Fintepla

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
PSUSA/10907 /202406	Periodic Safety Update EU Single assessment - fenfluramine	30/01/2025	24/03/2025	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10907/202406.
II/0029/G	This was an application for a group of variations. B.I.b.1.g - Change in the specification parameters	20/03/2025	n/a		

[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).

	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.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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.z - Quality change - Active substance - Other variation				
II/0030	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/03/2025		SmPC	
II/0025	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	13/02/2025		SmPC and PL	Update of section 4.8 of the SmPC in order to propose a combined Adverse Drug Reaction table for Dravet Syndrome and Lennox-Gastaut syndrome. For more information, please refer to the Summary of Product Characteristics.
II/0024	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	13/02/2025		SmPC and PL	

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
IA/0031/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/12/2024	n/a		
IB/0026/G	This was an application for a group of variations. 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 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.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	26/07/2024	n/a		
II/0022/G	This was an application for a group of variations. A grouped C.I.4: application comprised of three Type	25/07/2024	24/03/2025	SmPC, Labelling and	Update of sections 4.4 and 4.8 to modify the list of adverse drug reactions based on a revised safety ADR methodology for Dravet and Lennox-Gastaut syndromes, which includes

	II variations, as follows: Update of sections 4.4 and 4.8 of the SmPC in order to modify the list of adverse drug reactions based on a revised safety ADR methodology for Dravet and Lennox-Gastaut syndromes, which includes pooled analyses encompassing studies ZX008-1503 and ZX008-1601 cohort B. The Package Leaflet is updated accordingly. Update of section 5.1 of the SmPC in order to update clinical efficacy information for Dravet syndrome based on final results from study ZX008-1503 listed as a category 3 study in the RMP. This is an open-label extension trial to assess the long-term safety of ZX008 (fenfluramine hydrochloride) oral solution as an adjunctive therapy in children and young adults with Dravet syndrome. Update of section 5.1 of the SmPC in order to update clinical efficacy information for Lennox-Gastaut syndrome based on final results from study ZX008-1601 Part 1 cohort B and interim results for study ZX008-1601 Part 2 cohort B. Study 1601 Part 1 was an international, randomized, double-blind, parallel-group, placebo-controlled study in subjects with LGS 2 to 35 years of age, while study 1601 Part 2 is a long-term, open-label, flexible-dose extension for subjects who completed study 1601 Part 1. The RMP version 3.1 was also agreed. In addition, the MAH took the opportunity to introduce minor			PL	pooled analyses encompassing studies ZX008-1503 and ZX008-1601 cohort B. Update of section 5.1 to update clinical efficacy information for Dravet syndrome based on final results from study ZX008-1503 listed as a category 3 study in the RMP. Update of section 5.1 to update clinical efficacy information for Lennox-Gastaut syndrome based on final results from study ZX008-1601 Part 1 cohort B and interim results for study ZX008-1601 Part 2 cohort B.

	changes to the Product Information, including to section 4.2 of the SmPC. 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				
IAIN/0023/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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	03/05/2024	n/a		
PSUSA/10907 /202306	Periodic Safety Update EU Single assessment - fenfluramine	25/01/2024	19/03/2024	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10907/202306.
II/0018	Update of sections 4.8 and 5.1 of the SmPC in order to update the summary of the safety profile and list of adverse drug reactions for Dravet Syndrome and to update clinical efficacy information, following the	31/08/2023	19/03/2024	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

	assessment of the Article 46 procedure LEG/009 based on final results from Study 3 (Study 1501/1502 Part 2). The Package Leaflet is updated accordingly. In addition, editorial updates and corrections were implemented in the Product Information. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				
II/0017	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	31/08/2023	n/a		
II/0015	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2023	25/08/2023	SmPC	SmPC new text For more information, please refer to the Summary of Product Characteristics.
PSUSA/10907 /202212	Periodic Safety Update EU Single assessment - fenfluramine	06/07/2023	n/a		PRAC Recommendation - maintenance
T/0020	Transfer of Marketing Authorisation	24/03/2023	12/04/2023	SmPC, Labelling and PL	
II/0012	Extension of indication to include treatment of seizures associated with Lennox-Gastaut syndrome	15/12/2022	24/01/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Fintepla-H-C-003933-II-0012'

	as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The due date of the final PASS Registry report as approved in the procedure EMEA/H/C/PSP/S/0093.3 has been reflected in Annex II. Version 2.11 of the RMP has also been agreed. The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0011/G	This was an application for a group of variations. - Update of section 4.2 and 5.2 of the SmPC to include the relevant information regarding patients with renal impairment following the study 1902 (Pharmacokinetic study of fenfluramine hydrochloride in subjects with varying degrees of impaired and normal renal function). - Update of section 4.4, 4.5 of the SmPC in order to reflect the relevant information on CYP1A2 or CYP2B6 or CYP2D6 inducers following the study 1904 (Pharmacokinetic drug-drug interaction study of fenfluramine hydrochloride with and without fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor) and rifampin (CYP2B6 inducer) in healthy subjects).	17/11/2022	23/01/2023	SmPC	Based on the available data, it is agreed that renal impairment has a limited effect on fenfluramine and norfenfluramine exposure that is not expected to be clinically significant. No dose adjustment is recommended when ZX008 is administered to patients with mild to severe renal impairment however a slower titration may be considered and if adverse reactions are reported, a dose reduction may be needed. No dose adjustment is recommended when ZX008 is co-administered with strong inhibitors of CYP1A2, CYP2B6, and CYP2D6 enzymes. A dose increase of ZX008 may be considered up to twice the maximum daily dose when ZX008 is administered with strong CYP1A2 or CYP2B6 inducers. See the updated Product Information for additional

	As requested, the recommendation of gastric lavage was also removed from section 4.9 of the SmPC. The RMP version 2.5 has been agreed. 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				information.
PSUSA/10907 /202206	Periodic Safety Update EU Single assessment - fenfluramine	12/01/2023	n/a		PRAC Recommendation - maintenance
PSUSA/10907 /202112	Periodic Safety Update EU Single assessment - fenfluramine	07/07/2022	n/a		PRAC Recommendation - maintenance
II/0010/G	This was an application for a group of variations. - Update of section 5.3 of the SmPC in order to update the non-clinical information following the study 20147822 (A 6-month Carcinogenicity Study of Fenfluramine Hydrochloride in Mice). - Update of section 5.3 in order to update the non-clinical information following the study 8001993 (A 2-year Oral Gavage Carcinogenicity Study of Fenfluramine Hydrochloride in Rats). - Submission of the final report of Study 20147821 (Dose range finding study for 20147822). - Submission of the final report of Study 20166554 (Dose range finding study for 20147822). - Submission of the final report of Study 2021006-	07/07/2022	23/01/2023	SmPC	No new toxic effects were observed in rats or mice in studies of longer duration compared to the already approved non-clinical dossier for Fintepla, including cardiac toxicity. No carcinogenic potential was observed in mice and rats. It appears that fenfluramine and norfenfluramine does not bind to melanin, and thus the risk of dermal-, ocular- and phototoxicity is limited.

	Z001-01 (In-vitro Evaluation of Potential Melanin Binding by Fenfluramine and Norfenfluramine). An RMP version 2.4 has also been agreed. 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 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				
IAIN/0014	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	27/06/2022	n/a		
IB/0009/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/03/2022	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/10907 /202106	Periodic Safety Update EU Single assessment - fenfluramine	13/01/2022	n/a		PRAC Recommendation - maintenance
II/0002	Update of section 4.2 of the SmPC to reduce the potential for confusion of the posology instructions by removing the dosing tables. This change is based on the inconsistencies found between the hand calculations and the values in the dosing tables following unsolicited comments from doctors and a recommendation from Zogenix Advisory Board. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	13/06/2022	SmPC	The individual dosing instructions for different weights are removed from Section 4.2 of the SmPC. However, a graphic summary of complex dosing with side by side comparison of stiripentol use or not is included to help the health personnel to minimize number of possible mistakes. For more information, please refer to the Summary of Product Characteristics.
IB/0007	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	08/09/2021	n/a		
IA/0006/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	18/08/2021	n/a		

IB/0003/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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	03/08/2021	n/a		
IAIN/0004/G	This was an application for a group of variations. 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 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	12/07/2021	n/a		
IA/0001	Deletion of manufacturer responsible for batch release of the finished product. A.7 - Administrative change - Deletion of manufacturing sites	28/05/2021	13/06/2022	Annex II and PL	