Summary of risk management plan for Fintepla (fenfluramine)

This is a summary of the risk management plan (RMP) for Fintepla. The RMP details important risks of Fintepla, how these risks can be minimised, and how more information will be obtained about Fintepla's risks and uncertainties (missing information).

Fintepla's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Fintepla should be used.

This summary of the RMP for Fintepla should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Fintepla's RMP.

I. The medicine and what it is used for

Fintepla is authorised for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other antiepileptic medicines for patients 2 years of age and older (see SmPC for the full indication). It contains fenfluramine as the active substance and it is given by mouth.

Further information about the evaluation of Fintepla's benefits can be found in Fintepla's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/fintepla.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Fintepla, together with measures to minimise such risks and the proposed studies for learning more about Fintepla's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Fintepla, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety updated report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Fintepla is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Fintepla are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Fintepla. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Valvular heart disease Pulmonary arterial hypertension Suicidal ideation and behaviour Growth retardation
Missing information	Long-term use in Patients with Dravet syndrome Off-label use (in wider paediatric epilepsies; obesity) Use in patients with renal impairment Use in patients with hepatic impairment

II.B Summary of important risks

Important identified risk: None	
Important potential risk: Valvular heart disease	
Evidence for linking the risk to the medicine	Based on historical experience with fenfluramine use in obese adults, in which valvular heart disease was reported.
Risk factors and risk groups	Patients with pre-existing valvular heart disease.
Risk minimisation measures	Routine risk minimisation measures - SmPC sections 4.3, 4.4 and 4.8 - PL sections 2 and 4 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures - Guide for healthcare professionals - Patient/carer guide - CAP
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: - ZX008-1503: 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 - A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine - A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome. - A Drug Utilisation Study of Fenfluramine In Europe.
Important potential risk: Pulmonary arterial hypertension	
Evidence for linking the risk to the medicine	Based on historical experience of fenfluramine use in obese adults, in which pulmonary arterial hypertension was reported.

Risk factors and risk groups	Patients with pulmonary hypertension. Diseases associated with an increased risk of PAH include connective tissue disorders, cirrhosis of the liver, HIV infection, schistosomiasis, chronic obstructive pulmonary disease, interstitial lung disease, left heart disease including congestive heart failure, and congenital heart diseases (atrial septal defect, ventricular septal defect). Several factors may be responsible for the disease; these include stimulation of 5-HT1B, 5-HT2B or 5-HT2A receptors, nitric oxide deficiency, oestrogen, and mutations in the BMPR2 gene
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.3, 4.4 - PL sections 2, 4 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: - Guide for healthcare professionals - Patient/carer guide - CAP
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: - ZX008-1503: 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 - A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine - A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome. - A Drug Utilisation Study of Fenfluramine In Europe.
Important potential risk: Suicidal ideation and behaviour	
Evidence for linking the risk to the medicine	Based on data from studies showing that epilepsy increases the risk for suicidal thoughts and ideation, and AEDs increase the risk of suicidal thoughts in people with epilepsy.
Risk factors and risk groups	Psychiatric illness is one of the risk factors for suicidal ideation and behaviour in the general population. The risk and benefit of treatment with fenfluramine should be carefully weighed for patients with a history of depression and/or suicidal ideation or behaviour.
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.4 - PL section 2 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: - ZX008-1503: 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.

Important potential risk: Growth retardation	
Evidence for linking the risk to the medicine	Based on data from studies showing that fenfluramine can cause weight reduction which can impact physiological growth.
Risk factors and risk groups	Patients in the target population with a significant history of nutritional or growth problems or those treated with concurrent medications known to cause appetite or weight loss
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.2, 4.4 and 4.8 - PL section 2 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities (See section II.C of this summary for an overview of the post-authorisation development plan).	Additional pharmacovigilance activities: - A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine
Missing information: Long-term safety in Dravet syndrome patients	
Risk minimisation measures	Routine risk minimisation measures: - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - ZX008-1503: 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 - A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine
Missing information: Off-label use (in wider paediatric epilepsies; obesity)	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.1, 4.2, 4.4 - PL sections 1, 2 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: - CAP to address potential off-label use for weight management
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - A Drug Utilisation Study of Fenfluramine In Europe - A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome.
Missing information: Use of patients with renal impairment	

Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.2, 5.2 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - ZX008-1902: A Phase 1, Open-Label, Single-Dose, Adaptive, Multipart Study to Evaluate the Effects of Renal Impairment on the Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects with Varying Degrees of Impaired and Normal Renal Function
Missing information: Use of patients with hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.2, 5.2 - Legal status: prescription only medicine, restricted medical prescription Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: - A Phase 1, Open-Label, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects With Varying Degrees of Hepatic Impairment

Abbreviations: AED=Anti-epileptic drug; BMPR2=Bone Morphogenetic Protein Receptor Type 2; HIV=human immunodeficiency virus

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine
Purpose of the study:
This observational registry will provide data to further assess the long-term safety of fenfluramine as prescribed in routine practice in patients with Dravet Syndrome, with a focus on characterising and quantifying the important potential risks of valvular heart disease and pulmonary arterial hypertension. In addition, the registry will provide data to characterise and quantify the important potential risk of growth retardation. Moreover, the data collected on the frequency of echocardiographic monitoring will also contribute to assess the effectiveness of risk minimisation measures.

II.C.2 Other studies in post-authorisation development plan

ZX008-1503: **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**
Purpose of the study:
This study will provide data to further assess the long-term safety of fenfluramine in patients with Dravet syndrome, with a focus on characterising decreased weight, VHD, PAH, and suicidal ideation and behaviour.

ZX008-1902: A Phase 1, Open-Label, Single-Dose, Adaptive, Multipart Study to Evaluate The Effects of Renal Impairment on the Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects with Varying Degrees of Impaired and Normal Renal Function
Purpose of the study:

This study will provide data to characterise the effect of varying degrees of renal impairment on the PK of fenfluramine.

Study ZX008-1903: A Phase 1, Open-Label, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ZX008 (Fenfluramine Hydrochloride) in Subjects With Varying Degrees of Hepatic Impairment

Purpose of the study:

This study will provide data to characterise the effect of varying degrees of hepatic impairment on the PK of fenfluramine.

A drug utilisation study of fenfluramine in Europe

Purpose of the study:

This observational study will provide data to further characterise the use of fenfluramine in routine practice, with a focus on potential off-label use in children younger than two years, in other rare paediatric epilepsies and in obesity. Data on the extent and frequency echocardiographic monitoring will also contribute to assess the effectiveness of risk minimisation measures.

A European Study of the Effectiveness of Risk Minimisation Measures for Fenfluramine in Dravet Syndrome

Purpose of the study:

This observational study will assess the effect of these additional risk minimisation measures by describing the awareness, knowledge, and compliance of fenfluramine prescribers to the physician - specific educational material, as well as the distribution of the patient/carer educational material by the physicians.