Pifeltro

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
WS/2706	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning on Severe cutaneous adverse	05/09/2024		SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

[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).

	reactions (SCARs) and to add "toxic epidermal necrolysis (TEN)" to the list of adverse drug reactions (ADRs) with frequency not known, based on clinical trials, literature and post-marketing safety data. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4. and to implement editorial changes to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0029	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	23/11/2023	n/a		
WS/2553/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a	28/09/2023	n/a		

	starting material/reagent/intermediate for AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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				
R/0027	Renewal of the marketing authorisation.	26/04/2023	07/07/2023	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Pifeltro in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10729 /202208	Periodic Safety Update EU Single assessment - doravirine	16/03/2023	n/a		PRAC Recommendation - maintenance
IA/0026	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	13/12/2022	n/a		
IG/1535	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/10/2022	07/07/2023	SmPC and PL	

WS/2249	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of SmPC based on two non-clinical studies (Study PD011: Assessment of in vitro antiviral activity against HIV-1 Resistant mutant, Y318F, alone and in combination with 12 other NNRTI mutants and Study PD012: In vitro antiviral activity of doravirine (MK-1439) Against a panel of viruses bearing NNRTI resistance-associated Mutations). In addition, the MAH took the opportunity to implement editorial changes in the SmPC and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/07/2022	07/07/2023	SmPC and PL	Based on two non-clinical studies, Section 5.1 of the SmPC has been updated as follows: SmPC new text: Doravirine-resistant strains were selected in cell culture starting from wild-type HIV 1 of different origins and subtypes, as well as NNRTI-resistant HIV 1. Observed emergent amino acid substitutions in RT included: V106A, V106M, V106I, V108I, F227L, F227C, F227I, F227V, H221Y, M230I, L234I, P236L, and Y318F. The V106A, V106M, V108I, H221Y, F227C, M230I, P236L, and Y318F substitutions conferred 3.4-fold to 70-fold reductions in susceptibility to doravirine. Y318F in combination with V106A, V106M, V108I, and F227C conferred greater decreases in susceptibility to doravirine than Y318F alone, which conferred a 10-fold reduction in susceptibility to doravirine. For more information, please refer to the Summary of Product Characteristics.
IG/1514	A.4 - Administrative change - Change in the name 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	21/06/2022	n/a		
PSUSA/10729 /202108	Periodic Safety Update EU Single assessment - doravirine	07/04/2022	n/a		PRAC Recommendation - maintenance
WS/2065	This was an application for a variation following a worksharing procedure according to Article 20 of	24/02/2022	07/04/2022	SmPC, Annex	Please refer to Scientific Discussion 'Delstrigo-H-C-004746/WS2065/0026' and 'Pifeltro-H-C-

	Commission Regulation (EC) No 1234/2008. Extension of indication to include the new indication to the paediatric population weighing at least 35 kgs for PIFELTRO and DELSTRIGO. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3 of the RMP for each product have also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial corrections and to update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II and PL	004747/WS2065/0019'.
IG/1497	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS	28/03/2022	n/a		
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/07/2021	07/04/2022	PL	
PSUSA/10729 /202008	Periodic Safety Update EU Single assessment - doravirine	09/04/2021	n/a		PRAC Recommendation - maintenance
IG/1352	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	11/02/2021	n/a		

	(excluding manufacturer for batch release)				
WS/1983/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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.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.e.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supportive data	21/01/2021	n/a		
PSUSA/10729 /202002	Periodic Safety Update EU Single assessment - doravirine	01/10/2020	n/a		PRAC Recommendation - maintenance
IAIN/0014	B.II.g.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supporting data	18/06/2020	n/a		
IA/0012/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	25/03/2020	n/a		

	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier				
PSUSA/10729 /201908	Periodic Safety Update EU Single assessment - doravirine	12/03/2020	n/a		PRAC Recommendation - maintenance
II/0010/G	This was an application for a group of variations. B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.I.e.3 - Deletion of an approved change management protocol related to the AS	05/03/2020	n/a		
IB/0011/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.e.5.a - Implementation of changes foreseen in an approved change management protocol - Requires no further supportive data	07/02/2020	n/a		
IB/0008	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/11/2019	08/04/2020	SmPC, Annex II and Labelling	
PSUSA/10729 /201902	Periodic Safety Update EU Single assessment - doravirine	03/10/2019	n/a		PRAC Recommendation - maintenance

IB/0007	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/09/2019	08/04/2020	SmPC and PL	
IG/1108	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)	31/05/2019	n/a		
II/0003	Update of section 5.1 of the SmPC in order to reflect the week-96 results from studies P021, a phase 3 multicenter, double-blind, randomized active comparator-controlled clinical trial to evaluate the safety and efficacy of doravirine/ /lamivudine/ tenofovir disoproxil fumarate once daily compared with efavirenz/emtricitabine/tenofovir disoproxil fumarate once daily in treatment-naïve HIV-1 infected patients, as well as the study P018, a phase 3 multicenter, double-blind, randomized, active-comparator-controlled trial to evaluate the safety, efficacy, and pharmacokinetics of doravirine compared with ritonavir-boosted darunavir, each given in combination with emtricitabine/ tenofovir disoproxil fumarate or abacavir/lamivudine, in treatment-naïve HIV-1 infected patients. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/04/2019	08/04/2020	SmPC	No new safety findings are reported as a result of the week-96 CSRs of studies P018 and P021. However, section 5.1 of the SmPC has been updated to include resistance data up to week 96 in protocol defined virologic failure population or at early discontinuation population.

II/0001	Update of sections 4.8 and 5.1 of the SmPC in order to update the efficacy and safety information based on the results from the clinical study P024, a phase III multicenter, open-Label, randomized study to evaluate a switch to doravirine/lamivudine/tenofovir disproxil in virologically suppressed pateints. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity implement editorial changes in the SmPC and Package Leaflet, as well as to update the contact details of the local representative in Portugal in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/02/2019	08/04/2020	SmPC and PL	The efficacy of switching from a baseline regimen consisting of two nucleoside reverse transcriptase inhibitors in combination with a ritonavir- or cobicistat-boosted PI, or cobicistat-boosted elvitegravir, or an NNRTI to Delstrigo was evaluated in a randomized, open-label trial (DRIVE-SHIFT), in virologically-suppressed HIV-1 infected adults. In the DRIVE-SHIFT trial, an immediate switch to Delstrigo was demonstrated to be non-inferior at Week 48 compared to continuation of the baseline regimen at Week 24 as assessed by the proportion of subjects with HIV-1 RNA < 40 copies/mL. Consistent results were seen for the comparison at Study Week 24 in each treatment group. Sections 5.1 of the SmPCs (Delstrigo, Pifeltro) have been updated with this data. The safety evaluation from this switch study did not reveal any new issues as compared to the safety findings in the prior pivotal studies. However, section 4.8 of the SmPC has been updated to include revised adverse reaction based on the Summary of Product Characteristics of 3TC and/or TDF.
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/01/2019	n/a		