospective next generation sequencing (NGS) and phenotype susceptibility

[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).

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	category 3 studies in the RMP. The data presented in the addenda are the results of retrospective next generation sequencing (NGS) and phenotype susceptibility testing on blood samples to further assess the potential development of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in women with unrecognized or acute HIV-1 infection. The tested samples are all from women who were initially enrolled in the Phase III clinical trials IPM 027 and MTN-020 and then had the option to participate in the open-label extension (OLE) studies IPM 032 and MTN-025. If the women became infected with HIV during any of the trials, they could enroll in the observational studies IPM 007 and MTN-015. The RMP version 0.9 has also been submitted. Additionally, the MAH would like to take the opportunity to update the EMA on other commitments outlined in the RMP as additional risk minimization measures. These include the development of a Healthcare Professional Guide (HCP Guide) and a User Guide with agreed objectives and key messages. 1is recommended for approval. 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 C.I.13 - Other variations not specifically covered				testing on blood samples to further assess the potential development of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in women with unrecognized or acute HIV-1 infection. Overall, no new insights into resistance development were generated. The addenda showed that NGS genotype in general correlated well with population-based genotyping. The SOH stated that an update of the pharmacodynamic section of the SmPC based on these data was not warranted. This was agreed by the CHMP.

	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				
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/07/2022	n/a		
II/0016	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	23/06/2022		Annex II	
II/0014/G	This was an application for a group of variations. 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	10/06/2022	n/a		
IA/0018/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	24/03/2022	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IA/0017	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	09/02/2022	n/a		
II/0012/G	This was an application for a group of variations. Update of sections 4.5 and 5.2 of the SmPC in order to add drug-drug interaction information with vaginal products (e.g. vaginal miconazole) that are metabolized by CYP and UGT enzymes and to update pharmacokinetic information based on the final study reports of 3 in vitro enzyme/transporter studies evaluating the interactions between dapivirine and transporters (study NPK/0025), dapivirine-miconazole interactions on CYP (study NPK/0026) and UGT enzymes (study NPK/0027). Submission of the final report from study evaluating the impact of dapivirine and miconazole on cellular tight junctions and assessing the impact of miconazole on dapivirine tissue permeability (study NPK/0028). These 4 in vitro studies were submitted to fulfil post-authorisation measures requested in the initial	09/12/2021		SmPC	Based on the results of the studies, the following paragraphs have been agreed for the SmPC: SmPC Section 4.5 […] Dapivirine inhibited several CYP450 and UGT enzymes (see section 5.2), and therefore there is the potential for drug-drug interactions, specifically in the vaginal tissues, with co-administered vaginal products that are metabolized by these enzymes. Vaginal miconazole […] Under these circumstances miconazole concentrations in vaginal fluids were approximately 6 fold higher and miconazole concentrations in plasma were 4 fold higher following co-administration. While these changes are explained by the inhibitory potential of dapivirine towards the metabolism of miconazole (via CYP3A4), these changes are not considered clinically relevant. During the first few days following co-administration, dapivirine vaginal fluid levels were approximately 2 to 3 fold lower than levels observed in the absence of miconazole. Plasma concentrations of dapivirine did not

	marketing authorisation application assessment report. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority 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				change significantly. The underlying mechanisms are not fully resolved and clinical relevance is unclear. Even so, women should be advised to use additional preventive measures against HIV, when co-treated with vaginal miconazole. SmPC Section 5.2 Biotransformation […] Dapivirine is a substrate of CYP1A1 and CYP3A4 enzymes, but is not a substrate of CYP1A2, CYP1B1, CYP2B6, CYP2C8 or CYP2C19, or of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9 or UGT2B7. […] Dapivirine was not a substrate of drug transporters P-gp, BCRP, MRP1, MRP4, and ENT1 in vitro at concentrations observed in the vaginal fluid and had no inhibitory effects on the activity of these transporters at maximal vaginal concentrations and maximal plasma concentrations. In vitro dapivirine showed varying degrees of inhibition of CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. At maximal plasma concentrations, dapivirine is not an inhibitor of UGT1A1, 1A3, 1A4, 1A6, 1A7, 1A8, 1A9 and 2B7. In vaginal tissue no UGT enzyme activity was detected. Dapivirine was not an inducer via AhR (CYP1A2), CAR (CYP2B6) and PXR (CYP3A4) at 0.3 µM (0.1 µg/mL). For more information, please refer to the Summary of Product Characteristics.
IA/0013/G	This was an application for a group of variations.	14/10/2021	n/a		

	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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites				
II/0011	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/09/2021	n/a		
PSUV/0008	Periodic Safety Update	02/09/2021	n/a		PRAC Recommendation - maintenance
II/0007	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/09/2021	n/a		
IB/0010	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	18/06/2021	n/a		
IA/0009/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	03/05/2021	n/a		

	procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0006	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	24/03/2021	n/a		
II/0003	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	04/02/2021	n/a		
IB/0005	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	01/02/2021	n/a		
IB/0001/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size 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) 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.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	12/01/2021		SmPC	

IB/0004	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/12/2020	n/a		
IA/0002/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.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	09/12/2020	n/a		