Fexinidazole Winthrop

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/0021	Submission of the final report for study DNDi-FEX-09-HAT. This is a phase 3b, open-label study assessing effectiveness, safety and compliance with fexinidazole in patients with human African trypanosomiasis due to T.b. gambiense at any stage. Section 4.2 of the SmPC is updated to allow for the	25/04/2025		SmPC and PL	Based on data emerging from study DNDi-FEX-09-HAT, SmPC section 4.2 and corresponding package leaflet section 3 were updated with language that describes the possibility of treatment being allowed to be carried out at home with supervision by an informed caregiver. Children weighing <35 kg were part of the patient

[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).

	possibility of treatment at home with supervision by an informed caregiver. SmPC section 4.4 is also revised, to remove the stipulation that children with a body weight <35 kg had to be treated in the hospital under strict supervision of trained health staff. The corresponding Package Leaflet section 3 and section 2, respectively, are also revised accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				population in DNDi-FEX-09-HAT and there were no specific compliance or safety issues associated with treatment at home. Therefore, section 4.4 of the SmPC and section 2 of the package leaflet were also revised, to remove the stipulation that children with a body weight <35 kg must be treated in the hospital under strict supervision of trained health staff. For more information, please refer to the Summary of Product Characteristics.
PSUV/0020	Periodic Safety Update	16/01/2025	n/a		PRAC Recommendation - maintenance
II/0018	Update of sections 4.5 and 5.2 of the SmPC in order to update information regarding the interaction with CYP3A4/3A5 drugs based mainly on final results from study INT17144; this is an open-label, non-randomized, two-treatment, one-sequence crossover pharmacokinetic interaction study of 5-day repeated oral doses of fexinidazole on a single oral dose of midazolam used as probe substrate for CYP3A4 in healthy male and female participants. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2024		SmPC	The SmPC of Fexinidazole Winthrop was updated to • Add the potential of induction of CYP3A4/3A5 in vitro, • Remove the predicted risk of interaction by CYP3A4 inhibition in vivo, • Add the clinical interaction data of fexinidazole on midazolam and the risk of interaction by induction on drugs highly metabolized by CYP3A4/3A5 and, • Add a statement to describe how to manage fexinidazole coadministration with such drugs, i.e., monitor for lack of efficacy". For more information, please refer to the Summary of Product Characteristics.
II/0017	Update of sections 4.2, 4.3, 4.4 and 5.2 of the SmPC in order to add PK information in participants with mild and moderate hepatic impairment based on final	25/07/2024		SmPC and PL	As a result of this variation sections 4.2, 4.3, 4.4 and 5.2 of the SmPC were updated in order to add PK information on participants with mild and moderate hepatic impairment

	results from study POP17145 - A multicentric, open-label, non-randomized, pharmacokinetic and tolerability study of fexinidazole given as an oral single 1200 mg dose in participants with mild and moderate hepatic impairment, and in matched participants with normal hepatic function. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				based on final results from study POP17145. Section 2 of the Package Leaflet (PL) was updated accordingly. For more information, please refer to the Summary of Product Characteristics.
IA/0019	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	19/07/2024	n/a		
II/0016	Extension of indication to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei rhodesiense for Fexinidazole Winthrop based on final results from study DNDI-FEX-07-HAT. As a consequence, sections 4.1, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP version 3.1 has been approved. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan.	14/12/2023		SmPC and PL	Please refer to Scientific Discussion Fexinidazole Winthrop/H/W/002320/II/0016

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0015/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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	23/05/2023	n/a		
T/0014	Transfer of Marketing Authorisation	22/12/2022		SmPC, Labelling and PL	
II/0010	Update of section 4.4 of the SmPC in order to add a new warning on severe irreversible hepatotoxicity in patients with Cockayne syndrome based on case reports and literature reviews; the Package Leaflet is	23/06/2022		SmPC and PL	Based on review of the Sanofi global PV database, worldwide scientific literature, main reference PV textbooks, and biological plausibility of metronidazole, the available cumulative evidence is sufficient to support a

	updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				causal association between fexinidazole and irreversible hepatotoxicity/acute liver failure in patients with Cockayne syndrome. Section 4.4 of the SmPC was updated to include the following new text: "Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, another nitroimidazole agent structurally related to fexinidazole, have been reported in patients with Cockayne syndrome. In this population, fexinidazole should therefore be used only if no adequate alternative treatment is available. Patients treated with fexinidazole, and suffering from Cockayne syndrome should be hospitalized in order to allow close monitoring and stop treatment if necessary." For more information, please refer to the Summary of Product Characteristics.
IAIN/0013/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	13/06/2022		SmPC	
IA/0012	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	06/05/2022	n/a		

	manufacturer of a novel excipient				
IA/0011	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	06/05/2022	n/a		
IA/0009	A.7 - Administrative change - Deletion of manufacturing sites	15/03/2022		Annex II and PL	
PSUV/0008	Periodic Safety Update	16/12/2021	n/a		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0008.
PSUV/0005	Periodic Safety Update	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0007	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)	31/05/2021		SmPC	SmPC was updated to reflect extension of the shelf life of the finished product from 48 months to 60 months.
IAIN/0006/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	23/04/2021		Annex II and PL	
PSUV/0004	Periodic Safety Update	26/11/2020	n/a		PRAC Recommendation - maintenance

IB/0003	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)	25/05/2020		SmPC, Labelling and PL	
II/0002	Update of section 4.5 of the SmPC with data on pharmacokinetic interactions, based on results obtained from five in vitro pharmacokinetics study reports and the Drug Drug Interaction phase I study (INT15307), the latter mentioned in the RMP as "other study" in post-opinion development plan. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/03/2020		SmPC	The reports for the 5 in vitro drug interaction studies and the in vivo interaction study are submitted within this variation application. Based on the new study results, modifications of the current approved SmPC have been identified. As a result of this variation, sections 4.5 and 5.2 of the SmPC are being updated in order to incorporate the observed and predicted data on drug metabolism and risk of drug interactions.
PSUV/0001	Periodic Safety Update	28/11/2019	n/a		PRAC Recommendation - maintenance