EU-RISK MANAGEMENT PLAN FOR FINTEPLA (FENFLURAMINE)

2.2MG/ML ORAL SOLUTION

Version 5.0

Date: 10 Jul 2025 20250710-rmp-v5.0 RTN004006

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ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 5.0

Data lock point for this RMP: 30 Nov 2024

Date of final sign off: 10 Jul 2025

Rationale for submitting an updated RMP: To merge corresponding RMP submissions (EMEA/H/C/003933/II/0028 and the Marketing Authorization Renewal) as well as address feedback provided by European Medicine Agency's (EMA's) Pharmacovigilance Risk Assessment committee (PRAC in the frame of CHMP and PRAC Rapporteurs' preliminary joint assessment report/Request for supplementary information (EMA/R/0000256601) regarding renewal of the marketing authorisation assessment report.

Summary of significant changes in this RMP:

- Merged RMP versions 4.1 and 4.3 including:
  - Information merged from v4.1
    - VHD reclassified as Important identified risk
    - Added information from Study ZX008-1601 (EP0214) to Part II
    - Recommendations for post-discontinuation echocardiograms added to routine VHD/PAH risk minimization measures in Part V
    - Details of important identified risks updated for PAH, VHD and suicidal ideation in Part II Module SVII.3.1
  - Information merged from 4.3
    - Added "Incidence of valvulopathy" as primary objective for EP0218 (Part III.2, III.3 and Annex 2)
    - Removed the list of study countries and geographies cited under the subheading "Study design" for EP0218 (Part III.2)
    - Milestones for EP0218 and EP0219 were updated in the applicable modules (Part III, Part V and Part VII) of the RMP
    - Protocols for EP0218 (Protocol Amendment 6.0) and EP0219 (Protocol Amendment 5.1) were updated
    - Updated the targeted questionnaire for valvular heart disease and pulmonary arterial hypertension (Annex 4)
- To implement corrections, as requested from MAA Renewal list of questions:
  - Updated wording regarding post-treatment echocardiograms in Table V-1 as well as added the same verbiage to Table V-2
  - Removed patient/carer handout for off-label use from Table V-2

- Added HCP handout for off-label use to section II.B under ‘Summary of missing information’ (formerly Table VI-4)
- In section II.C.1, corrected that valvular heart disease and pulmonary arterial hypertension are important risks

Other RMP versions under evaluation (if applicable): None

Details of currently approved RMP(s):

Version number: 4.3

Approved with procedure: EMEA/H/C/003933/II/0028

Date of approval (opinion date): 19 Jun 2025

Qualified Person for Pharmacovigilance (QPPV) name: Bart Teeuw

Please see the electronic signature of the EEA QPPV or his deputy on the last page of this report.

LIST OF ABBREVIATIONS

ADHD	attention deficit and hyperactivity disorder
ADR	adverse drug reaction
AE	adverse event
AED	anti-epileptic drug
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
BMI	body mass index
BMPR2	bone morphogenetic protein receptor type 2
CAP	controlled access programme
cATU	cohort temporary authorization for use
CBD	cannabidiol
CDC	Centers for Disease Control
CLB	clobazam
CNS	central nervous system
C-SSRS	Columbia-suicide severity rating scale
CWM	Cincinnati water maze
CYP	cytochrome P450
DDI	drug-drug interaction
DLP	data lock point
EAP	expanded access programme
ECHO	echocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
f.	former
GLP	good laboratory practice
GTC	generalized tonic-clonic
HCP	healthcare professional
IBD	international birth date
IDN	identification number
ISS	integrated summary of safety
LGS	Lennox-Gastaut syndrome
LTS	long term safety
MAOI	monoamine oxidase inhibitor

MedDRA	Medical Dictionary for Regulatory Activities
NEJM	New England journal of medicine
OLE	open-label extension
PAH	pulmonary arterial hypertension
PK	pharmacokinetics
PL	package leaflet
PRAC	pharmacovigilance risk assessment committee
PSUR	periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
REMS	risk evaluation and mitigation strategy
RMP	risk management plan
SBA	summary basis of approval
SE	status epilepticus
SERT	serotonin transporter
SmPC	summary of product characteristics
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy
THC	tetrahydrocannabinol
US	United States
VHD	valvular heart disease
VPA	valproate
WHO	World Health Organization
ZAP	Zogenix access program
ZDC	Zogenix distribution centre

PART I PRODUCT(S) OVERVIEW

Table Part I–1: Product overview

Active substance(s)	Fenfluramine
Pharmacotherapeutic group(s)	N03AX26
Marketing Authorization Holder	UCB Pharma S.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Fintepla
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class**: Serotonin releasing agent
	Summary of mode of action: fenfluramine is a serotonin releasing agent, and thereby stimulates multiple 5-HT receptor sub-types through the release of serotonin. Fenfluramine may reduce seizures by acting as an agonist at specific serotonin receptors in the brain, including the 5-HT_{1D}, 5-HT_{2A}, and 5-HT_{2C} receptors, and also by acting on the sigma-1 receptor. The precise mode of action of fenfluramine in Dravet syndrome and Lennox-Gastaut Syndrome is unknown.
	Important information about its composition: Fintepla does not contain any novel excipients, or excipients of animal or human origin. Each mL contains 2.2mg of fenfluramine (as fenfluramine hydrochloride). Excipients with known effect include glucose (maize) 0.627mg/mL, sodium ethyl para-hydroxybenzoate (E215) 0.23mg/mL, sodium methyl para-hydroxybenzoate (E219) 2.3mg/mL and sulfur dioxide (E220) 0.000009mg/mL. Additional excipients include sucralose (E955), hydroxyethylcellulose (E1525), monosodium phosphate (E 339), disodium phosphate (E339), cherry flavouring powder, potassium citrate (E332), citric acid monohydrate (E330), and water for injection.
Hyperlink to the Product Information	Module 1.3.1 SmPC, Labelling and Package Leaflet.
Indication(s) in the EEA	**Current**: Treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other antiepileptic medicines in patients 2 years-of-age and older.
	Proposed: Not applicable
Dosage in the EEA	**Current:**

Table Part I–1: Product overview

Posology

Paediatric (children aged 2 years and older) and adult populations

Table 1: Dosage recommendations for Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS)

<table>
<tr><td></td><td colspan="2"><u>without concomitant</u> stiripentol*</td><td colspan="2"><u>with concomitant</u> stiripentol (DS patients only)</td></tr>
<tr><td></td><td><u>Weight based dosage</u>++</td><td><u>Maximal recommended daily dose</u></td><td><u>Weight based dosage</u>++</td><td><u>Maximal recommended daily dose</u></td></tr>
<tr><td>Day 0 (Starting dose)+</td><td>0.1 mg/kg taken twice daily</td><td rowspan="3">26 mg
(13 mg twice daily i.e. 6.0 mL twice daily)</td><td>0.1 mg/kg taken twice daily</td><td rowspan="3">17 mg
(8.6 mg twice daily i.e. 4.0 mL twice daily)</td></tr>
<tr><td>Day 7</td><td>0.2 mg/kg twice daily</td><td>Maintenance dose
0.2 mg/kg twice daily</td></tr>
<tr><td>Day 14 **</td><td>0.35 mg/kg twice daily</td><td>Not applicable</td></tr>
</table>

*For patients not on concomitant stiripentol requiring more rapid titration, the dose may be increased every 4 days.

+For patients with Dravet syndrome, dosage may be increased based on clinical response to the maximum recommended dosage, as needed.

**For patients with Lennox-Gastaut syndrome, dosage should be increased as tolerated to the recommended maintenance dosage (i.e., Day 14)

++To calculate the dose volume up to the maximal recommended dose, you must use the formula:

Weight (kg) x Weight-based dosage (mg/kg) ÷ 2.2 mg/mL = mL dose to be taken **twice daily**

The calculated dose should be rounded to the nearest graduated increment.

If the calculated dose is 3.0 mL or less, the green printed 3 mL syringe should be used.

If the calculated dose is more than 3.0 mL, the purple printed 6 mL syringe should be used.

The table below must only be used as a check on the calculated dose volume. Table 2 does **not replace** the requirement to calculate the specific dose volume.

Table Part I–1: Product overview

Table 2: Range of dose volumes in mL for calculation check

	Dosing without concomitant STP*			Dosing with concomitant STP**	
Weight category	**Starting dose**	**Day 7-13**	**Day 14 and further**	**Starting dose**	**Day 7 and further**
	0.1 mg/kg twice daily	0.2 mg/kg twice daily	0.35 mg/kg twice daily	0.1 mg/kg twice daily	0.2 mg/kg twice daily
3-5 kg	0.2-0.3 mL	0.3-0.5 mL	0.5-0.8 mL	0.2-0.3 mL	0.3-0.5 mL
5-7 kg	0.3-0.4 mL	0.5-0.7 mL	0.8-1.2 mL	0.3-0.4 mL	0.5-0.7 mL
7-10 kg	0.4-0.5 mL	0.7-1 mL	1.2-1.6 mL	0.4-0.5 mL	0.7-1 mL
10-15 kg	0.5-0.7 mL	1-1.4 mL	1.6-2.4 mL	0.5-0.7 mL	1-1.4 mL
15-20 kg	0.7-1 mL	1.4-1.9 mL	2.4-3.2 mL	0.7-1 mL	1.4-1.9 mL
20-30 kg	1-1.4 mL	1.9-2.8 mL	3.2-4.8 mL	1-1.4 mL	1.9-2.8 mL
30-38 kg	1.4-1.8 mL	2.8-3.5 mL	4.8-6 mL (maximum dose)	1.4-1.8 mL	2.8-3.5 mL
38-43 kg	1.8-2 mL	3.5-4 mL	6 mL (maximum dose)	1.8-2 mL	3.5-4 mL (maximum dose)
43-55 kg	2-2.5 mL	4-5 mL	6 mL (maximum dose)	2-2.5 mL	4 mL (maximum dose)
55-65 kg	2.5-3 mL	5-6 mL (maximum dose)	6 mL (maximum dose)	2.5-3 mL	4 mL (maximum dose)

Table Part I–1: Product overview

65-86 kg	3-4 mL	6 mL (maximum dose)	6 mL (maximum dose)	3-4 mL (maximum dose)	4 mL (maximum dose)
86-130 kg	4-6 mL (maximum dose)	6 mL (maximum dose)	6 mL (maximum dose)	4 mL (maximum dose)	4 mL (maximum dose)

*Without concomitant STP: The maximum dose 13 mg twice daily corresponds to 6 mL twice daily.

**With concomitant STP: The maximum dose of 8.6 mg twice daily corresponds to 4 mL twice daily.

Discontinuation of treatment

When discontinuing treatment, the dose should be decreased gradually. As with all anti-epileptic medicines, abrupt discontinuation should be avoided when possible to minimize the risk of increased seizure frequency and status epilepticus. A final echocardiogram should be conducted 3-6 months after the last dose of treatment with fenfluramine.

Special populations

Patients with renal impairment

Generally, no dose adjustment is recommended when Fintepla is administered to patients with mild to severe renal impairment, however, a slower titration may be considered. If adverse reactions are reported, a dose reduction may be needed.

Fintepla has not been studied in patients with end-stage renal disease. It is not known if fenfluramine or its active metabolite, norfenfluramine, is dialyzable.

There are no specific clinical data on the use of Fintepla with stiripentol in patients with impaired renal function. Fintepla is therefore not recommended for use in patients with impaired renal function treated with stiripentol.

Patients with hepatic impairment

Generally, no dose adjustment is recommended when Fintepla is administered without concomitant stiripentol to patients with mild and moderate hepatic impairment (Child-Pugh Class A and B). In patients with severe hepatic impairment (Child-Pugh C) not receiving concomitant stiripentol, the maximum dosage for these patients is 0.2 mg/kg twice daily, and the maximal total daily dose is 17 mg.

There are limited clinical data on the use of Fintepla with stiripentol in patients with mild impaired hepatic function. A slower titration may be considered in patients with hepatic impairment. If adverse reactions are reported, a dose reduction may be needed.

There are no clinical data on the use of Fintepla with stiripentol in patients with moderate and severe impaired hepatic function. Fintepla is therefore not recommended for use in patients with moderate and severe hepatic impairment treated with stiripentol.

Proposed: Not applicable

Table Part I–1: Product overview

Pharmaceutical form(s) and strength(s)	**Current**: Dosage form - Oral solution. Strength - Each mL contains 2.2mg of fenfluramine (as 2.5mg fenfluramine hydrochloride). Each bottle contains 60mL, 120mL, 250mL or 360mL of fenfluramine oral solution.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

EA=European Economic Area; EU: European Union; RMP=Risk Management Plan; DS=Dravet syndrome; LGS=Lennox-Gastaut syndrome; STP=Stiripentol

PART II SAFETY SPECIFICATION

Part II Module SI Epidemiology of the indication(s) and target population(s)

SI.1 Dravet syndrome

SI.1.1 Incidence

The incidence of Dravet syndrome is estimated to range from 1 in 20,000 to 1 in 40,000 (Hurst, 1990; Dravet, 2011). Research suggests it may affect 1 out of every 15,700 live births in the United States (US) (Wu et al, 2015). In the European Union (EU), Dravet syndrome has been reported to affect fewer than 1 in 20,000 people (EMA, 2014), although most experts agree that the incidence is likely the same regardless of region, race, and ethnicity. Dravet syndrome is responsible for 7% of the severe epilepsies starting before the age of 3 years (Ceulemans et al, 2004).

SI.1.2 Prevalence

In Dec 2001, Diacomit® (stiripentol) (STP), was granted Orphan designation by the European Medicines Agency (EMA) for the treatment of Dravet syndrome (EU designation: EU/3/01/071). According to information submitted by the Sponsor at the time of submission (2001), the estimated number of persons affected with Dravet syndrome in the EU was 15,000 based on the population of the EU at that time, of 377,000,000 (source: Eurostat http://ec.europa.eu/eurostat.en, 2001) i.e., 0.4 cases per 10,000 of the population.

In 2013, at the time of submission of the application for orphan drug designation for fenfluramine, a literature search of the Embase and MEDLINE databases, using the search term "Dravet[ti] AND (incidence[ti] OR prevalence[ti])" failed to identify any new European publications since 2007 (the date when an updated public summary of Orphan designation for Dravet syndrome was published [EMEA/COMP/269/04 for stiripentol]). It was therefore justified, at that time, to assume that, based on no new evidence to the contrary being made available, the prevalence of Dravet syndrome in the EU was unchanged. Only 3 additional European prevalence sources regarding Dravet syndrome specifically, were identified since 2013 (the date when a public summary of Orphan designation for fenfluramine was published (EMA/COMP/700717/2013). These sources are summarised in Table Part II–1 below.

In Sep 2019, the Committee for Orphan Medicinal Products assessed the orphan designation for Epidiolex® and the prevalence was confirmed as 0.11 per 10,000 people.

Table Part II–1: Summary of Prevalence Data on Dravet Syndrome Identified Post 2013

Prevalence Source	Region	Years	Prevalence of Dravet syndrome per 10,000 of population
Rosander and Hallbook, 2015	Sweden	2007-2011	0.2
Syvertsen et al, 2017	Norway	1999-2014	0.1

Table Part II–1: Summary of Prevalence Data on Dravet Syndrome Identified Post 2013

Prevalence Source	Region	Years	Prevalence of Dravet syndrome per 10,000 of population
Gil-Nagel et al, 2019	Spain	2016-2017	0.1

Therefore, the prevalence of Dravet syndrome in the EU remains no higher than 0.5 per 10,000 of the population, as per the initial fenfluramine Orphan designation, and based on the current population of the EU (EU 28, Norway, Iceland and Lichtenstein) of 513,500,000 (source: Eurostat, Jan 2019), the disease affects no more than 25,675 persons in the EU.

SI.1.3 Demographics of the population in the authorised indication and risk factors for the disease

The diagnosis of Dravet syndrome is based on clinical signs and symptoms, though the presence of a mutation in the SCN1A gene is considered a likely, though not definitive, marker for the disorder (Dravet, 2011; Fujiwara, 2006; Zuberi et al, 2022); approximately 80-90% of patients with Dravet syndrome have a SCN1A mutation.

Dravet syndrome is characterized by medically intractable seizures. Onset of the first seizure typically occurs in the first year of life (usually at 5 to 8 months of age) in otherwise healthy infants and most often consists of prolonged, unilateral or generalized, clonic seizures provoked by fever (Orphanet, 2014; Ceulemans et al, 2004; Dravet, 2011). Patients will have poor response or worsening seizures to standard anti-epileptic drugs (AEDs), in particular, sodium channel antagonist medications (Dravet, 2011). There is a preponderance in boys of about 67% (Dravet, 2011).

SI.1.4 The main existing treatment options

The treatment strategy for Dravet syndrome is focused on 3 main principles: (1) prevention of hyperthermia-induced febrile seizures triggered by core body temperatures above 37°C; (2) use of adequate rescue treatment with benzodiazepines to prevent long-lasting status epilepticus (SE); and (3), maintenance therapy with AEDs to minimize the frequency and duration of all seizure types (Schoonjans, 2016). Treatment for Dravet syndrome involves finding the best combination of medicines to treat seizures with tolerable side effects, prevent seizure related emergencies, and to lessen mortality risk. Elimination, or significant reduction, of prolonged convulsive seizures and SE should represent the highest priority in treatment (Wirrell et al, 2017; Wirrell et al, 2022).

Diacomit® (stiripentol) (STP) has been approved for many years in Canada, EU, and Japan and was more recently approved in the US to treat seizures associated with Dravet syndrome. Stiripentol must be co administered with clobazam (CLB) (US label) or CLB and valproate (VPA) (ex-US labels). The clinical basis for approval for STP comes from 2 small randomized, placebo-controlled studies each conducted in a single country (STICLO France, N=41; STICLO-Italy, N=23) and a number of longer-term uncontrolled open-label studies (Thanh et al, 2002; Wirrell et al, 2013; Inoue and Ohtsuka, 2015; De Liso et al, 2016). The

2 placebo-controlled studies compared an 8-week treatment duration to baseline and demonstrated a statistically significant reduction in seizure frequency for subjects on STP compared to those on placebo. Importantly, STP can significantly impact plasma concentrations of other AEDs, most notably CLB. In these trials, the placebo group received a dose of CLB on the lower end of what is most commonly used in clinical practice and thus may have been inadequately or sub-optimally treated by this dose of CLB alone. Stiripentol elevates levels of norclobazam (an active metabolite of CLB), which may have contributed to efficacy in the STP groups and theoretically could have potentially overestimated the true benefit of STP. The most common adverse reactions, occurring in at least 10% of STP-treated patients and more frequently than on placebo, included somnolence (67%), decreased appetite (45%), agitation (27%), ataxia (27%), weight decreased (27%), hypotonia (24%), nausea (15%), tremor (15%), dysarthria (12%), and insomnia (12%). In addition, STP can cause a significant decline in neutrophil and platelet counts, and hematologic testing should be obtained prior to starting treatment with STP, and then every 6 months.

A second treatment option for seizures associated with Dravet syndrome, Epidiolex® (cannabidiol; CBD) was approved by the US FDA in June 2018, while Epidiolex® was granted marketing authorization in EU by the European Commission on 19 Sep 2019 (http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-receives-european-commission-approval). Of note, in EU Epidiolex® must be co-administered with clobazam. The approval of Epidiolex® followed 3 randomized, controlled, Phase 3 trials, incorporating data from 714 patients with either Dravet or Lennox-Gastaut syndrome. The most common adverse events (>10% frequency) in the cannabidiol group were somnolence, decreased appetite, diarrhea, pyrexia, fatigue, and vomiting. Cannabidiol was reported to cause dose-related elevations of liver transaminases, especially when prescribed with VPA, that requires periodic monitoring. Transaminase elevation was the most frequent cause of discontinuation.

Other therapies, topiramate, levetiracetam, and bromide, may provide efficacy as adjunctive therapy for some patients (Chiron, 2011). Published uncontrolled studies with levetiracetam (Striano et al, 2007), verapamil (Iannetti et al, 2009), ketogenic diet (Caraballo, 2011a; Caraballo et al, 2011b), deep brain stimulation (Andrade et al, 2010), and vagal nerve stimulation (Zamponi et al, 2011) show infrequent clinically meaningful improvement. Commonly prescribed anticonvulsant medications including sodium channel antagonists such as phenytoin and carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, and high doses of intravenous phenobarbital should be avoided because they often exacerbate seizures in Dravet syndrome and are thus not useful (Sazgar and Bourgeois, 2005; Wirrell, 2016; de Lange et al, 2018). Rescue medications (clonazepam, diazepam, lorazepam, and midazolam, etc) are often used to stop prolonged seizures that may evolve to SE and require emergency intervention.

Adverse drug reactions are common with chronic use of all AEDs for seizure control in patients with Dravet syndrome. From a safety perspective, achieving balance between a meaningful reduction in seizures and minimizing treatment-related adverse effects is a main goal of treatment (Wirrell et al, 2017). New treatment options, which maximize efficacy, while maintaining a favorable safety and tolerability profile continue to be a major unmet need in this patient population.

SI.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Dravet syndrome is characterized by medically intractable seizures. Onset of the first seizure typically occurs in the first year of life (usually at 5-8 months of age) in otherwise healthy infants and most often consists of prolonged, unilateral or generalized, clonic seizure provoked by fever (Orphanet, 2014; Dravet, 2011; Ceulemans et al, 2004).

After the first year, other types of seizures often begin to occur with high frequency and include (Dravet 2011):

- Convulsive seizures consisting of generalized clonic seizures, generalized tonic-clonic (GTC) seizures or alternating unilateral clonic seizures (in the youngest patients, they often evolve into SE)
- Myoclonic seizures (appearing between the ages of 1 and 5 years)
- Atypical absences (appearing at different ages between 4 months and 6 years, or later)
- Focal seizures with or without secondary generalization (appearing between the ages of 4 months and 4 years)
- Rarely, tonic seizures

Individuals with Dravet syndrome are at higher risk for SE that often results in hospitalization (Ceulemans et al, 2004). A high incidence for sudden expected death in epilepsy (SUDEP) exists in Dravet syndrome compared with other epilepsies. A known major risk factor for SUDEP is the frequency of uncontrolled GTC seizures, ie, the higher the frequency of uncontrolled GTC seizures, the higher the SUDEP risk (Harden et al, 2017).

SI.1.6 Important co-morbidities

In addition to the intractable seizures that define Dravet syndrome, the condition has wide-ranging comorbidities including hypotonia, speech delay, temperature dysregulation, nocturnal seizures, autistic traits, sleep issues, some psychiatric issues, and frequent infections (Wirrell et al, 2017; Villas et al, 2017; Gataullina and Dulac, 2017; Vial et al, 1992). Patients with Dravet syndrome also experience a progressive disturbance in cerebral function that leads to significant impairment of psychomotor, behavioral, and neurological development (Dravet, 2011). Developmental delay and stagnation usually become apparent within the second year of life and are followed by cognitive impairment and neurobehavioral disorders, often including autistic-like behavior and attention deficit hyperactivity disorder. The degree of cognitive impairment and other neurologic co-morbidities appear to correlate, at least partially, with the frequency of uncontrolled seizures and have been hypothesized to occur because of repeated cerebral hypoxia and possibly neuroinflammation associated with seizures (Acha et al, 2015); the refractory seizures are especially deleterious to the brain during the critical developmental periods of infancy and childhood. Given the high seizure burden and associated comorbidities, most patients with Dravet syndrome require continuous support. The majority of subjects who survive to adulthood are wholly dependent on round-the-clock caregivers and most eventually end-up living in institutional care homes.

SI.2 Lennox-Gastaut syndrome

SI.2.1 Incidence

The incidence of Lennox-Gastaut syndrome (LGS) is estimated to range from 0.1 to 0.28 per 100,000, with a greater frequency amongst males (Amrutkar and Riel-Romero, 2023; Trevathan et al, 1997). In children, the incidence is estimated as 2 per 100,000, with LGS accounting for 1-2% of all epilepsies and 2-5% of all childhood epilepsies (Amrutkar and Riel-Romero, 2023; Heiskala, 1997).

SI.2.2 Prevalence

The European prevalence sources used by the sponsor, in 2004, are summarized below in Table Part II–2. Five studies were identified as reporting prevalence rates of LGS. The prevalence was 0.9 per 10,000 population across all age groups and 0.7, 1 and 2 in age groups between 0 and 19 years.

Table Part II–2: Summary of European Prevalence Data on LGS used for the Designation of Rufinamide as an Orphan Medicinal Product - EU/3/04/240

Prevalence Source	Region	Years	Age Range (years)	Point prevalence (per 10,000)
Sidenvall et al, 1996	Sweden	1985	0 - 16	2.0
Eriksson and Koivikko, 1997	Finland	1992	0 - 15	0.7
Waaler et al, 2000	Norway	1994-1996	6 - 12	2.1
Olafsson and Hauser, 1999	Iceland	1993	All ages	0.9
Beilmann et al, 1999	Estonia	1995-1997	1 month – 19	1.0

LGS=Lennox-Gastaut syndrome

Only 2 additional European prevalence sources, regarding LGS specifically, were identified since 2004 (the date when a public summary of orphan designation for rufinamide was published [EMEA/122307/2004 Rev.1]) (Table Part II–3). It was therefore concluded, in 2016, that the prevalence of LGS in Europe remained no higher than 2 per 10,000 population as per the rufinamide orphan designation and was likely in the range of 1.0 to 2.0 per 10,000 population.

Table Part II–3: Summary of European Prevalence Data on LGS Identified Post 2004

Prevalence Source	Region	Years	Age Range (years)	Point prevalence (per 10,000)
Syvertsen et al, 2015	Norway	1999-2014	All ages	0.3

Table Part II–3: Summary of European Prevalence Data on LGS Identified Post 2004

Prevalence Source	Region	Years	Age Range (years)	Point prevalence (per 10,000)
Orphanet, 2016	EU	2016	All ages	1.5

LGS=Lennox-Gastaut syndrome

In 2021, to support this report on the maintenance of designation criteria for fenfluramine hydrochloride in LGS, literature searches were conducted using BIOSIS Previews®, Embase® and MEDLINE® databases and the following search string (Ti,ab,if,su(("lennox gastaut") and (incidence or prevalence))) and (pd(20170101-20210831) NOT rtype.exact("Conference Abstract" OR "Meeting Abstract")), using the dates of 2017 to 2021 to ascertain whether the prevalence of LGS had changed since 2017 (the date when a public summary of orphan designation for fenfluramine hydrochloride was published (EMA/71973/2017).

Three additional European prevalence sources, regarding LGS specifically, were identified. These sources are summarized in Table Part II–4.

Table Part II–4: Summary of European Prevalence Data on LGS Identified Post 2017

Prevalence Source	Region	Years	Age Range (years)	Point prevalence (per 10,000)
Strzelczyk et al, 2020	Germany	2016	All ages	0.65[a] 3.92[b]
Chin et al, 2021	UK	2017	All ages	0.29*[c] 0.42*[d] 0.58*[e]
Orphanet, 2021	EU	2021	All ages	1.5

LGS=Lennox-Gastaut syndrome
[a] Probable LGS narrowly defined (≥1 ICD-10 diagnosis of epilepsy / status epilepticus before their 6th birthday and ≥ 1 claim of RUF/FLB)
[b] Probable LGS broadly defined (≥1 ICD-10 diagnosis of epilepsy / status epilepticus and ≥ 1 claim of RUF/FLB); *1 year period prevalence reported
[c] Confirmed LGS diagnosis
[d] Probable LGS (ICD-10/Read Code for Epilepsy and at least 1 prescription of RUF within a year of diagnosis)
[e] Full cohort: Confirmed + probable LGS

The estimated number of persons affected with LGS in the EU, was 46,000 - 92,000 according to the orphan drug application submitted to EMA by Eisai Limited. This fell within the EU orphan designation prevalence limit of not more than 5 in 10,000 (EMA, 2007).

SI.2.3 Demographics of the population in the proposed indication and risk factors for the disease

Lennox-Gastaut syndrome is a rare, pediatric-onset developmental and epileptic encephalopathy, “a condition in which the epileptic activity itself may directly contribute additional cognitive and behavioral impairments over those expected from the underlying etiology alone and that

suppression of epileptic activity might minimize this additional impairment" (Scheffer et al, 2017). The diagnosis of LGS includes clinical signs combined with typical electroencephalogram features associated with LGS. The clinical presentation of LGS is heterogeneous. Onset of LGS occurs most commonly before the age of 11 years, with a peak between 3 and 5 years of age (Arzimanoglou et al, 2009; Hancock and Cross, 2013; Specchio et al, 2022). Patients with LGS account for 5% to 10% of children with seizures (Panayiotopoulos, 2005). Nearly all patients with LGS have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: approximately 5% of patients die, 80% to 90% continue having seizures into adulthood, and most patients have cognitive and behavioral problems (Panayiotopoulos, 2005). Children and adults with LGS have an enormous disruptive impact on their families, and efforts to improve the quality of life for these patients are complex due to the severe lifelong limitations associated with drug-resistant epilepsy, intellectual disability, and other comorbidities (Camfield et al, 2014).

SI.2.4 The main existing treatment options

The main existing treatment options for LGS includes antiepileptic drugs. Apart from fenfluramine, there are currently 7 antiepileptic drug products approved for the treatment of LGS in the US: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, and cannabidiol; 9 antiepileptic drugs approved for the treatment of LGS in Europe: felbamate, topiramate, lamotrigine, rufinamide, clonazepam, clobazam, valproate, nitrazepam, and cannabidiol; and 2 antiepileptic drugs approved in Japan for the treatment of LGS: lamotrigine and rufinamide. Other pharmacologic (eg, benzodiazepines, zonisamide, levetiracetam, brivaracetam) and nonpharmacologic treatments (eg, ketogenic diet, vagus nerve stimulation, corpus callosotomy, resective surgery) also are prescribed based on clinical experience. The use of carbamazepine, oxcarbazepine, eslicarbazepine, tiagabine, and phenytoin in LGS is not recommended due to the potential risk of aggravation of drop attacks with a myoclonic component (Cross et al, 2017).

Because patients with LGS experience a range of different seizure types and underlying etiologies, the condition is notoriously difficult to treat (Arzimanoglou et al, 2009; Cross et al, 2017), and seizures in LGS are usually not fully controlled with currently available antiepileptic drug treatments (Hancock and Cross, 2013). Initial treatment for LGS is usually monotherapy with 1 of the currently approved AEDs. If this is not successful, which is the most common case, a second agent is usually added, although some physicians will prescribe the second drug as monotherapy (Wheless et al, 2007; Arzimanoglou et al, 2009). The treatment of LGS frequently requires a combination of 2 or more AEDs with an individualized regimen; seizure control is suboptimal in most patients in the clinical population. The recommendation is to attempt to use drugs that have different mechanisms of action and the least amount of interaction with one another. After lack of response to 2 or more AEDs, nonpharmacological treatments such as ketogenic diet, vagus nerve stimulation, or surgery may be considered. A treatment that has been shown to be effective in certain common seizure types cannot be assumed to be effective in patients with LGS to treat that seizure type.

SI.2.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Lennox-Gastaut syndrome is a severe and complex epileptic encephalopathy. Lennox-Gastaut syndrome is considered by experts to be a "catastrophic epilepsy" (Camfield and Camfield, 2002; Shields, 2000) because of the inability to control seizures with anti-epileptic drugs

(AEDs), the likelihood of injury from falls related to seizures, and intellectual impairment in >90% of patients, all leading to significant psychosocial effects with poor long-term prognosis. In the setting of rare complete seizure freedom, behavioural and psychiatric disorders are nearly always present, language is frequently affected, and mental and psychiatric disorders tend to worsen with time (Hancock and Cross, 2013).

Nearly all patients with LGS have treatment-resistant, lifelong epilepsy. Prognosis for LGS is very poor: 5% of patients die prematurely, 80% to 90% continue having seizures into adulthood, and most have cognitive and behavioural problems (Panayiotopoulos 2005).

Unsurprisingly, LGS is associated with extensive healthcare utilization and poorly quantified but likely substantial indirect cost burdens related to under-/unemployment, sleep, stress, social relationships, and mental health, in addition to the significant burden to the patients' caregivers (Reaven et al, 2018; Story et al, 2018).

The impact of LGS on the family is emotionally, physically, and potentially financially devastating. Parents/caregivers suffer emotional and psychological stress due to the constant waiting for the next seizure to occur, fear of SUDEP, arranging 24/7 patient care, sleep deprivation, isolation, guilt, grief, and numerous other burdens taken on, including physical injuries as a result of seizures or aggressive behaviors (Berg et al, 2019).

Due to the heterogeneity in etiology, pathophysiology, and type of seizures experienced by patients with LGS, many different treatments are currently tried (Verotti et al, 2018), often with little success and a high rate of drug resistance. There has yet to be evidence of high efficacy for any single AED, nor data to assert the superiority of 1 drug over another (Hancock and Cross, 2013). Due to the refractory nature of seizures in LGS, seizure freedom is an unlikely goal of treatment; a main objective is to improve the patient's quality of life via a compromise between seizure control of the most severe seizures, avoidance of additional comorbidities, and tolerability (Cross et al, 2017).

SI.2.6 Important comorbidities

Many children with LGS also develop behavioral problems such as inattention, anxiety, hyperactivity, aggression, psychosis, and depression. Hyperactivity, insecurity, psychosis, aggression, hypokinesia, and autism spectrum disorders are present in approximately 50% of patients with LGS (Verrotti et al, 2018, Strzelczyk et al, 2021, Mastrangelo 2017, Asadi-Pooya 2018). Some develop autistic features and most require specialized educational settings (Crumrine 2011; Arzimanoglou et al, 2009). These comorbidities are considered to be, at least in part, due to sequelae of repeated brain insult from poorly treated seizures. Most children have developmental impairment that predates seizure onset in LGS, but developmental stagnation or decline can occur with onset of frequent seizures. Less commonly, development and behavior may be normal at seizure onset (Specchio et al, 2022).

The behavioral and cognitive impairment associated with LGS may be the hardest features of this condition to cope with for many families (Hancock and Cross, 2013).

Part II Module SII Nonclinical part of the safety specification

The non-clinical program conducted by legacy Zogenix included the following completed good laboratory practice (GLP)-compliant studies. These studies were conducted with fenfluramine HCl, once daily oral administration frequency:

- Juvenile toxicity studies in rats
- Repeat dose toxicity studies in mice, rats, and dogs
- Genetic toxicity studies
- Carcinogenicity studies in mice and rats
- Developmental and reproductive toxicity studies in rats and rabbits

The juvenile and repeat-dose toxicity studies, and the carcinogenicity studies, included histopathology of the brain and the heart valves (aortic and mitral) to examine the potential for neuro- and cardiotoxicity.

In addition to the results from the toxicity studies conducted by legacy Zogenix, non-clinical toxicity data on fenfluramine or dexfenfluramine from the Pondimin SBA and the Redux SBA, as well as from studies available from the published literature, are summarised below in Table Part II–5.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
Toxicity	**Single and Repeat-Dose Studies** Non-GLP single- and repeat-dose toxicity studies were conducted with fenfluramine and summarised in Gilbert, 1971. These studies showed that the primary immediate effects of fenfluramine are decreased food consumption and decreased body weight gain at lower doses and CNS-related clinical observations at higher doses. At higher doses, behavioural changes, including tremors, piloerection and decreased locomotion were observed. Acutely, death occurs because of respiratory arrest and cardiac ischaemia (Hunsinger, 1990). At lower, chronic doses, the primary effect observed in mice, rats, dogs and monkeys is decreased food consumption and decreased body weight gain. • Mice Two repeat-dose toxicity studies in mice were conducted by legacy Zogenix. These studies in CByB6F1 hybrid mice were dose range finding studies for the definitive 6-month carcinogenicity	The nature of the findings observed in studies with Pondimin, including decreased food consumption and decreased body weight, were consistent with the known pharmacology of fenfluramine. In general, the animal toxicity profile was similar to that seen in humans. The results from the legacy Zogenix conducted studies indicated that the non-clinical safety profile of fenfluramine is consistent with the toxicity data in the published literature. Fenfluramine induces primary pharmacodynamic-related early effects of decreased food consumption and decreased body weight gain.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	study in CByB6F1/Tg rasH2 hemizygous (transgenic) mice. A non-GLP 14-day repeat-dose toxicity study was conducted at dose levels of 0 , 40, 80, 120 and 140mg/kg/day in CByB6F1 hybrid mice. Dose-related moribundity resulted in early death/unscheduled euthanasia (designated as mortality) at ≥ 120mg/kg/day in males and ≥ 80mg/kg/day in females. Poor or variable body weight gains or losses were observed at ≥ 40mg/kg/day in males through Day 14 and ≥ 80mg/kg/day in females through Day 8. Clinical pathology changes included increased neutrophils at ≥ 80mg/kg/day in females only; decreased white blood cell counts and red blood cell mass at ≥80mg/kg/day in males and ≥120mg/kg/day in females; Target organ effects were observed at Day 15 termination in the thymus, pancreas, and liver at ≥ 40mg/kg/day reaching a level of adversity in the thymus only at ≥ 80mg/kg/day. Based on the study results, the NOAEL was considered to be 40mg/kg/day. A GLP 28-day repeat-dose toxicity study was conducted at dose levels of 0, 10 , 20, and 40mg/kg/day in CByB6F1 hybrid mice . Fenfluramine HCl was well tolerated at all dose levels and the NOAEL was considered to be 40mg/kg/day, administered as a single dose of 40mg/kg/day or as 2 doses of 20mg/kg/dose. • **Rats** Two repeat-dose toxicity studies in rat were conducted by legacy Zogenix. There were no fenfluramine HCl-related microscopic changes in the brain or cardiac valves (both mitral and aortic) in both studies. In a GLP 13-week repeat-dose toxicity at dose levels of 0, 3.5, 5.0, 8.0, 13, and 20 mg/kg/day, fenfluramine HCl was well tolerated at all dose levels and the NOAEL was identified as 20mg/kg/day. In a GLP 26-week repeat-dose toxicity study in rats at doses of 0, 3.5, 5.0, 8.0, 13 and 20mg/kg/day, fenfluramine HCl was well-tolerated at all dose levels. There were significant lower body weights and body weight gain with correlated lower food consumption.	While decreased body weight and decreased food consumption were the intended effect in adults being treated for obesity, chronic decreased body weight/food consumption in pediatric patients may lead to long-term negative effects.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	The body weight/appetite effects were consistent with the known pharmacological activity of fenfluramine and considered non-adverse. The NOAEL was identified as 20mg/kg/day. • **Dogs** A GLP 43-week repeat-dose toxicity was conducted in 7 dose groups, intended dose levels were 0,2.5, 5, 10, 20, 30 and 50mg/kg/day. All animals in the last 3 groups were given a dosing holiday starting on Day 2 due to presence of clinical observations after having been dosed on Day 1. After the first dose the animals in the last 3 dose groups were subsequently dosed at 15, 20, 25mg/kg/day, respectively. Fenfluramine HCl-related clinical observations in male and female dogs included soft feces, dilated pupils, uncoordinated, and decreased activity, salivation, tremors, splayed hind limbs, vocalization, panting, hyperactivity and convulsions (non-sustained or sustained, only on the first day of dosing). These findings subsided during the recovery period but were not completely resolved at the end of the recovery period. There were adverse clinical findings such as thin appearance and convulsions at ≥ 15 mg/kg/day. In addition, lower mean body weight was noted and was considered adverse at ≥ 25 mg/kg/day. Therefore, the NOAEL was considered as 10mg/kg/day. There were no fenfluramine HCl-related microscopic changes in the brain or cardiac valves (both mitral and aortic) in mice, rats and dogs.	
Genetic Toxicity Studies	Legacy Zogenix conducted GLP in-vitro and in-vivo genotoxicity studies. Fenfluramine HCl was not found to be mutagenic in a bacterial mutation assay or genotoxic in micronucleus and comet assay in rats.	The data from these studies suggest that fenfluramine is unlikely to be a genotoxic risk to humans.
Carcinogenicity	Two carcinogenicity studies in mice and rat with fenfluramine HCl were conducted by legacy Zogenix. A GLP 6-month carcinogenicity study in Tg.rasH2 mice was conducted at dose levels of 0, 10/5, 20/15, 40 and 60mg/kg/day. Animals in Groups 2 and 3 were dosed at 10 mg/kg/day and	Non-clinical data revealed no special hazard for humans based on conventional carcinogenic studies.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	20mg/kg/day, respectively, from Days 1 to 14. As per recommendation from the US FDA, the dose levels for Groups 2 and 3 were lowered to 5mg/kg/day and 15mg/kg/day, respectively, beginning on Day 15. A GLP 2-year carcinogenicity study in rats at dose levels of 0, 1, 2.5, and 8mg/kg/day was also conducted. No carcinogenic effects related to fenfluramine HCl were found in the mice at doses up to 60mg/kg/day and rats at doses up to 8mg/kg/day. There was no evidence of macroscopic or microscopic adverse histopathological changes in brain or the aortic and mitral valves in these carcinogenicity studies in mice and rats.	
Reproductive and Developmental Studies	Legacy Zogenix conducted the full battery of GLP DART studies, including a fertility and early embryo-fetal development study in rats, embryo-fetal development studies in rats and rabbits, and a pre- and post-natal development study in rats. All findings of potential concern identified DART studies occurred at fenfluramine HCl dose levels that were also associated with maternal and/or paternal toxicity. The findings primarily manifested as decreased food consumption and subsequent significant decreased body weight and/or decreased body weight gains. In addition, the clinical observations in rats included piloerection, dehydration, hunched posture and chromodacryorrhea, decreased motor activity, vocalisation, hyperreactivity to touch, tachypnoea, clonic convulsions, salvation and pale extremities. In rabbits, the clinical observations included tremors, convulsions, dilated pupils, increased respiratory rate and laboured breathing. • **Fertility and early embryonic development to implantation study in rats** In the GLP fertility and early embryonic development to implantation study both male and female rats were dosed at 0, 3.5, 8 or 20mg/kg/day. The clinical signs (eg, dehydration and clonic convulsions at 20mg/kg/day),	Reproductive and developmental studies conducted in experimental animals with fenfluramine identified fetal mortality and embryo-fetal abnormalities; however, these were at exposure levels that are not considered clinically relevant and that were associated with maternal toxicity. The findings associated with toxicity in animals are not clinically relevant. Importantly, controlled clinical trials in which pregnant women were exposed to fenfluramine did not reveal evidence for risk to offspring (Vial 1992; Jones 2002). The safety profile of fenfluramine has been well characterised due to its extensive use in the past as an appetite suppressant in adults (Orphanet Physicians' Desk Reference 1998). The doses studied in the ZX008 programme are 2 to 4 times lower than those prescribed in the past to treat adult obesity.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	decreased food consumption, and adversely decreased body weight gain and body weight loss at 8 and 20mg/kg/day were noted in both males and females during the premating and gestational phases, with effects on fertility and reproductive outcome including reduction in viable embryos, implantation sites, and increased pre- and post-implantation losses. Findings as related to fertility were noted in males and females at 20mg/kg/day. There were increases in abnormal sperm morphology and epididymal vacuolation at 20mg/kg/day, however, there were no effects on sperm count or motility, and the vacuolation was not associated with degeneration. There also was no correlation of the morphology findings and vacuolation, nor were either correlated with the decreased fertility index. Thus, the fertility findings were attributed to effects in the females occurring at a maternally toxic dose. Based on the findings, 8 mg/kg/day was identified as the NOAEL for mating and fertility in males, while 3.5 mg/kg/day was established as the NOAEL for mating, fertility, and early embryonic development in females. • **Embryo-Fetal Development in Rats** A GLP embryo-foetal development study was conducted at dose levels 0 , 5, 10 or 40mg/kg/day. There were reduced food consumption and body weight gain or body weight loss at ≥10mg/kg/day. Increases in malformations occurred at 40mg/kg/day. Reduced fetal body weights and an increased incidence of malrotated hindlimb and cleft palate were noted at 40mg/kg/day. The effects on the fetus occurred at a maternally toxic dose. The maternal NOAEL was considered as 5mg/kg/day. The developmental NOAEL was considered as 10mg/kg/day. • **Embryo-Fetal Development in Rabbits** A GLP embryo-foetal development study was conducted at dose levels 0, 5, 10 or 15mg/kg/day. There were decreased food consumption and reduced body weight gain and body weight loss at all doses and post-implantation loses at all doses. There were no fenfluramine HCl-related external, visceral, or skeletal malformations or	An additional independent review of clinical safety (Scialli, 2020) similarly concluded that the incidence of malformations in dexfenfluramine or fenfluramine was not above background rates. The potentially beneficial effects of fenfluramine in patients outweighs the findings from animal studies of DART effects in pediatric and adult patients.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	variations. Based on the significant maternal body weight loss and reduction in food consumption at all dose levels, the maternal NOAEL was not identified. • **Developmental and Perinatal/Postnatal Reproduction in Rats** A GLP-compliant developmental and perinatal/postnatal reproduction study was conducted at dose levels of 0 , 5, 10 or 40mg/kg/day. The clinical signs (eg, piloerection, dehydration) were noted at 40mg/kg/day with adverse reductions in food consumption and decreased body weight gains or body weight loss and adverse effects on the offspring occurring at the same dose. Viability of F1 pups was affected at 40mg/kg/day, with a significant increase in the percentage of dams with stillborn pups, mean number of stillborn pups and the total percentage of stillborn pups. The effects on the F1 pup occurred at a maternally toxic dose. There were no effects on reproductive function in the F1 generation. Based on the substantial weight loss and reduced food consumption observed at 40mg/kg/day, the maternal NOAEL was considered as 10mg/kg/day. Based on the decreased F1 pup viability at 40mg/kg/day, the F1 NOAEL for this study was considered as 10mg/kg/day.	
Juvenile Toxicity Studies	Two juvenile toxicity studies in rats were conducted by legacy Zogenix • **Dose Range study** A GLP dose range finding 7-day study in juvenile rats (PND 7 through 13) conducted at dose levels of 0 , 25, 50 and 100mg/kg/day, primary effects were reductions in body weight gain and food consumption at all doses, with CNS-related clinical findings (tremor, incoordination, decreased activity, piloerection, abnormal gait, and head tilt) observed at higher doses (≥ 35mg/kg/day) and mortality in 100/50mg/kg/day groups. • **10-week toxicity study** A GLP 10-week study in juvenile rats (PND 7 through 76) was conducted at dose levels of 0, 3.5, 9, and 20mg/kg/day orally. The primary	Juvenile toxicity studies conducted by legacy Zogenix demonstrated that no new target organs were identified in the juvenile animals, and the toxicity profile in the juvenile animals appears similar to that of adults.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	effects were reductions in body weight gain and food consumption, with CNS-related clinical findings (primarily tremor and lack of co-ordination) observed at higher doses (≥ 9mg/kg/day) and mortality at the highest dose (20mg/kg/day). Some errors in learning and memory were noted, as assessed by the CWM and occurred in all dose groups. Based on the clinical observations and mortality at 20mg/kg/day, the NOAEL was identified as 9mg/kg/day. There were no fenfluramine HCl-related microscopic changes in the brain or cardiac valves (both mitral and aortic).	
Safety Pharmacology	Literature based safety pharmacology studies included studies of the central and peripheral nervous system in rats, rabbits, cats, dogs and non-human primates, the cardiovascular system in dogs, and the respiratory, gastrointestinal and genitourinary system in dogs. The results from study conducted by Lewis 1971 in healthy male volunteers, indicated that fenfluramine reduced Rapid Eye Movement sleep and increased the transitions from deep sleep to light slow wave sleep. Similar effects on sleep were found in rats (Fornal 1983a; Fornal 1983b), although fenfluramine increased sleep time in cats (Foxwell 1969) and had no effect on sleep time in non-human primates (Tang 1971). Safety pharmacology studies conducted in rats, rabbits, dogs and cats as part of the Pondimin SBA did not identify any safety concerns on the cardiovascular, CNS, respiratory, gastrointestinal or urogenital systems. Neurobehavioral assessment results in the GLP 10-week juvenile study included a functional observation battery, startle reflex, motor activity, and learning and memory. Changes in neurobehavioral performance included lower body temperatures in animals from all groups, reduced motor activity for males noted across all groups, a decreased incidence of rearing in the arena for males at 20mg/kg/day, and an increased number of errors in performance of the water maze test of learning and memory in males and females at 9 and 20mg/kg/day. These findings	Safety pharmacology studies have not identified any safety concerns.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	were indicative of an excess fenfluramine HCl pharmacological effect in rats administered ≥3.5mg/kg/day and those effects noted at the end of recovery are attributed to a prolonged effect. In the absence of neuropathological effects, the functional differences were not considered adverse (see juvenile toxicity section for additional study information). No fenfluramine HCL-related changes were noted in electrocardiography parameters in the GLP 43-week repeat-dose toxicity study dogs at dose levels up to 50/25 mg/kg/day (see repeat-dose toxicity section for additional study information).	
Other toxicity-related information or data		
Cardiotoxicity	Some in vitro studies have suggested a possible role of serotonin or agonist activity of norfenfluramine in cardiac valve disease [Redux SBA 144590A page 425]. However, in vivo studies using animal models have not been able to reliably demonstrate the effect (Norris 2018). No changes in the mitral or aortic valves were noted in any of the GLP studies conducted by legacy Zogenix, which include 13-, 26- and 43-week repeat dose toxicity study in rats and dogs, 10-week juvenile toxicity study in rats, 6-months and 2-year carcinogenicity studies in mice and rats (see respective sections for additional study information).	Reports of cardiac valve abnormalities associated with use of fenfluramine in adults treated for obesity, mainly when co-prescribed with phentermine, emerged in 1997 and fenfluramine was withdrawn from world-wide markets (Wong, 1998; Centres for Disease Control and Prevention 1997; Connolly, 1997). The exact mechanism of the effect remains poorly understood with the main hypothesis being due to agonism at the 5-HT_{2B} receptor, although this has not been scientifically confirmed. Subsequent controlled investigations reported the rates of VHD were lower than originally reported. The largest controlled investigation (Weissman, 1998; N > 1,000) found rates of aortic regurgitation in patients exposed to dexfenfluramine at 5.4%, vs 3.6% for unexposed (95% confidence interval, 0.9 to 4.4 percentage points), and

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
		mitral regurgitation rates of 1.8% vs 1.2% for unexposed (95% confidence interval, 1.0 to 2.1 percentage points). The mechanism of thickening of heart valves that has been associated with fenfluramine is complex and not well understood. The occurrence of valvulopathy due to treatment with fenfluramine cannot be ruled-out.
Neurotoxicity (neuropathology)	There is a very large and diverse body of literature on the neurotoxicity of fenfluramine. Studies focused on neuropathology show the absence of serotonin as a marker of serotonergic neurons which is consistent with the pharmacological effect of fenfluramine to deplete serotonin. However, this lack of serotonin has been incorrectly interpreted by some researchers to be evidence of destruction of the serotonergic pathway. In fact, it occurs in the absence of traditional markers of neuropathology such as Glial fibrillary acidic protein immunohistochemistry, a marker of activated astrocytes, and silver staining to detect damaged axons. Similarly, the disappearance of the SERT protein as measured by binding or Western blot has been interpreted as destruction of the protein, when, in fact, the protein can relocate from the cell membrane to internal compartments in the cell in response to signaling pathways or the presence of some drugs such as SSRIs. Although 2 animal studies, 1 in neonatal rats (Morford, 2002) and 1 in adult rats (Williams, 2002) suggest), suggest that dexfenfluramine and fenfluramine, respectively, adversely affect learning and memory in the CWM, published studies in humans have shown variable results. Data from the ZX008 (fenfluramine) clinical programme suggest an improvement in some areas of cognition in patients with Dravet syndrome. Together, these data show that fenfluramine is not neurotoxic as measured by appropriate	Studies in humans, including paediatric patients, have shown variable results. In 2 studies conducted in cognitively impaired paediatric patients, 1 found no effect of fenfluramine after daily dosing for 4 weeks (Aman, 1993) while the other reported improved performance after 4 months of treatment (Ho, 1986). Additional studies in adults are inconsistent, with some reporting no effect of fenfluramine on learning and memory tasks while others report decrements in performance. Fenfluramine is not expected to have a negative impact on cognition in humans.

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	neuropathology markers, which consider the pharmacology of fenfluramine and an understanding of the regulatory processes of the SERT protein. Furthermore, animal data show that while fenfluramine may have some effect on learning and memory, that effect seems to be dependent on the specific task and the conditions under which the task is performed. No adverse histopathological findings were noted in the brain in the GLP studies conducted by legacy Zogenix, which include 13-, 26- and 43-week repeat dose toxicity study in rats and dogs, 10-week juvenile toxicity study in rats, 6-months and 2-year carcinogenicity studies in mice and rats (see respective sections for additional study information).	
Pulmonary Arterial Hypertension	Due to a clinical association of fenfluramine with development of PAH in case reports (Abenhaim, 1996; Pouwels, 1990; McMurray, 1986; Douglas, 1981), animal models have been utilised to explore the mechanism of the effect. One possibility is that increased serotonin from pulmonary artery endothelial cells constricts pulmonary artery smooth muscle cells (Maclean, 2010) increasing pulmonary vascular pressure. The hypothesis has been questioned (Zolkowska, 2006) as a dose equivalent to 60mg/day in humans proved too low to produce contraction of pulmonary arteries or adverse pulmonary effects. Alternative hypotheses suggest (+)-norfenfluramine is responsible for vasoconstriction of the pulmonary artery (Hong, 2004; Ni, 2004) or implicated nitric oxide deficiency (Archer, 1998) or oestrogen and the oestrogen metabolising enzyme CYP1B1 (Dempsie, 2013) in the development of the condition**.**	A clinical association of development of PAH after fenfluramine use has been reported in the literature based on several case report publications (Abenhaim, 1996; Pouwels, 1990; McMurray, 1986; Douglas, 1981), though a definitive causative link has been challenging to identify as animal models do not fully account for the human disease (Chan, 2018). Notably, existing relevant studies are either case reports, retrospective studies, or prospective observational in patients diagnosed with PAH. No publication presents baseline pulmonary arterial pressures and/or the presence of other risk factors prior to initiation of therapy and all but 1 (N=15) fails to provide information about the doses of fenfluramine or dexfenfluramine used (Brenot, 1993).

Table Part II–5: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
		While the results of these epidemiological studies seem to support a possible association between anorexic agents and PAH, a definite causative link cannot be concluded from the available clinical data at hand. As the incidence of PAH in the population is extremely low, 2-5 per million (Montani, 2013), better estimates are unlikely to become available.

AE=adverse event; BID=bis in die (twice/day [dosing]); BRIEF=behavior rating instrument of executive function; BRIEF-P=BRIE--preschool; CNS=central nervous system; CWM=Cincinnati water maze; CYP=cytochrome P450; DART=development and reproductive toxicity; F1=first generation; FDA=Food and Drug Administration; FAERS=FDA Adverse Event Reporting System ;GLP=good laboratory practice; ICH=the international council for harmonization of technical requirements for pharmaceuticals for human Use; NOAEL=no observed adverse effect level; PAH=pulmonary arterial hypertension; SBA=summary basis for approval; SSRI=selective serotonin re-uptake inhibitors; VHD=valvular heart disease; WHO=World Health Organization.

Part II Module SIII Clinical trial exposure

Since the Development International Birth Date (15 Feb 2015) until 30 Nov 2024 (the data lock point [DLP] of the EU-RMP), 1189 unique study participants have been randomized in the legacy Zogenix/UCB-sponsored clinical studies with ZX008 (fenfluramine developmental name). Of the 1189 study participants, 350 were adult volunteers who received at least one dose of ZX008 in the Phase 1 studies (ZX008-1505, ZX008-1603, ZX008-1604, ZX008-1803, ZX008-1902, ZX008-1903, and ZX008-1904), including 16 participants with renal impairment (ZX008-1902) and 45 participants with hepatic impairment (ZX008-1903). Of the 1189 total individuals, 696 patients diagnosed with Dravet or LGS received ZX008 in ZX008 studies (ZX008-1501, ZX008-1502, ZX008-1503, ZX008-1504, ZX008-1601, ZX008-1602).

Table Part II–6 provides the estimated cumulative number of participants exposed to investigational medicinal product (fenfluramine), Placebo and Blinded Study Drug in Phase 1-3 clinical studies.

The estimates of cumulative study participant exposure are based on actual exposure data from completed (unblinded or open-label) clinical studies and ongoing open-label clinical studies as well as estimates of exposure in ongoing blinded clinical studies according to enrolment/randomization schemes presented in footnote.

Table Part II–6: Estimated cumulative study participants exposure in fenfluramine Phase 1-3 clinical studies

Treatment	Participants dosed with Fenfluramine	Participants dosed with Placebo	Participants dosed with Blinded Study Drug	Total number of unique Study Participants[c]
Pediatric and Adult Dravet syndrome or LGS	696	230	0	704
Pediatric and Adult CDD	50[b]	0	75[a]	75
Adult volunteers	350	60	0	410
Total number of Study Participants	1096	290	47	1189

CDD=CDKL5 Deficiency Disorder; LGS=Lennox-Gastaut syndrome; STP=stiripentol
Note: A participant can be counted under both fenfluramine and placebo columns if they received both treatments.
Note: Study participants who entered the Expanded Access Program (Study ZX008-1800) are excluded from the clinical exposure calculations. The exposure of these study participants was previously considered in this Section (clinical trial exposure).
[a] 1:1 ratio of Fenfluramine (ZX008) 0.8 mg/kg/day (maximum dose 30 mg/day) (or 0.5 mg/kg/day, maximum 20 m
taking concomitant STP) - placebo.
[b] The study participants from EP0216 Part 1 (double-blind period) who entered the ongoing open-label extension period (Part 2) and received at least 1 dose.
[c] The study participants who received more than 1 treatment are only counted once in the total row.
Cut-off date: 30 Nov 2024

Table Part II–7: Cumulative study participant exposure to investigational drug from completed clinical studies by gender and age group

Number of study participants			
Age range	**Male**	**Female**	**Total**
Infants, <2 years	0	0	0
Children, 2 to <12 years	196	172	368
Adolescents, 12 to <18 years	109	84	193
Adults, 18 to <65 years	300	163	463
Elderly, ≥65 years	18	2	20
Total	623	421	1044

Data from completed clinical trials as of 30 Nov 2024.

Table Part II–8: Cumulative study participant exposure to investigational drug from completed clinical studies by racial/ethnic group

Racial group	Number of study participants
American Indian or Alaskan Native	4
Asian	108
Black	73
Native Hawaiian or Other Pacific Islander	3
White	742
Other or Mixed	31
Not Reported	66
Unknown	10
Missing	7
Total	1044

Data from completed clinical trials as of 30 Nov 2024.

The cumulative patient exposure to fenfluramine from other therapeutic programs (EU Early Access Program [EAP] and US Risk Evaluation and Mitigation Strategy [REMS]) has been presented in section Part II SV.1

Part II Module SIV Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The main exclusion criteria in pivotal clinical studies in Dravet syndrome and LGS within the ZX008 development program are discussed in Table Part II–9. Exclusion criteria applied to ensure standardization of the study population (rather than safety-related exclusion criteria) are not presented.

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Known hypersensitivity to fenfluramine or any of the excipients in the study medication	
Reason for exclusion	Patients who are hypersensitive to any component of the product should not receive fenfluramine on grounds of safety.
Is it considered to be included as missing information?	No
Rationale	Fenfluramine use is contraindicated in patients with hypersensitivity to fenfluramine or any of the excipients.
Existing pulmonary arterial hypertension	
Reason for exclusion	Development of PAH was reported after fenfluramine use in obese adults. Including patients with pre-existing PAH may affect the safety evaluation of fenfluramine and put these patients at risk.
Is it considered to be included as missing information?	No
Rationale	Fenfluramine use is contraindicated in patients with PAH which is considered an important identified risk with fenfluramine.
Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke.	
Reason for exclusion	VHD has been reported to be a complication of fenfluramine administration in obese adults. Including patients with cardiovascular disease may affect the safety evaluation of fenfluramine and put these patients at risk
Is it considered to be included as missing information?	No
Rationale	Fenfluramine use is contraindicated in patients with VHD and is considered an important identified risk with fenfluramine.
Current or recent history of anorexia nervosa or bulimia within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month	
Reason for exclusion	Given the known anorectic effect of fenfluramine, inclusion of patients with anorexia nervosa or bulimia may interfere with the safety evaluation of fenfluramine.
Is it considered to be included as missing information?	No

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Rationale	The anorectic effect of fenfluramine is known and would not be safe to study against a background of anorexia nervosa or bulimia, 2 eating disorders
Imminent risk of self-harm or harm to others; depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month	
Reason for exclusion	Suicidal thoughts and behavior are considered a class-based risk of anti-epileptic medications (FDA, 2008). Including these patients may affect the safety evaluation of fenfluramine
Is it considered to be included as missing information?	No
Rationale	Suicidal ideation and behavior are considered an important potential risk for the class of AEDs.
Current or past history of glaucoma	
Reason for exclusion	Acute angle-closure glaucoma thought to be precipitated by dexfenfluramine was previously reported in a 50-year-old patient with a history of narrow glaucoma angles (Denis et al, 1995). Fenfluramine can cause mydriasis (Kramer et al, 1973). In patients with narrow angles, mydriasis can lead to pupillary block and precipitate acute angle-closure glaucoma (Tripathi et al, 2003). Including these patients may affect the safety evaluation of fenfluramine and put the patients at risk.
Is it considered to be included as missing information?	No
Rationale	Glaucoma is not considered an important risk for the intended patient population. Appropriate warnings are included within the SmPC.
Moderate or severe hepatic impairment	
Reason for exclusion	Fenfluramine is metabolized by the liver and the impact of moderate or severe hepatic impairment on fenfluramine and norfenfluramine exposure was unknown. Including these study participants may interfere with the evaluation of the efficacy and safety of fenfluramine.
Is it considered to be included as missing information?	No

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Rationale	Legacy Zogenix sponsored Study ZX008-1903, investigating the effects of hepatic insufficiency on the pharmacokinetics of fenfluramine. The results from this clinical study indicated that fenfluramine was well tolerated, and no safety issues were identified in subjects with various degrees of hepatic impairment. The SmPC describes appropriately the recommended dosage adjustment, if applicable, depending on level of the hepatic function impairment for patients without concomitant stiripentol. There are no clinical data on the use of Fintepla with stiripentol in patients with moderate and severe impaired hepatic function. Therefore, per SmPC, Fintepla is not recommended for use in patients with moderate and severe hepatic impairment treated with stiripentol.
Concomitant therapy with centrally acting anorectic agents; MAOIs; any centrally acting compound with a clinically appreciable amount of serotonin agonist or antagonist properties, including SRIs; triptans, atomoxetine, or other centrally acting noradrenergic agonists; cyproheptadine, and/or cytochrome P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates	
Reason for exclusion	Including these patients may affect the safety and efficacy evaluation of fenfluramine and put patients at risk, based on the potential for PK and/or pharmacodynamic drug-drug interactions: • Coadministration of fenfluramine, an anorectic agent, with other centrally acting anorectic agents may affect the safety evaluation of fenfluramine • Coadministration of fenfluramine, a serotonin agonist, with other serotonergic drugs increases the risk of serotonin syndrome • Coadministration of fenfluramine, a serotonin agonist, with serotonin antagonists, such as cyproheptadine, may affect the efficacy evaluation of fenfluramine • Fenfluramine and norfenfluramine are inhibitors of CYP2D6 and may induce CYP2B6 and CYP3A4 in vitro. Including patients on concomitant P450 (CYP) 2D6/3A4/2B6 inhibitors/substrates may affect safety and/or efficacy evaluation of fenfluramine
Is it considered to be included as missing information?	No

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Rationale	• Coadministration of fenfluramine with other centrally acting anorectic agents is considered likely to cause an increased risk of anorexia/weight loss. Weight loss should be monitored as recommended in the SmPC. • Coadministration of fenfluramine with MAOIs and other serotonergic agents is proposed to be contraindicated with fenfluramine use, due to the risk of serotonin syndrome. • Coadministration of fenfluramine with cyproheptadine may decrease the efficacy of fenfluramine; however, this is not considered a safety concern. Appropriate language regarding the potential for decreased efficacy is included in the SmPC. • As demonstrated in metabolism studies, at clinically relevant doses of fenfluramine, no effect of fenfluramine or norfenfluramine on the clearance of substrates of any CYP450 enzymes is expected. Based clinical data, PK modelling results, and an exposure-response analysis, dose adjustments of fenfluramine may be required when it is co-administered with single-CYP inhibitors of CYP1A2 or CYP2D6, or with inducers of CYP2B6. There was little or no evidence that fenfluramine or norfluramine were a time-dependent or metabolism-dependent inhibitor of any CYP3A4 enzyme examined. • The results from Study ZX008-1904 that evaluated the effect of fluvoxamine (strong CYP1A2 inhibitor), paroxetine (strong CYP2D6 inhibitor), and rifampin (CYP2B6 inducer) on the PK of fenfluramine and norfenfluramine, showed that the effects of strong inhibitors of CYP1A2 or CYP2D6 on fenfluramine and norfenfluramine PK are not considered clinically significant. Administration of a single dose of fenfluramine with rifampicin (a CYP1A2 and CYP2B6 inducer) decreased plasma concentrations of fenfluramine as compared to fenfluramine administered alone, which will lower the efficacy of fenfluramine. An increase in fenfluramine dose may be necessary when coadministered with a strong CYP1A2 or CYP2B6 inducer. Fenfluramine administered alone and in combination with fluvoxamine, paroxetine, or rifampicin had an acceptable safety profile and was well tolerated by the healthy study participants in the study.

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy	
Reason for exclusion	AEDs with sodium channel antagonist properties are known to be ineffective in treating seizures in Dravet syndrome and may worsen the seizures in some patients. As Dravet syndrome is a clinical diagnosis, patients maintained on sodium channel antagonist AEDs may not be properly diagnosed and for this reason, these products were exclusionary.
Is it considered to be included as missing information?	No
Rationale	Coadministration of these medicines may increase seizures and confound the objectives of the study. Most experts state these medications are contraindicated for the treatment of Dravet syndrome.
Unwilling to refrain from large or daily servings of grapefruits and/or Seville oranges, and their juices beginning with the Baseline Period/Visit 1 and throughout the study	
Reason for exclusion	Potential for drug-food interactions due to inhibition of CYP450 enzymes involved in fenfluramine metabolism.
Is it considered to be included as missing information?	No
Rationale	As demonstrated in metabolism studies, CYP3A4/5 is involved only to a minor extent in fenfluramine metabolism; therefore, grapefruit and/or Seville orange is unlikely to cause a significant change in the clearance of fenfluramine. There are no expected safety concerns in this population.
Positive result on urine THC Panel or whole blood CBD at the Screening Visit/Visit 1	
Reason for exclusion	Tetrahydrocannabinol or CBD was available from a variety of unapproved sources with unknown and possibly inconsistent potency and purity. Inclusion of these patients may affect efficacy and safety evaluation of fenfluramine.
Is it considered to be included as missing information?	No

Table Part II–9: Exclusion criteria in pivotal clinical studies within the development program

Rationale	A DDI study in healthy volunteers was completed after the completion of the Phase 3 studies in Dravet syndrome. This DDI study examined the effect of CBD on the PK profile of fenfluramine and norfenfluramine (Study 1604). The study demonstrated a small increase in exposure to fenfluramine and small decrease in exposure to norfenfluramine; the difference is within the range of exposures observed during the Phase 3 program and is deemed not clinically relevant. This is supported by the exposure-response analysis, which showed that substantially larger changes in fenfluramine exposure would not be expected to have clinically relevant effects on the AE profile. Tetrahydrocannabinol is primarily metabolized by CYP2C9 and CYP3A4, which play a minor role in fenfluramine metabolism. The concomitant use of CBD with fenfluramine does not require a dose adjustment.

AED=anti-epileptic drug; CBD=cannabidiol; CYP=cytochrome (P450); DDI=drug-drug interaction; MAOIs=monoaminoxidase inhibitors; PAH=pulmonary arterial hypertension; PK=pharmacokinetics; SmPC=summary of product characteristics; SRI=serotonin reuptake inhibitor; THC= tetrahydrocannabinol; VHD=valvular heart disease

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rarer adverse reactions (frequency less than 1%), those with a very long latency, or those associated with prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table Part II–10 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table Part II–10: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Children <2 years of age	Fintepla® is currently approved for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older in the US, EU, Great Britain, and Japan. Study EP0213 is an ongoing study that was primarily designed to evaluate safety and tolerability of fenfluramine HCl in infants 1 to <2 years of age with Dravet syndrome.
Elderly	Not included in the clinical development program
Pregnant women	Not included in the clinical development program

Table Part II–10: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Breastfeeding woman	
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with moderate or severe hepatic impairment were not included in the initial clinical development program in order to allow an unbiased assessment of fenfluramine safety, as fenfluramine is metabolized by the liver (Section SIV.1). Asymptomatic study participants with mild hepatic impairment (elevated liver enzymes <3xULN and/or elevated bilirubin <2xULN) were not excluded from the clinical development program. Legacy Zogenix conducted the ZX008-1903 study in study participants with varying degrees of hepatic impairment. The results from this clinical study indicated that ZX008 was well tolerated by all study participants in this study, and no safety issues were identified in study participants with varying degrees of hepatic impairment. No dose adjustment is recommended when fenfluramine is administered to patients with mild and moderate hepatic impairment (Child Pugh Class A and B). In patients with severe hepatic impairment (Child-Pugh C), the maximum dosage for these patients is 0.2 mg/kg twice daily, and the maximal total daily dose is 17mg. There are limited clinical data on the use of fenfluramine with stiripentol in patients with mild impaired hepatic function. A slower titration may be considered in patients with hepatic impairment. If adverse reactions are reported, a dose reduction may be needed. There are no clinical data on the use of fenfluramine with stiripentol in patients with moderate and severe impaired hepatic function. Fenfluramine is therefore not recommended for use in patients with moderate and severe hepatic impairment treated with stiripentol. Monitoring of patients should be considered
Patients with relevant comorbidities: • Patients with renal impairment	There were no exclusion criteria for patients with renal impairment. The results from a clinical study (ZX008-1902) indicated that the increase in fenfluramine exposure in study participants with severe renal impairment was clinically insignificant. Generally, no dose adjustment is recommended when fenfluramine is administered to the patients with mild to severe renal impairment; however, a slower titration may be considered. If adverse reactions are reported, a dose reduction may be needed.

Table Part II–10: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with cardiovascular impairment	Patients with cardiovascular impairment were not included in the clinical development program (Section SIV.1).
Patients with relevant comorbidities: • Immunocompromised patients	There were no exclusion criteria for immunocompromised patients
Patients with relevant comorbidities: • Patients with a disease severity different from inclusion criteria in clinical trials	A wide range of severity was included in the clinical program based on convulsive seizure frequency without an upper limit for disease severity.
Population with relevant different ethnic origin	There were no inclusion/exclusion criteria for patients based on ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder is a rare genetic disorder that is caused by a mutation in the CDKL5 gene, located on the X chromosome. It is a debilitating developmental disease with severe sequelae including frequent seizures that cause multisystemic abnormalities. Study ZX008-2103 (EP0216), a Phase 3, randomized, Double-Blind, placebo-controlled, fixed-Dose, multicenter study was designed to examine the efficacy and safety of ZX008 in participants with CDLK5 deficiency disorder.

CDLK-5=cyclin-dependent kinase-like 5; ULN=upper limit of normal

Part II Module SV Postauthorization experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

As highlighted in the Pharmacovigilance Risk Assessment Committee (PRAC) preliminary assessment report (AR) for PSUR No.4 (EMEA/H/C/PSUSA/00010907/202212), the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) Index was updated to add a DDD for fenfluramine (8mg [ATC: N03AX26]). As this new DDD was valid as of 01 Jan 2023, it will be used in this and future EU-RMPs when calculating patient exposure.

The WHO DDD is assumed to be 8mg. For calculation purposes, a year is defined as 365.25 days.

$$\text{Patient-years} = \frac{\text{(total amount of product distributed [in mg])/DDD}}{\text{365.25 days in year}}$$

0.25 is added to account for leap years.

SV.1.2 Exposure

It is acknowledged that post-marketing data will most likely not be available by age group or by gender but, when available, this should be provided. Total exposure and exposure by indication should always be presented.

The total amount of product sold since first approval (International Birth Date [IBD] 25 Jun 2020) to 30 Jun 2024 was CCI [redacted] mg, as derived from the UCB sales data. According to the methodology described above, patient exposure to fenfluramine (excluding US) is estimated at approximately CCI [redacted] patient years cumulatively. Table Part II–11 provides post-authorization exposure by region (excluding US).

It should be noted that while patients enrolled in the US Risk Evaluation and Mitigation Strategy (REMS) are supplied with commercial product, REMS exposure is presented separately.

Table Part II–11: Estimated Exposure Data from Post Marketing Sources

Region	Country	Patient-years cumulatively (25 Jun 2020 to 30 Jun 2024)
EEA	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Table Part II–11: Estimated Exposure Data from Post Marketing Sources

Region	Country	Patient-years cumulatively (25 Jun 2020 to 30 Jun 2024)
	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Total EEA	CCI [redacted]
Asia Pacific	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Total Asia Pacific	CC [redacted]
Europe/non-EEA	CCI [redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Total Europe/non-EEA	CC [redacted]
Middle East & Africa	CCI [redacted]	[redacted]

Table Part II–11: Estimated Exposure Data from Post Marketing Sources

Region	Country	Patient-years cumulatively (25 Jun 2020 to 30 Jun 2024)
	CCI [redacted]	[redacted]
	Total Middle East & Africa	CC
US & Canada	CCI [redacted]	[redacted]
Other	CCI [redacted]	[redacted]
Overall total		CCI

EEA=European economic area

US Risk Evaluation and Mitigation Strategy

In the US, all patients who have received fenfluramine must be enrolled in the REMS program. As of 24 Jun 2024, cumulatively, a total of CCI patients have received treatment. The REMS exposure data are included in the cumulative exposure presented in Table Part II–13.

Table Part II–12: Cumulative Exposure Data from US REMS

	Pediatric		Adults		Total	
	Number of patients on treatment	**Patient-years**	**Number of patients on treatment**	**Patient-years**	**Number of patients on treatment**	**Total patient-years**
Cumulative	CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

REMS=risk evaluation and mitigation strategy.

Table Part II–13: Cumulative REMS exposure by gender, naive/non- naive and age-group

	Cumulative
Gender	
Male	CCI
Female	CCI
Neutral	C
Prefer not to say	C
Previous exposure	
Naïve	CCI
Non-naïve	CC
Age-group[a]	

Table Part II–13: Cumulative REMS exposure by gender, naive/non- naive and age-group

	Cumulative
<18 years	CCI
≥18 years	CCI
Totals	CCI

REMS=Risk Evaluation and Mitigation Strategy.

[a]Age at time of enrollment.

Part II Module SVI Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Non-clinical studies, including receptor binding and functional assays, toxicokinetic, and abuse-related behavioral pharmacology studies have been conducted in several species and are consistent in showing that fenfluramine does not exhibit abuse potential. Studies of drug self-administration in rats, dogs, baboons, and rhesus monkeys demonstrate that fenfluramine does not initiate, or maintain, drug self-administration. Conditioned place preference studies demonstrate that fenfluramine does not induce conditioned place preference.

Human abuse liability studies have demonstrated that fenfluramine does not substitute in amphetamine-like patterns of abuse.

In short-term studies with healthy individuals, adverse events related to abuse potential (feeling drunk, euphoric mood, and disinhibition) occurred at low rates following fenfluramine treatment, which support the lack of abuse potential.

The overall clinical safety evaluation of fenfluramine in the treatment of Dravet syndrome has shown no abuse, withdrawal symptoms or dependence findings due to fenfluramine.

Part II Module SVII Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The following analysis pools are discussed as part of the safety analysis:

- The ISS-DB-SAF population: study participants enrolled in double-blind, placebo-controlled, fixed-dose studies, Study 1 (N=119) and Study 1504 Cohort 2 (N=87);
- The LTS population: study participants enrolled in open-label Study 1503 who previously participated in the double-blind, placebo-controlled, fixed-dose studies, Study 1 (N=110), Study 1504 Cohort 2 (N=83), and Study 2 (N=121) and PK Study 1504 Cohort 2 (N=16); where all study participants are first on a low dose (0.2 mg/kg/day) for the first month and then flexibly titrated in order to balance effectiveness, safety and tolerability (N=330);
- ISS-ALL population: includes all study participants enrolled in Study 1, Study 2, Study 1504 Cohort 2 or Study 1504 Cohort 1 who received at least 1 dose of ZX008. Exposure time for Study 2 participants only includes time in Study 1503. The double-blind exposure for Study 2 participants is still blinded and exposure estimates are therefore not included (N=341).

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

The following are not classified as important risks based on the nature of the ADRs observed in clinical studies, and are expected to be easily managed during the use of fenfluramine:

- Bronchitis
- Upper respiratory tract infection
- Ear infection
- Abnormal behavior
- Irritability
- Lethargy
- Tremor
- Constipation
- Diarrhea
- Vomiting
- Pyrexia
- Fatigue
- Blood glucose decreased

No study participant developed VHD (≥ moderate mitral regurgitation or ≥ mild aortic regurgitation and/or clinical symptoms/signs of VHD) or PAH in the double-blind studies or in the open-label extension study at any time, and this continues to be the case as of 24 June 2021 (the DLP of the PSUR#1). Adverse events of echocardiogram abnormal were confined to findings of non-pathologic regurgitation on an echocardiogram, the vast majority were trace mitral regurgitation (which fluctuated between readings of trace and absent), which is seen in normal healthy persons, including children.

In the double-blind studies, 17.9%, 9.3%, 22.5% and 6% (0.2 mg, 0.5 mg, 0.8 mg and placebo arms, respectively) reported events of trace mitral regurgitation that were captured on the AE log as per reporting convention. Only 1 study participant (2.3%) in 0.5 mg arm showed mild mitral regurgitation, and 3 study participants (7.5%) showed trace aortic regurgitation during the double-blind studies, both of which are also considered non-pathologic; the 1 study participant who had 1 echo showing mild mitral regurgitation had a screening baseline echo also showing mild mitral regurgitation and was enrolled in error. In the OLE study, 19.4% of study participants reported AEs of trace mitral regurgitation, and the majority of study participants with 1 reading of trace mitral regurgitation had subsequent readings of absent mitral regurgitation (14 Oct 2019 data cut-off). Of note, trace mitral, trace aortic, and mild mitral regurgitation are seen in normal healthy children and are not a pathologic finding (Webb, 2015).

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated

- Falls

Falls have been observed infrequently in the clinical studies. Falls in a Dravet syndrome population can be associated with seizures, as well as gait disturbances, which is also associated with the syndrome. Falls can affect the safety of patients dependent on their surroundings. The clinical study population was small thus it is difficult to accurately evaluate the frequency of falls. Routine pharmacovigilance will better define this in the larger post-marketing population.

- Status epilepticus

Status epilepticus (SE) is a serious condition associated with epilepsy and it is frequent in some patients with Dravet syndrome. Outcomes of episodes of SE can be serious with associated morbidity and mortality. The clinical study population was small; thus, it is difficult to accurately evaluate the frequency of SE. This event will therefore be monitored with routine pharmacovigilance.

Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized)

- Hypersensitivity reactions

Anaphylactic reactions have not been observed in the clinical development program, but it is recognized that life-threatening anaphylactic reactions may occur with all medications. Within the proposed SmPC, the administration of fenfluramine is contraindicated in individuals with

known hypersensitivity to fenfluramine or any of the formulation components. The SmPC also states: This medicinal product contains sodium ethyl para-hydroxybenzoate (E215) and sodium methyl para hydroxybenzoate (E219) and may cause allergic reactions (possibly delayed). It also contains sulphur dioxide (E220) which may rarely cause severe hypersensitivity reactions and bronchospasm.

- Serotonin syndrome

Fenfluramine increases extrasynaptic CNS serotonin, by a mechanism thought to involve its affinity to the axonal serotonin transporter (Baumann, 2014). As such, a very rare potential class effect is the risk of serotonin syndrome, particularly when used with other serotoninomemetics. There have been no reports of serotonin syndrome in the fenfluramine clinical development program. Appropriate contraindications, precautions and actions are proposed within the SmPC.

- Glaucoma

Glaucoma has not been observed in the fenfluramine clinical development program, but it has been reported that use of fenfluramine, which can cause transient mydriasis, has the potential to cause acute angle closure glaucoma in patients with narrow angles (Dempsie 2008; Denis 1995; Kramer 1973; Tripathi 2003). Acute angle closure glaucoma is considered an emergency and if left untreated can cause blindness (Khondkaryan 2013). However, angle closure is extremely rare in children and young adults (Chang, 2002). Therefore, the risk in the intended patient population is considered unlikely and acceptable in relation to the severity of Dravet syndrome. Appropriate precautions are proposed within the SmPC.

- Seizures secondary to abrupt discontinuation

No signs of withdrawal symptoms associated with fenfluramine have been identified in fenfluramine clinical studies; however, abrupt discontinuation of any antiepileptic agents may increase seizure frequency or result in SE. Directions for gradual dose reduction prior to discontinuation of fenfluramine are proposed within the SmPC.

- Overdose

Toxicity from overdose has not been observed in fenfluramine clinical studies but there are reports in the literature from prior marketed use to treat obesity. Doses as low as 5 mg/kg fenfluramine have been associated with toxicity in humans, with 5 to 10 mg/kg producing coma and convulsions (Von Mühlendahl, 1979). Reported single overdoses have ranged from 300 to 2,000 mg; the lowest reported fatal dose was a few hundred mg in a small child, and the highest reported nonfatal dose was 1,800 mg in an adult. Most deaths were apparently due to respiratory failure and cardiac arrest. Toxic effects appear within 30 to 60 minutes and may progress rapidly to potentially fatal complications in 90 to 240 minutes. Symptoms may persist for extended periods depending upon the dose ingested. The proposed Fintepla SmPC provides guidance on the symptoms of suspected overdose. Each bottle of fenfluramine is supplied with either 3 mL or 6 mL syringes which allows for precise dose measurement and a package leaflet (PL) describing how to administer the product; therefore, the risk of unintentional overdose is considered to be small and there is no reason to suspect a significant risk of intentional overdose in the treated population.

- Somnolence and sedation

As with most other AEDs, fenfluramine can cause somnolence and sedation. Other central nervous system (CNS) depressants, including alcohol, could potentiate the somnolence and sedation effect. Lethargy, somnolence, and fatigue were reported more frequently in fenfluramine treatment groups than in the combined placebo groups in the Phase3 placebo-controlled studies. There was no substantial difference in the reporting frequency of these AEs during the double-blind through open-label treatment periods as compared with the combined placebo group of the Phase 3 placebo-controlled studies. Discontinuation due to lethargy, somnolence, and fatigue did not occur often, and most study participants had these AEs improve or resolve with ongoing fenfluramine treatment. Somnolence is frequently associated with other antiepileptic drugs and often resolves with ongoing treatment, but if not improved is reversible upon discontinuation of drug. There is currently insufficient evidence to justify the inclusion of somnolence or sedation as an important risk of fenfluramine.

- Infections

The most commonly reported AEs in the Dravet syndrome clinical studies were infections. In the Phase 3 placebo-controlled studies (Study 1 and Study 1504 Cohort 2), 57/122 (46.7%) study participants in the ZX008 treatment groups and 47/84 (56.0%) study participants in the placebo treatment groups experienced at least 1 infection during the 16-17 week double-blind safety reporting periods. There were no substantial differences between the treatment groups in the types of infections reported. Nasopharyngitis was the most frequently reported infection, followed by upper respiratory tract infections. Infections, especially nasopharyngitis and upper respiratory tract infections, are common in this age group, and also susceptibility to infections is a well-described associated clinical feature of Dravet syndrome (Vial 1992, Villas 2017). There is currently insufficient evidence to justify the inclusion of infections as an important risk of fenfluramine.

- Seizures

Many anticonvulsants have been documented to be proconvulsant under specific conditions. Patients with Dravet syndrome are known to have worsening seizures when treated with standard AEDs that are sodium channel antagonists (Sazgar 2005; Wirrell 2016; de Lange 2018). In the Phase 3 placebo-controlled studies (Study 1 and Study 1504 Cohort 2), during the double-blind treatment period, 16/122 (13.1%) of study participants in any ZX008 group and 17/84 (20.2%) in the placebo group had a worsening of seizures or a seizure-related AE. Based on these data, ZX008 is not proconvulsant in study participants with Dravet syndrome and thus there is currently insufficient evidence to justify the inclusion of seizures as an important risk of fenfluramine.

- Interactions with other medicinal products

<u>Stiripentol with or without clobazam (and/or valproate)</u>

When co-administered with STP, the concentrations of fenfluramine were increased and its metabolite norfenfluramine decreased due to the inhibition of the metabolism of fenfluramine (Study 1505 Part 1, Study 1504 Cohort 1). Stiripentol inhibits multiple CYP450 enzymes and is the major contributor to the effect on fenfluramine. The proposed SmPC notes that the dose of

fenfluramine should be reduced when used in combination with STP (with or without clobazam and/or valproate).

Strong CYP1A2 or CYP2B6 inducers

Based on in vitro metabolism studies, it is expected that strong inducers of CYP1A2 and CYP2B6 may cause clinically significant decreases in fenfluramine concentration with the potential to decrease efficacy; however, there are no expected safety concerns. Dose adjustment considerations are included in the proposed SmPC.

Known risks that do not impact the risk-benefit profile

None

Other reasons for considering the risks not important

- Transmission of infectious agents

None of the excipients used in the manufacturing process for fenfluramine are derived from human or animal origin.

- Potential for misuse for illegal purposes

There is insufficient evidence to justify the inclusion of potential for misuse for illegal purposes as an important risk of fenfluramine.

The remaining adverse reactions reported in the clinical development program represent signs/symptoms or consequences of risks deemed important for inclusion in the list of safety concerns in the RMP.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table Part II–14: Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risks	
None	
Important potential risks	
Valvular heart disease	
Risk-benefit impact	Valvular Heart Disease has not been observed in the Dravet syndrome population and other pediatric populations treated at lower doses of fenfluramine. Cases of VHD, some severe or even fatal, were reported in adults taking fenfluramine for the treatment of obesity in doses of 60 - 120mg per day, usually in combination with phentermine (Connolly, 1997; Centers for Disease Control and Prevention, 1997; Wong, 1998). Based on the history in adult obese populations at higher doses, is considered an important potential risk for fenfluramine.
Pulmonary arterial hypertension	
Risk-benefit impact	Pulmonary arterial hypertension has not been observed with fenfluramine use in the Dravet syndrome population and other pediatric populations treated at lower doses. Fenfluramine is 1 of over 16 different compounds that has been purported to be

Table Part II–14: Risks considered important for inclusion in the list of safety concerns in the RMP

	associated with PAH (Perez, 2017). Rare cases of PAH, some severe or even fatal, have been reported in adults taking fenfluramine for the treatment of obesity in doses of 60 - 120 mg per day (Pouwels et al, 1990; McMurray et al, 1986; Douglas et al, 1981). Based on the history in adult obese patients, is considered an important potential risk for fenfluramine.
Suicidal ideation and behavior	
Risk-benefit impact	In double-blind Zogenix-sponsored studies (Study 1 and Study 504 Cohort 2), no study participants exhibited suicidal ideation or behavior. One study participant reported self-injurious behavior without suicidal intent but had this same behavior prior to initiating fenfluramine treatment at baseline. Additionally, in the OLE study, 1 study participant exhibited suicidal ideation as assessed by the C-SSRS at Visit 1 and persisted through to Month 6. Elevated bromide levels were noted at Month 3 and the dose was subsequently adjusted. The study participant had exhibited suicidal ideation 1 additional time at Month 16. Suicidal ideation is considered a class-based risk of all antiepileptic medications; therefore, suicidal ideation and behavior are considered an important potential risk for fenfluramine.
Growth retardation	
Risk-benefit impact	Decreased appetite and weight loss were among the most commonly reported AEs in fenfluramine clinical studies. As weight loss can impact growth and development, growth retardation is considered an important potential risk, and will be evaluated in a PASS Registry: A Registry of Subjects with Dravet Syndrome Treated with Fenfluramine.
Missing information	
Long-term safety in Dravet syndrome patients	
Risk-benefit impact	The long-term safe use of fenfluramine is being evaluated in an extension study: Study ZX008-1503. An interim analysis has been submitted. The study is continuing as a PASS. These data are considered to be missing until the PASS is completed. In addition: In a small, ongoing, open-label study of fenfluramine as an add-on to conventional therapy in Belgium, there are 37 patients being treated, of whom 5 have been treated for at least 30 years (range 30-36), 5 between 10-30 years (range 15-23), 8 between 5-10 years (range 5-9), and all others < 5 years. Long-term safety data are available for 21 children and adults with refractory Dravet syndrome who have been treated in 2 cohorts. Based on retrospective results from the first cohort of 12 patients treated with low doses of fenfluramine (10 to 20mg daily) from 1 to 19 years (Ceulemans, 2012) and prospective results from the second cohort of 9 patients treated with fenfluramine for approximately 4 months to 5 years (Schoonjans, 2016), there has been no evidence of VHD or PAH, and no evidence to suggest a different safety profile with long-term use.

Table Part II–14: Risks considered important for inclusion in the list of safety concerns in the RMP

Off-label use (in wider pediatric epilepsies; obesity)	
Risk-benefit impact	A number of small studies and case series have been published, describing the pediatric use of fenfluramine in epilepsy. Based on the potential for fenfluramine to be used off-label in other rare refractory developmental epileptic encephalopathies, and as an acceptable risk/benefit relationship for other catastrophic refractory childhood epilepsies at the same lower doses used in Dravet syndrome has not yet been established in formal clinical studies, off-label use in wider pediatric epilepsies is considered to be missing information and further evaluation of use in this population is warranted. The proportion of off-label use in the treatment of obesity cannot be anticipated at this stage, as any data related to the historical use of fenfluramine in obesity cannot be applied due to the change in the prescribing environment since the 1990s, the advent of other treatments for obesity, and awareness of the risks related to fenfluramine in the medical and patient community when used in higher doses to treat obesity, and also importantly due to the distinct orphan pediatric target population and different dosage and formulation. It is expected that the potential for off-label use of fenfluramine for obesity will be extremely limited (if at all). Furthermore, fenfluramine therapy will be initiated and supervised by physicians with experience in the treatment of epilepsy, not general physicians, therefore, most likely preventing the likelihood of the use of the product in indications other than those detailed in the SmPC. To prevent off-label use in weight management a CAP is required (see EU-RMP Annex 6).
Use in patients with renal impairment	
Risk-benefit impact	There are no clinical data that describe the use of fenfluramine and its effect on patients with renal impairment. Decreased renal function is unlikely to affect the PK of fenfluramine. However, as there are no data available on the use of fenfluramine in patients with renal, the latter is considered missing information.
Use in patients with hepatic impairment	
Risk-benefit impact	Administration of fenfluramine to patients with moderate or severe hepatic impairment is not recommended, as described in the SmPC. Patients with moderate to severe hepatic impairment were excluded from Zogenix-sponsored clinical studies so far, and as the PK profile of individuals with hepatic impairment may differ to that in the population with normal hepatic function, a PK study is currently being conducted, and the use of fenfluramine in patients with hepatic impairment is considered missing information.

AE=adverse event; CAP=controlled access program; C-SSRS=Columbia suicide severity rating scale; OLE=open label extension; PAH=pulmonary arterial hypertension; PASS=post authorization safety study; PK=pharmacokinetics; SmPC=summary of product characteristics; VHD=valvular heart disease.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Following the identification of a post marketing case adjudicated by the UCB Cardiovascular Adverse Event Committee as Definite VHD, a comprehensive review of VHD was undertaken. Based on the existing information, the historical body of information, biological plausibility of

VHD cases reviewed, overlapping pharmacokinetic exposure from the epilepsy and weight loss dose ranges, and the presence of an index case and other identified cases; an association between fenfluramine and VHD could not be excluded. Valvular heart disease was thus reclassified to an important identified risk, discussed through EMEA/H/C/PSUSA/00010907/202406.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Table Part II–15: Important identified risk: Pulmonary arterial hypertension

Potential mechanisms	There is biological plausibility for a potential causal association with PAH through the action of released serotonin on 5-HT2B in the pulmonary artery (Ayme-Dietrich et al, 2017). The exact mechanism is unknown; however, it has been hypothesized that serotonin promotes proliferation of both pulmonary arterial fibroblasts and pulmonary arterial smooth muscle cells leading to pulmonary vasoconstriction that may promote remodeling in the pulmonary arteries (Garg et al, 2017; Dempsie and MacLean, 2008). Importantly, an association between fenfluramine and PAH and cardiac valvular lesions has been reported previously when fenfluramine was marketed as a treatment for obesity in adults.
Evidence source(s) and strength of evidence	In 1981, a report was published describing 2 patients who developed pulmonary hypertension while taking fenfluramine for obesity. Additional rare cases, some of which were severe or even fatal, were reported subsequently (Douglas et al, 1981). It should be noted that medical history in these case reports was scant, especially regarding confounders for pulmonary hypertension (McLaughlin et al, 2009) which are commonly associated with obesity, eg, sleep apnea, left ventricular disease (diastolic dysfunction). In a report by Souza (2008), of 109 cases of PAH in patients treated with fenfluramine, the median duration of fenfluramine exposure was 6 months, with a median of 4.5 years between exposure and onset of symptoms. Median survival was 6.4 years and duration of exposure had no relation to survival. Fenfluramine-induced PAH patients share clinical, functional, hemodynamic and genetic features with idiopathic PAH patients, as well as similar overall survival rates. These observations suggest that fenfluramine derivatives may potentially act as a trigger for PAH without influencing its clinical course. While the risk in adult patients with obesity is well documented, experimental use of fenfluramine in studies in over 500 children with autism and attention deficit and ADHD at doses from 0.65 mg/kg/day to 3.6 mg/kg/day found no evidence of PAH (summarized in the ISS). In addition, in Belgium, fenfluramine has been used successfully for over 35 years in some patients with Dravet syndrome (infants, children, young adults, and adults), to control seizures, without emergence of PAH (Ceulemans et al, 2012; Ceulemans et al, 2004; Schoonjans et al, 2016). Currently, 5 of these patients have been treated with daily fenfluramine for at least 30 years (range: 30-36 years), 5 patients treated between 10-30 years (range: 15-23), and 8 patients treated for 5-10 years (range: 5-9 years).

Table Part II–15: Important identified risk: Pulmonary arterial hypertension

	As described below, no evidence of PAH has been identified in UCB-sponsored clinical trials Dravet syndrome or LGS patients treated with fenfluramine; however it must be acknowledged that PAH is very rare and can have a long latency. These 2 factors potentially limit the ability to detect PAH in clinical trials, including in the OLE for fenfluramine which extends for up to 3 years of exposure in some participants. Along with data from clinical studies and literature, data from post-marketing sources was also utilized for a complete characterization of this risk.
Characterization of the risk	Pulmonary arterial hypertension is a very rare condition in the general population; the prevalence of PAH in several European registries has reported rates of 5 to 52 per million (Badesch 2007; Peacock 2007). <u>Clinical study data</u> The legacy Zogenix ZX008 clinical development program incorporated an intensive evaluation for signs of PAH in patients with Dravet syndrome and LGS being treated with low dose fenfluramine for up to 3 years. There was no evidence of PAH during the entire UCB-sponsored fenfluramine development program for DS or LGS. <u>Postmarketing data</u> Postmarketing cases of PAH associated with fenfluramine have been reported at doses within the approved dosing range for Dravet Syndrome and LGS, including an index case of PAH in a child receiving treatment for Dravet syndrome. The patient discontinued fenfluramine and the reaction resolved post-discontinuation. During the signal assessment for PAH, 9 cases had completed or were in the process of adjudication, with 3 cases adjudicated as PAH: 1 case of definite PAH with preexisting ASD, 1 case of probable PAH with no underlying contributory factors except for fenfluramine use (index case), and 1 case of possible PAH likely attributable to recent pneumonia. The remaining cases in the SSAR were in the adjudication process at the time of SSAR authoring, adjudicated as Not PAH, or contained insufficient information or documentation errors not warranting adjudication. No other discernable patterns were identified in the SSAR analysis with the cohort of cases adjudicated as PAH and dose, either with regards to total daily dose, weight-based dose, or with regards to clinically relevant drug interactions increasing exposure to fenfluramine or norfenfluramine.
Risk factors and risk groups	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). The risk factors for developing fenfluramine-induced PAH are unknown. Several factors have been hypothesized to be responsible for the disease, none with good evidence; these include stimulation of 5-HT_{1B}, 5-HT_{2B} or 5-HT_{2A} receptors, nitric oxide deficiency, estrogen, and mutations in the BMPR2 gene. Since the probability of developing PAH is extremely low, it is likely that 1 or more risk factors are responsible for susceptibility to PAH.

Table Part II–15: Important identified risk: Pulmonary arterial hypertension

Preventability	Effective measures to prevent fenfluramine-induced PAH are not known; Increased monitoring of patients using echocardiography performed at baseline prior to starting fenfluramine and at regular intervals while on treatment, will aid in early detection and treatment if present, which can improve quality-of-life and extend life expectancy, as well as stopping treatment with fenfluramine in such individuals. As discussed under the important identified risk of VHD, an ECHO must be performed prior to starting treatment with fenfluramine, and then every 6 months for the first 2 years of treatment, followed by once per year for subsequent years of fenfluramine administration.
Impact on risk-benefit balance of the product	Pulmonary arterial hypertension presents as increased pulmonary vascular resistance which eventually results in right heart failure and ultimately, death. Although PAH has no cure, early detection and treatment can help relieve symptoms and slow progression of the disease, thus improving quality of life and extending life expectancy. It is important to note that PAH is a very rare condition in the general population; the prevalence of PAH in several European registries has reported rates of 5 to 52 per million (Badesch 2007; Peacock 2007). Close monitoring of all patients treated with fenfluramine through echocardiography can lead to early subclinical detection and treatment, thus reducing the negative impact on the patient. Therefore, while the risk/benefit relationship for fenfluramine is considered unfavorable for the treatment of obesity in adults, establishing seizure reduction in Dravet syndrome and LGS patients leads to a positive risk/benefit profile for fenfluramine.
Public health impact	Not yet established in the Dravet syndrome or LGS population as estimated exposure to fenfluramine in the post-marketing setting is limited and the echocardiogram monitoring program for fenfluramine enables earlier identification and management of events.

ADHD=attention deficit hyperactivity disorder; BMPR2=bone morphogenetic protein receptor type 2; C-SSRS=Columbia suicide severity rating scale; ECHO= echocardiogram; HIV=human immunodeficiency virus; ISS=integrated safety summary; PAH=pulmonary arterial hypertension; VHD=valvular heart disease; 5-HT=5-hydroxytryptamine (serotonin).

Table Part II–16: Important identified risk: Valvular heart disease

Potential mechanism(s)	Significant efforts to reproduce cardiac valvular disease effects reported in humans exposed to fenfluramine in an intact in vivo animal model have had limited success. This may be because of inherent insensitivity of the animal models or because of limits to the study design and endpoints measured. There is a paucity of animal data that shows limited association between serotonin or fenfluramine in the induction of a cardiac valvular phenotype that accurately resembles the reported DIVHD in humans (Norris, 2018). In vitro and in vivo studies have been conducted to attempt to identify any association between fenfluramine and valvular disease. Polymerase chain reaction and immunohistochemistry staining have demonstrated the presence of various serotonergic receptors, the serotonin transporter and serotonin synthesizing enzymes on cardiac valves during development and in adult hearts (Gustaffson et al, 2005; Elangbam 2009; Sauls et al, 2012). Gene knockout studies have further revealed that 5-HT_{2B} receptors are critical for cardiac muscle development but are not required for valve morphogenesis (Nebigil et al, 1997; Nebigil et al, 2001; Nebigil et al, 2003). These data combined with a role for serotonin synthesizing enzymes (tph1) demonstrate a role for serotonin and serotonergic signaling in the regulation of cardiac morphogenesis. Although in vivo mechanistic studies are scant, in vitro studies have indicated that hyperactivation of this pathway can stimulate mitogenesis as well as extracellular matrix synthesis, possibly through a TGF crosstalk mechanism (Jian et al, 2002). Consistent with these basic scientific discoveries, clinical data on carcinoid valve disease, which results in high levels of circulating serotonin, has been shown to correlate with a right-sided valvulopathy in a subset of patients (Gustaffson et al, 2005; Robiolio et al, 1995). This is in contrast with the left-sided valvular disease associated with fenfluramine. Additionally, drugs that are known to have a high affinity for the main cardiac serotonin receptor, 5-HT_{2B} and function as agonists (eg, methysergide, methylergonovine, ergotamine), show a slight increase in the risk of cardiac valve thickening (Maréchaux et al, 2015; Ennezat 2016). However, this finding was contradicted in a follow-up study that failed to find an association in a large population of patients that were treated with known agents that either directly or indirectly stimulate the 5-HT_{2B} receptor (Lapi et al, 2012). The discrepancy in these studies is likely due to differences in sample size, which were inferior in the initial analyses, as well as inconsistent echocardiographic parameters. Thus, the serotonin hypothesis for the development of valvular disease remains hypothetical and unproven scientifically. In UCB sponsored nonclinical studies with fenfluramine hydrochloride, there were no fenfluramine hydrochloride–related microscopic changes in cardiac valves (mitral or aortic) at the highest dose levels evaluated in the chronic 26-week and 43-week repeat-dose toxicity studies in rats and dogs and in the 6-month and 2-year carcinogenicity studies in mice and rats.
Evidence source(s) and strength of evidence	Fenfluramine, the active ingredient in ZX008, was approved in France in 1965 and in the US in 1973 as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity. It was subsequently marketed in approximately 118 countries, with an estimated use in over 20 million individuals, corresponding to over 61 million patient months prior to its global withdrawal in 1997 (Department of Health and Human Services, 1996).

Table Part II–16: Important identified risk: Valvular heart disease

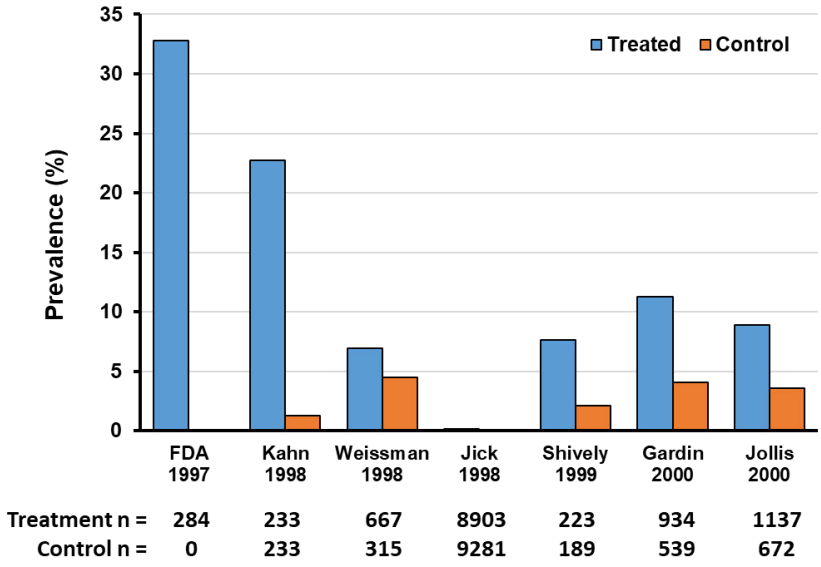
	In 1997, a case report series (Connolly et al, 1997) of 24 women with valve disease believed to be associated with use of fenfluramine and phentermine was published in NEJM. Shortly after, the US CDC issued a report on a total of 144 cases reported to them, including the 24 from Connolly et al. (Centers for Disease Control and Prevention 1997). Of the 132 spontaneous CDC reports with complete information, 113 (86%) met the case definition of aortic regurgitation of mild or greater severity and/or mitral regurgitation of moderate or greater severity. Of these 113 cases, 2 (2%) used fenfluramine alone; 16 (14%) dexfenfluramine alone and 89 (79%) used a combination of fenfluramine and phentermine. The median duration of drug use was 9 months (range: 1-39 months). Overall, 87 (77%) of the 113 cases were symptomatic; 24 patients (27%) required valve replacements and 3 patients died after surgery. To determine a course of action, the CDC commissioned 5 echocardiographic surveys to look at the prevalence of valve lesions in patients who were exposed to these drugs but who had no obvious history of cardiac disease or cardiac symptoms (in Florida, Minnesota, Wisconsin, Indiana, and Pennsylvania). These surveys demonstrated a prevalence of valvular disease meeting the CDC case definition ranging from 30.0% to 38.3% (overall: 32.8%; 95% confidence interval=27.7% 38.9%), where the prevalence in a normal adult population was expected to be below 5% (Klein et al, 1990; Reid et al, 1994). It is noteworthy that only 2 of the 5 surveys were random samples, and these had the widest confidence intervals (lowest confidence). The signal from these investigations and similar work in the EU prompted US and EU regulators to request voluntary withdrawal of fenfluramine and dexfenfluramine from the market in 1997. Over the ensuing years, additional case series, case-control, cohort, and trial reports were published by multiple investigator groups – including the original Connolly et al. group – indicating the risk of valve disease associated with use of fenfluramine (with or without phentermine) was not as pronounced as initially reported (Borer 2013; Gardin et al, 2000; Teramae et al, 2000; Sachdev et al, 2002). Early investigations to characterize the effect of fenfluramine and phentermine on cardiac valves suggested both a relationship to dose (Li et al, 1999) and duration of treatment (Jick et al, 1998; Dahl et al, 2008). The body of non-clinical literature investigating the potential mechanisms between serotonin or norfenfluramine and the induction of a cardiac valvular phenotype resembling the human disorder remains insufficient to conclude direct causation (Norris and Milan, 2018). Review of data from publications on experimental animal models showed that only 3 in vivo studies have been conducted using fenfluramine or dexfenfluramine, while an additional 6 studies have been conducted using pergolide or serotonin as the serotonin receptor agonist. Some studies report valvular disease while others do not, and some report valvular disease in a few animals but not all animals. One major limitation of these studies is the absence of dose-response and time-course data, as well as the use of a variety of routes of administration while none of the studies measured plasma concentration of norfenfluramine, so it is not possible to identify an in vivo exposure level associated with valvular disease.
Characterization of the risk	Characterization of the risk from data when fenfluramine was used as an appetite suppressant:

Table Part II–16: Important identified risk: Valvular heart disease

From the data obtained when fenfluramine was used as an appetite suppressant at a dose of 60 to 120 mg/day for the treatment of adult obesity, left-sided cardiac valvulopathy was reported to be related to fenfluramine use, often when co-prescribed in combination with phentermine, in the NEJM in 1997. The mechanism of the effect is believed to be related to fenfluramine's role as a serotonin releaser, but it is not fully understood and has not been replicated in any animal model to date.

Weissman et al (2001) reported prevalence rates of fenfluramine-associated valvular regurgitation while using fenfluramine for treatment of adult-obesity (Figure 1) (Weissmann, 2001).

Figure 1: Prevalence of valvular regurgitation (using the FDA criteria) in patients on diet pills using large, published controlled studies with standardized ECHO (Weissmann, 2001)



Adapted from: Weissman, N.J. *Am. J. Med. Sci.* 2001; 321: 285-91

Characterization of risk using UCB fenfluramine safety program:

One of the most important features of the ZX008 safety program includes an intensive prospective cardiac monitoring program that was designed and instituted with FDA and expert input, due to fenfluramine's prior history when marketed for the treatment of obesity in adults with higher doses (60-120 mg/day).

Clinical trial data

Repeated echocardiograms utilizing core lab review of children and young adults receiving low dose ZX008 for the treatment of seizures in Dravet syndrome and LGS did not reveal any cardiotoxic effects in studies lasting up to 3 years. No patients in the fenfluramine clinical development program developed VHD in any of the studies, some having been treated now for more than 3 years.

Postmarketing data

Table Part II–16: Important identified risk: Valvular heart disease

	Valvular heart disease in a child associated with fenfluramine for Dravet syndrome has been reported in the postmarketing setting. In addition to this case, 3 other cases adjudicated as Definite or Possible VHD with WHO-UMC causality assessed by UCB as possibly related to fenfluramine were identified during the signal assessment. Cases occurred in both pediatric and adult patients. All 4 cases had plausible time to onset, with 3 of 4 cases occurring after 2 years of fenfluramine exposure (the remaining case had a shorter exposure of almost 4 months but had other preexisting conditions predisposing to cardiac abnormalities). Of the 4 cases, in 2 cases fenfluramine was withdrawn in response to ECHO abnormalities, resulting in improvement in ECHO parameters in 1 case and progression of regurgitation following fenfluramine cessation in the other case. No patterns were identified with regards to dosing of fenfluramine or potential drug interactions. None of the identified cases reported associated symptoms of VHD.
Risk factors and risk groups	Many studies in the historical literature have attempted to identify risk factors associated with the development of fenfluramine-associated valvular disease. Risk factors identified for aortic regurgitation (FDA criteria) include increased age, history of heart murmur, lower body mass index, history of hypertension, and female sex (Gardin et al, 2000). Dahl et al (2008) identified the following factors associated with mild or greater aortic regurgitation: increasing age, female gender, duration of use, and time elapsed between market withdrawal for fenfluramine and scan date. Factors associated with mild or greater mitral regurgitation included increasing age, female gender, duration of use, time elapsed, and the presence of pulmonary hypertension. Moderate or greater mitral regurgitation was only associated with age and female gender (Dahl et al, 2008).
Preventability	Monitoring of patients using echocardiography aids in rapid identification of any subclinical valve issues before they are symptomatic. An echocardiogram must be performed prior to starting treatment with fenfluramine, and then every 6 months for the first 2 years of treatment, followed by once per year for subsequent years of fenfluramine administration.
Impact on risk-benefit balance of the product	Clinically significant VHD can result in volume overload of the ventricle and left ventricular cavity enlargement with systolic dysfunction, which may lead to heart failure if left untreated over time. Some follow-up studies of patients with fenfluramine-induced valvular disease report that regression or stability of valvular disease may occur in some patients. For instance, Hensrud described regression of valvular disease after 6 months in 8 of 15 participants who had discontinued fen-phen, while no worsening was found in the remaining participants (Hensrud , 1999). Other studies estimate regression occurs in about one-quarter to one-third of individuals (Mast et al, 2001b; Weissman et al, 2001). Conversely, a subset of fenfluramine-treated patients with ongoing lesion proliferation after drug cessation or long-latency cases of fenfluramine-associated VHD, with one case occurring 7 years after drug cessation, have also been identified in the literature (Greffe et al, 2007; Volmar & Hutchins, 2001). Close monitoring of all patients treated with fenfluramine through echocardiography can lead to early subclinical detection and treatment, thus reducing the negative impact on the patient. Therefore, while the risk/benefit relationship for fenfluramine

Table Part II–16: Important identified risk: Valvular heart disease

	is considered unfavorable for the treatment of obesity in adults, establishing seizure reduction in Dravet syndrome and LGS patients leads to a positive risk/benefit profile for fenfluramine.
Public health impact	Not yet established in the Dravet syndrome or LGS population, as estimated exposure to fenfluramine in the postmarketing setting is limited and the echocardiogram monitoring program for fenfluramine enables earlier identification and management of events .

AEDs=anti-epileptic drugs; C-SSRS=Columbia suicide severity rating scale; DS=Dravet syndrome; f=former; FDA=Food and Drug Administration (USA); LGS=Lennox-Gastaut Syndrome; OLE=open-label extension.

Table Part II–17: Important potential risk: Suicidal ideation and behavior

Potential mechanisms	Suicidal ideation and behavior are included in the label for AEDs; however, the exact mechanism is not known. Suicide attempts, both incident and recurrent, are associated with epileptic disorders with an unknown mechanism or etiology.
Evidence source(s) and strength of evidence	Depression and suicidal behavior are common in chronic illnesses, including epilepsy. Studies show that epileptic patients have a stronger tendency towards suicidal ideation and behavior, compared to healthy controls (Hesdorffer et al, 2016). Based on these associations, clinicians have concluded that epilepsy increases the risk for suicidal thoughts and ideation. However, in a meta-analysis of clinical trial data, the FDA concluded that AEDs increase the risk of suicidal thoughts in people with epilepsy (Hesdorffer et al, 2016). These data are reported from epileptic syndromes that are adult onset, or not as debilitating as epileptic encephalopathies including Dravet syndrome. Further, the risk identified by FDA in a meta-analysis of AEDs conducted many years ago is low overall: in the AED treated group the incidence was 0.43%, compared to 0.24% among placebo-treated patients in studies of 12 weeks average duration, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated.

Table Part II–17: Important potential risk: Suicidal ideation and behavior

Characterization of the risk	Clinical study data Overall, patients who received ZX008 (fenfluramine hydrochloride) in doses of 0.1 and 0.7 mg/kg/day in Study 1 (DS), did not report instances of suicidal ideation and behavior. In Study 3 (DS) (f. Study 2), 1 study participant was reported to exhibit non-suicidal self-injurious behavior. In the same study, a P -year-old PPD study participant reported suicidal ideation. During the Screening visit for the study, P mother reported that the study participant sometimes verbalized P wished to be dead, without an implementation plan, as a way to show P anger. The study participant transitioned into OLE Study 1503 on PPD , and suicidal ideation was reported at several study visits through PPD . The investigator stated these events were precipitated by PPD . Elevated bromide levels were noted in PPD and were suspected to affect the participants' mood; the dose was subsequently adjusted. Upon examination by the Principal Investigator at multiple visits after the ideations, the PP was 'satisfied and cooperative' without indication toward self-harm. At the time of the interim database snapshot, the study participant had reported 'Wish to be dead' PPD on PPD . In Study 1504 Cohort 2 (DS), 1 patient in the 0.5mg/kg/day group - a P year-old PPD reported self-injurious behavior, without suicidal behavior, at Baseline and in the study. The study participant completed Study 1504 Cohort 2 and transitioned to the OLE Study 1503 on PPD . On PPD (Baseline visit for Study 1503), the study participant had non-suicidal self-injurious behavior as reported on the C-SSRS questionnaire. This behavior was again reported at all study visits between PPD (Month 3 OLE) and PPD (Month 18 OLE). In Study 1601 (LGS), CCI . Based on the overall C-SSRS results, ZX008 did not appear to increase the risk of suicidal thoughts and behavior. Postmarketing data To date, no change to the characterization of the risk has been identified from postmarketing sources regarding fenfluramine use and suicidal ideation and behavior.
Risk factors and risk groups	The risk of suicide-related events is higher in individuals with severe epilepsy, temporal lobe epilepsy, and following epilepsy-related surgery (Arana et al, 2010). Additionally, individuals with comorbid psychiatric disorders have a higher risk of suicide within the epilepsy population (Tellez-Zenteno et al, 2007). Epilepsy patients with a previous suicide attempt are at a 40 % greater risk of a completed suicide (Harris and Barraclough, 1997). With the limited data on this risk for fenfluramine, there is no risk factor identified specifically for fenfluramine use. The risk and benefit of treatment with fenfluramine should be carefully weighed for patients with a history of depression and/or suicidal ideation or behavior.

Table Part II–17: Important potential risk: Suicidal ideation and behavior

Preventability	Effective measures to successfully prevent suicidal ideation are not known. However, patients with Dravet syndrome typically live with full time caregiver(s). In order to minimize the risk, it is recommended that health care professionals pay special attention to the patient's subjective mood state (including depressiveness and anger), as well as prior history of suicidal behavior in order to evaluate the patient's suicide risk factors and take the appropriate preventative measures. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.
Impact on risk-benefit balance of the product	The risk and benefit treatment of fenfluramine should be carefully evaluated for patients with a history of depression and/or suicidal ideation or behavior, or for patients who develop such symptoms following administration of fenfluramine. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation and behavior. Although suicidal ideation and behavior are important potential risk, establishing seizure reduction in patients with Dravet syndrome or LGS leads to an acceptable risk/benefit profile for fenfluramine.
Public health impact	Not yet established in the Dravet syndrome or LGS population, as estimated exposure to fenfluramine in the post-marketing setting is limited.

AEDs=anti-epileptic drugs; C-SSRS=Columbia suicide severity rating scale; DS=Dravet syndrome; f=former; FDA=Food and Drug Administration (USA); LGS=Lennox-Gastaut Syndrome; OLE=open-label extension

Table Part II–18: Important potential risk: Growth retardation

Potential mechanisms	Appetite suppression is a known effect of fenfluramine caused by its mechanism of action as a centrally acting serotonergic agent. Increased serotoninergic transmission in the centers of feeding behavior in the hypothalamus suppress appetite, leading to decreased food intake and malnutrition, which could ultimately impact physical development based on chronic suboptimal caloric intake.
Evidence source(s) and strength of evidence	This important potential risk is based on the fenfluramine mechanism of action, non-clinical studies, findings from the fenfluramine clinical development program and the drug's previous indication as an appetite suppressant which indicate an association between fenfluramine intake and weight loss, which could in turn possibly have an impact on physical development. However, in the clinical program, most patients resumed the expected measured increases in weight during the OLE study. Furthermore, 1 study of Dravet syndrome children demonstrated issues with appetite, eating habits, and growth, the latter of which the authors concluded may be due to an underlying endocrine abnormality (Eschbach et al, 2017).
Characterization of the risk	Clinical study data In the DS double-blind studies (ISS-DB-SAF population; ie, all study participants from the double-blind Study 1 and Study 2 Cohort B), more participants randomized to any fenfluramine treatment group compared to placebo had a decreased appetite (34.4% vs 8.3%) and weight decrease of ≥ 7% (18.9% vs 2.4%).

Table Part II–18: Important potential risk: Growth retardation

	In Study 3, the study participant incidence of decreased appetite was highest in the ZX008 0.8 mg/kg/day group (6.3% in the placebo group, 26.1% in the ZX008 0.2 mg/kg/day group, and 37.5% in the ZX008 0.8 mg/kg/day group). A dose response was observed for weight decreased, which was reported by 8.3% of participants in the ZX008 0.8 mg/kg/day group, 2.2% of participants in the ZX008 0.2 mg/kg/day group, and 0 participants in the placebo group. In the OLE study 1503 (at the time of the last patient last visit [27 Jan 2023]), 41 (11.7%) participants experienced a body weight loss of ≥7% of the OLE Baseline value at the Month 6 visit in the OLE Treatment Period, the number of the participants experiencing this level of body weight loss at the last postbaseline assessment was 30 (8.0%) indicating that 26.8% of these participants had regained weight. This was also observed for participants who experienced a body weight loss of ≥10%.Thus, although loss of appetite and weight loss may occur following administration of fenfluramine to Dravet syndrome patients, there is limited evidence to suggest administration of fenfluramine can independently impact physical development which is known to be abnormal in this patient population. In the OLE Part of study 1601 (LGS) for the non-Japanese Cohort at the time of the interim cutoff (19 Oct 2020), a body weight gain of ≥ 7% of the Part 2 Baseline value was reported at any visit for 32.4% of study participants. A greater percentage of pediatric participants (2 to < 18 years of age) than adult participants (≥ 18 years of age) (40.8% and 12.3%, respectively) experienced body weight gains ≥ 7% of the Part 2 Baseline value, as expected. A body weight decrease of ≥ 7% of the Part 2 Baseline value at any visit was reported for 17.0% of study participants. Similar percentages of pediatric (2 to < 18 years of age) and adult (≥ 18 years of age) study participants (16.1% and 19.2%, respectively) experienced body weight losses ≥ 7% of the Part 2 Baseline value. Also, similar percentages of pediatric and adult study participants (8.6% and 12.3%, respectively) experienced body weight losses ≥ 10% of the Part 2 Baseline. In the OLE Part of study 1601 (LGS) for the Japanese Cohort at the time of the interim cutoff (09 September 2022); a greater percentages of adult participants (≥18 years of age) experienced body weight losses ≥ 7% or ≥ 10% of the OLE Baseline value at any visit in the OLE compared to the pediatric participants (2 to <18 years of age). No consistent differences in the percentages of participants having such decreases were noted between the various pediatric age subgroups. Though 4 (25.0%) pediatric participants experienced a body weight loss of ≥ 7% of the OLE Baseline value at any visit in the OLE, the number of participants experiencing this level of weight loss at the last post-baseline assessment was 2 (12.5%), indicating that 2 (12.5%) of the participants who had a ≥ 7% loss in weight regained weight to within 7% of their OLE Baseline weight. Seven (43.8%) adult participants experienced a body weight loss of ≥ 7% of the OLE Baseline value at any visit in OLE, and 4 (25.0%) participants had this level of body weight loss at the last post-baseline assessment, indicating that 3 (18.8%) of the adult participants regained weight to within 7% of their OLE Baseline body weight. Similar percentages of pediatric and adult participants who experienced a weight loss of ≥ 10% at any visit remained with a ≥ 10% weight loss at the last post-baseline assessment.

Table Part II–18: Important potential risk: Growth retardation

	Postmarketing data The postmarketing data to date did not show an impact on height (no events with PTs Body height decreased, Body height abnormal, Body height below normal were received). It should be noted that it is difficult to follow longitudinal progression of height with postmarketing data. In none of the case there was any evidence suggesting an impact of the event on overall development of the patient. To date, no change to the characterization of the risk has been identified from postmarketing sources regarding fenfluramine use and growth retardation/developmental delay secondary to loss of appetite.
Risk factors and risk groups	Patients with Dravet syndrome are known to have issues with appetite, eating habits, and growth (Eschbach et al, 2017; Vial et al, 1992; Villas et al, 2017). 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 (such as use of topiramate or the ketogenic diet) may be at increased risk for clinically significant weight loss and growth retardation, although this was not observed in ZX008 Phase 3 studies in patients receiving ZX008 and topiramate (ISS). A recent study demonstrated abnormal head circumference growth in children with Dravet syndrome (Lo Barco et al, 2020).
Preventability	In children, growth retardation can be mitigated by careful monitoring of nutrition, calorie intake as well as weight and height measurements. Increasing prescriber and patient caregiver awareness that growth retardation may possibly occur with fenfluramine due to decreased appetite, and routine monitoring of patient growth may reduce severity of weight loss and prevent long-term growth suppression, apart from that expected in children with Dravet syndrome or LGS, through prompt diagnosis and treatment.
Impact on risk-benefit balance of the product	Given the known anorectic action of fenfluramine, the challenges with dietary habits in patients with Dravet syndrome or LGS, the known natural history of growth in this patient population, and the importance of growth and metabolism in the studied age group, growth retardation is considered an important potential risk for fenfluramine. Growth can be and currently is already monitored routinely and treated, if needed, with nutritional intervention and pharmacological treatment. Considering the potential impact of seizure reduction in the Dravet syndrome and LGS population, the benefits of treatment outweigh this risk.
Public health impact	Not yet established, as estimated exposure to fenfluramine in the post-marketing setting is limited.

AE=adverse event; DS=Dravet Syndrome; ISS-DB-SAF=integrated summary of safety-double-blind-safety (analysis population); LGS=Lennox-Gastaut Syndrome; LTS=long-term safety (analysis population); OLE=open-label extension; ZX008=fenfluramine.

SVII.3.2 Presentation of the missing information

Long-term safety

Evidence source:

Based on the information available from the long-term use of fenfluramine up to 3 decades in Dravet syndrome or LGS patients in Belgium, there is no evidence to suggest that long-term treatment with fenfluramine in this patient population will result in a different safety profile. In clinical trials of up to 3 years in duration, no patient receiving fenfluramine developed VHD or PAH. No effects on electrocardiogram parameters of atrioventricular conduction or cardiac depolarization were seen. Results taken together with the magnitude and durability of the positive effect on seizures previously reported in Phase 3 clinical trials in this severe pediatric-onset, refractory epileptic encephalopathy, strongly suggest that significant benefits of fenfluramine for this patient population outweigh potential cardiac risks, which can be monitored via echocardiography (Lai et al, 2020). Study ZX008-1900 (all study participants received ZX008 for up to 36 months [24 months for study participants in Denmark]) for study participants with LGS strongly supports the continued, long-term safety and favorable benefit-risk profile of ZX008 for the adjunctive treatment of seizures associated with LGS. Additionally, studies ZX008-1601, Part 1 Cohort A and ZX008-1601 Part 2 Cohort A and Part 2 Cohort B demonstrated a continued, favorable benefit-risk profile of ZX008 for the adjunctive treatment of seizures associated with LGS in children and adults. ZX008-1601 Part 1 was a randomized, double-blind, placebo-controlled study investigating the efficacy of fenfluramine for the treatment of seizures associated with LGS in patients 2 to 35 years of age over a 12 week maintenance period. Part 1 includes 2 independently analyzed cohorts, Cohort A and Cohort B. Cohort A is the primary analysis cohort and includes subjects from North America, Europe, and Australia, and Cohort B includes subjects from Japan. ZX008-1601 Part 2 was an open-label, 52-week, flexible-dose extension study to assess the long-term safety and tolerability of fenfluramine at doses of 0.2 mg/kg/day to 0.7 mg/kg/day. 279 participants were enrolled in this study and received fenfluramine 0.2 mg/kg/day for 1 month, then the dose was titrated to optimize treatment. The safety data from open-label phase of ZX008-1601 Part 2 are consistent with known safety profile of fenfluramine.

Recently concluded OLE study EP0212 (ZX008-1503) assessed long-term safety and tolerability of ZX008 in participants with Dravet syndrome. A total of 374 study participants received ZX008 in this OLE study for up to 36 months. Adjunctive treatment with ZX008 in children and adults with Dravet syndrome over a long-term open label period – up to 36 months- had an acceptable safety profile and was well tolerated. The study thus far supports the persistent profound effectiveness of ZX008 with a favorable benefit: risk profile.

Population in need of further characterization:

Long-term safety will continue to be evaluated through the PASS Registry of patients treated with fenfluramine.

Off-label use (in wider pediatric epilepsies; obesity)

Evidence source:

During the time that fenfluramine was previously available commercially, it was used experimentally in a variety of pediatric conditions thought to be potentially responsive to

increased CNS serotonin levels, including autism, ADHD and epilepsy. Fenfluramine was experimentally used in children with these indications from doses of 0.65 mg/kg/day to 3.6 mg/kg/day. Though efficacy was not established in the treatment of autism and ADHD, safety at these doses was acceptable and no cardiopulmonary AEs or any serious AEs were reported in over 40 publications. Due to the lack of established efficacy, it is unlikely to be used off-label in ADHD or autism.

A number of small studies and case series had been published describing the pediatric use of fenfluramine in epilepsy. These studies reported mild AEs, none of which were cardiac related, but no data on cardiac valve pathology were discussed (summarised in the ZX008 Investigator Brochure). Based on the potential for fenfluramine to be used off-label in this pediatric population with other rare refractory developmental epileptic encephalopathies, it is considered to be missing information.

Based on fenfluramine's mechanism of action and previous indication for obesity, there exists a possibility that fenfluramine could be used off-label for weight management, though other treatments are approved for weight management and due to the negative benefit-risk ratio, prescribing for this use seems unlikely. Prescribing fenfluramine off-label for the management of weight would be inconsistent with European and national guidance for the treatment of obesity (NICE Guidance).

The marketing authorization holder (MAH) does not recommend off-label use in obesity, especially due to the negative benefit/risk ratio, nor do they recommend off-label use of fenfluramine for wider pediatric epilepsies where efficacy has not been established.

Population in need of further characterization:

Further characterization of off-label use will be limited, as the extent of exposure is likely to be minimal based on the known safety profile of fenfluramine and the cardiac monitoring prescribed in the product labelling. However, off-label use of fenfluramine in these populations is considered missing information and will be assessed in the post-marketing setting through a PASS drug utilization study which will provide data to further characterize the use of fenfluramine in routine practice, with a focus on potential off-label use in other rare pediatric epilepsies and in obesity.

Part II Module SVIII Summary of the safety concerns

Table Part II–19: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Pulmonary arterial hypertension Valvular heart disease
Important potential risks	Suicidal ideation and behavior Growth retardation
Missing information	Long-term safety Off-label use (in wider pediatric epilepsies; obesity)

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Assessment of Fintepla sales patterns**: UCB will analyze sales and ordering patterns, and patient exposure data in each EU Member State in PSURs, in order to identify potential abnormal or suspicious increases, indicative of potential diversion (off-label use/misuse) and will introduce corrective and preventative actions (CAPAs) if abnormal or suspicious fenfluramine use patterns are identified.
- **A specific adverse reaction follow-up questionnaire for suicidal ideation and behavior:** UCB employs a targeted follow-up questionnaire for post-marketing reports of potential cases of attempted suicide, suicidal thinking and behavior, or intentional self-harm.
- **A specific adverse reaction follow-up questionnaire for valvular heart disease (VHD) and pulmonary arterial hypertension (PAH):** UCB employs a targeted follow-up questionnaire for post-marketing reports of potential cases of VHD and PAH.

  The respective follow-up questionnaire forms are provided in EU RMP Annex 4.
- **Other forms of routine pharmacovigilance activities**: None

III.2 Additional pharmacovigilance activities

III.2.1 EP0219: A drug utilization study

Study short name and title

A drug utilization study of fenfluramine in Europe

Rationale and study objectives

This observational study will provide data to further characterize the use of fenfluramine in routine practice, with a focus on potential off-label use in children younger than 2 years, in other rare paediatric epilepsies and for weight management. Data on the extent and frequency of echocardiographic monitoring will be collected within this observational study to assess the effectiveness of risk minimisation measures, given within the summary of product characteristics (SmPC), for:

• Echocardiogram assessment to confirm absence of VHD and PAH prior to fenfluramine treatment initiation

• Echocardiogram monitoring during use of fenfluramine

Primary objective:

- Describe fenfluramine use in routine clinical practice with a focus on its use in epilepsies other than any fenfluramine approved indications.

Secondary objectives:

- Describe the dose, frequency and duration of fenfluramine treatment.

- Describe the demographic characteristics (eg, age, sex, weight) of patients treated with fenfluramine in routine clinical practice.
- Describe the extent and frequency of echocardiographic monitoring.

Exploratory objective:

- Identify and describe prescriptions of fenfluramine other than for epilepsies, with a focus on obesity.

Study design

The primary and secondary objectives will be addressed via a retrospective medical chart review of patients treated with fenfluramine, with centers/physicians prescribing fenfluramine in routine practice (expectedly neuro-pediatricians, pediatricians or neurologists with experience in the treatment of epilepsy) in at least 5 European countries. This design will allow collection of epilepsy diagnoses with high granularity. The eligibility period, defined as the period of time within which patients should have initiated fenfluramine, will last up to 4 years from fenfluramine earliest market entry. Earliest market entry was Feb 2021 (Germany).

The exploratory objective will be addressed via a stepwise approach using electronic healthcare databases in Europe:

1. Patient count: The first step will consist of identifying if any prescriptions of fenfluramine, with no lifetime epilepsy diagnoses codes, are recorded in the databases of interest. These patient counts will be communicated annually to the PRAC.
2. Analysis (upon signal): If ≥ 5% of the patients with identified fenfluramine prescriptions have no lifetime epilepsy diagnoses, a historical cohort study will be conducted in relevant databases to describe patient and prescriber characteristics and fenfluramine treatment patterns.

Study population

Primary and secondary objectives.

- Inclusion criteria
  - Patients having initiated a treatment with fenfluramine in routine practice (that is, with at least 1 prescription of fenfluramine since its availability through Zogenix Access Program (ZAP)* or its commercial launch as applicable, and without any fenfluramine prescription before) within the eligible period.
  - Patients treated by centers/physicians prescribing fenfluramine in routine practice (expectedly neuro-pediatricians, pediatricians or neurologists with experience in the treatment of epilepsy)

  Provided informed consent or assent, as required by local regulations
- Exclusion criteria
  - None.

Exploratory Objective.

- Inclusion criteria for patient counts.

  - Patients with at least 1 fenfluramine prescription

- Inclusion criteria for analysis.
  - Patients with at least 1 fenfluramine prescription and no lifetime epilepsy-related diagnosis
- Exclusion criteria for analysis.
  - None.

Milestones

Primary and secondary objectives:

Estimated date of:

- Initial protocol approved by PRAC: 12 Jan 2023.
- Start of data collection (patient counts): Q2 2024
- Start of data collection (chart review): Q2 2024.
- End of data collection: Q4 2026.
- Final study report submission: Q4 2027.

Timelines are conditional on the actual date of market entry in each country.

Exploratory objective:

The exploratory objective (to identify patients with at least 1 fenfluramine prescription and upon signal to describe use of fenfluramine in patients without epilepsy diagnosis), will be addressed via a historical cohort study of patients treated with fenfluramine in 6 European countries, using data from secondary databases.

The study period will start when fenfluramine enters the market until end of study period (earliest market entry + 3 to 4 years), corresponding to the period when patients could receive a fenfluramine prescription (index event). The start date of the study period is conditional on the actual date of market entry in each country. Access to the study data can vary by country/database as each database has its own lag time for data availability, and it can also vary over time.

- First patient counts: Q2 2024
- Third patient counts: Q2 2026

Timelines are conditional on the actual date of market entry in each country. Yearly patient counts will be reported in the PSURs.

For further details please see EU RMP Annex 3.

III.2.2 EP0218: A Cardiovascular (CV) Registry of Patients Treated with Fenfluramine

Study short name and title

A Registry of Patients Treated with Fenfluramine.

Rationale and study objectives

This observational registry will provide data to further assess the long-term safety of fenfluramine as prescribed in routine practice in patients treated with fenfluramine, with a focus on characterizing and quantifying the important identified risks of VHD and PAH. In addition, the registry will provide data to characterize and quantify the important potential risk of growth retardation. Moreover, the data collected on the frequency of echocardiographic monitoring will also contribute to assessing the effectiveness of risk minimization measures.

The primary objective of this study is to assess the long-term cardiac safety of fenfluramine as prescribed in routine practice for fenfluramine approved indications, with a focus on:

- Incidence of valvulopathy
- Incidence of VHD
- Incidence of PAH

The secondary objectives of this study are:

- To assess the occurrence of growth retardation, if any, in patients treated with fenfluramine in routine clinical practice for fenfluramine approved indications
- To describe patients' ECHO monitoring for patients treated with fenfluramine in routine practice for fenfluramine approved indications.
- To assess the primary and secondary objectives abovementioned for all patients treated with fenfluramine enrolled in the registry

Study design

This is an observational prospective multi-country longitudinal cohort study (a registry) of patients treated with fenfluramine hydrochloride oral solution, conducted at centers prescribing fenfluramine in routine practice (physicians specializing in pediatrics or neurology – e.g., neuro-pediatricians, pediatricians or neurologists – with experience in the treatment of epilepsy).

- The enrolment period will be 5 years from the registry start date in the first participating country.
- The study period will be 10 years from the registry start date in the first participating country.
- Patients will be followed up until 6 months after the end of fenfluramine treatment, loss to follow-up, death, or end of study period, whichever occurs first.
- The maximum follow-up period in the registry for the first patient included will be 10 years.
- The maximum follow-up period in the registry for the last patient included will be 5 years.
- Current users (e.g., continuing treatment from an open-label, long-term follow-up, an access program, or treated with fenfluramine commercial product) will also be included, and the registry follow-up will add to any previous follow-up time while being treated with fenfluramine

The incidence rate of VHD and PAH in the general population younger than 40 years old is expected to be extremely low. Echocardiographic surveillance in this age group is rarely done and is performed only in very specific cases where medically indicated (e.g., treatment with specific chemotherapies known to have a cardiac effect or driven by clinical signs). Children and young adults with DS or other rare epilepsies treated with other drugs are not routinely monitored via echocardiographic surveillance. Consequently, in view of the low background risk and in the absence of a suitable comparator group, an external reference will be used to benchmark the incidence rates observed in the registry.

An external reference will be used to benchmark the incidence rates of the cardiovascular events of interest observed in the registry against background risks. Background risks will be obtained via electronic healthcare databases in Europe to assess the incidence rate of valvulopathy, VHD, and PAH in the:

- General population within the same age range as the registry population (Cohort 1)
- General population within the same age range as the registry population, with the exclusion of patients with congenital cardiac malformation (Cohort 2)

Background incidence rates will be assessed over the same study period as the registry. This assessment will be performed only if at least 1 case is observed in the registry.

Study population

The study population are patients aged in accordance with the indication statement in the SmPC and treated with fenfluramine according to the product label. The patients are either new users of fenfluramine or current users (e.g., continuing treatment from an open-label, long-term follow-up or from an early access program), and will be treated at centers/by physicians prescribing fenfluramine in routine practice (expectedly neuro-pediatricians, pediatricians or epileptologists).

Milestones

- Protocol approved by PRAC: 01 Sep 2022
- Start of data collection: 09 Jun 2023
- Progress reports: At the time of PSUR submissions
- Interim safety update reports: Estimated Q4 2028 (first interim report 5 years +6 months from start of data collection) and second interim report Q2 2031.
- End of data collection: + 10 years: Q2 2033
- Final study report submission: Q1 2034

Annual progress reports will be communicated as part of the PSURs and will include information on patient count data to evaluate the success of recruitment.

For further details please see EU RMP Annex 3.

III.2.3 EP0220: Study to assess risk minimization effectiveness

Study short name and title

A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS.

Rationale and study objectives

Patients on fenfluramine treatment are to be monitored via regular echocardiograms to detect signs of VHD or PAH and to minimise the important risks of VHD and PAH. As an additional risk minimization measure, educational material is/will be communicated to prescribers and to patients/carers based on marketing status. As an additional risk minimisation measure, educational materials are planned to be communicated to fenfluramine prescribers and to patients/carers. In addition, off-label use for weight management is an important missing information and will also be addressed in the physician educational material. This is in addition to the implementation of the Controlled Access Program (CAP) to prevent off-label use of fenfluramine for weight management and to confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking fenfluramine.

This observational study will assess the effect of these additional risk minimization measures by describing the awareness, knowledge, and compliance of fenfluramine prescribers to the physician specific educational material (Annex III Prescriber Educational Materials), as well as the distribution of the patient/carer educational material by the physicians.

Primary objectives:

- Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow-up.
- Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational material.

Secondary objective:

- Assess the physician-reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine on echocardiogram follow-up.
- Assess the awareness, knowledge and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material on prevention of off-label use for weight management.

Study design

Cross-sectional, multi-country, non-interventional survey conducted through an anonymous web questionnaire among physicians prescribing fenfluramine in routine practice in selected European countries.

The survey will be a structured questionnaire containing closed-ended questions, where the response format is either the selection of a single response or selection of several responses, as appropriate. It will be conducted online using a secure electronic data collection platform.

Study population

Physician selection is based on the inclusion and exclusion criteria listed below.

Physicians who meet each of the inclusion criteria and none of the exclusion criteria are eligible to participate in this study

- Physicians who prescribed fenfluramine at least once.

- Physician's primary country of practice is among selected study country
- Provided informed consent for using the survey data

Milestones

Current expected earliest date of market entry (Germany): Feb 2021.

The data will be collected 1 to 2 years after launch according to each country's launch date.

- Protocol approved by PRAC: 21 Jul 2022.
- Start of data collection: earliest date of market entry + 2 years: Q3 2022.
- Interim report submitted: 14 Jun 2023
- End of data collection: Q1 2025.
- Final study report submission: Q3 2025

For further details please see EU RMP Annex 3.

III.3 Summary Table of additional Pharmacovigilance activities

The summary of ongoing and planned additional pharmacovigilance activities is provided in Table Part III–1.

Table Part III–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
EP0218 A Registry of Subjects Treated with Fenfluramine *Ongoing*	**Primary objective:** Assess the long-term cardiac safety of fenfluramine prescribed in routine practice, with a focus on: • Incidence of valvulopathy • Incidence of VHD • Incidence of PAH **Secondary objective:** Assess the occurrence of growth retardation, if any, in patients treated with fenfluramine in routine clinical practice for fenfluramine approved indications.	Valvular heart disease Pulmonary arterial hypertension Long-term safety Growth retardation	Initial protocol approval	01 Sep 2022
			Annual progress reports	PSUR
			Interim safety reports	Interim safety update reports: Estimated Q4 2028 (5 years +6 months from start of data collection. Second interim report: Q2 2031.
			Final report	Q1 2034

Table Part III–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
EP0219 A Drug Utilization Study of Fenfluramine in Europe. *Ongoing*	**Primary objective:** Describe fenfluramine use in routine clinical practice with a focus on its use in epilepsies other than any fenfluramine approved indications. **Secondary objectives:** • Describe the dose, frequency, and duration of fenfluramine treatment • Describe the demographic characteristics (eg, age, sex, weight) of patients treated with fenfluramine in routine clinical practice • Describe the extent and frequency of echocardiographic monitoring **Exploratory objective:** Identify and describe prescriptions of fenfluramine other than for epilepsies, with a focus on obesity.	Off-label use (in wider pediatric epilepsies; obesity) Valvular heart disease Pulmonary arterial hypertension	Protocol approval	Initial protocol approved by PRAC on 12 Jan 2023
			Start of data collection (patient counts)	Q2 2024
			End of data collection	Q4 2026
			Final report	Q4 2027
EP0220 A European Study of the	**Primary objectives:**	Valvular heart disease	Protocol approval	Protocol approved by PRAC on 21 Jul 2022

Table Part III–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS. *Ongoing*	• Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow-up • Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational materials **Secondary objectives:** • Assess the physician reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine on echocardiogram follow-up • Assess the awareness, knowledge and self-reported compliance of physicians routinely prescribing fenfluramine regarding the physician-specific educational material to prevent off-label use for weight management	Pulmonary arterial hypertension Off-label use in wider pediatric epilepsies; obesity	Interim report	14 Jun 2023
			Final report	Q3 2025

LGS=Lennox-Gastaut syndrome; PAH=pulmonary arterial hypertension; PRAC=pharmacovigilance risk assessment committee; PSUR=periodic safety update report; VHD=valvular heart disease

PART IV PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There is no planned or ongoing imposed post-authorization efficacy studies that are conditions of the marketing authorisation or that are specific obligations for fenfluramine.

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN

V.1 Routine Risk Minimization Measures

Description of routine risk minimization measures by safety concern is presented in Table Part V–1.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Pulmonary arterial hypertension	**Routine risk communication:** SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8. PL section 2 and PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindications to fenfluramine treatment (PAH) in SmPC section 4.3. Direction for echocardiogram assessment to confirm absence of pulmonary hypertension prior to fenfluramine initiation in SmPC section 4.4. Direction for echocardiogram monitoring during use of fenfluramine and following discontinuation are included in SmPC section 4.4. Recommendations for actions to take with fenfluramine if PAH is detected on echocardiogram in SmPC section 4.4. Guidance that fenfluramine should not be used in patients with PAH in PL section 2. Guidance that doctors should perform echocardiogram monitoring prior to starting fenfluramine, during treatment, and after discontinuation in PL section 2. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription-only medicine, restricted medical prescription.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Valvular heart disease	**Routine risk communication:** SmPC section 4.3, SmPC section 4.4 and SmPC section 4.8. PL section 2 and PL section 4. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Contraindications to fenfluramine treatment (regurgitant aortic or mitral heart disease) in SmPC section 4.3. Direction for echocardiogram assessment to confirm absence of regurgitant aortic or mitral valvular disease prior to fenfluramine initiation in SmPC section 4.4. Direction for echocardiogram monitoring during use of fenfluramine and following discontinuation are included in SmPC section 4.4. Recommendations for actions to take with fenfluramine if pathologic level of regurgitation is detected on echocardiogram in SmPC section 4.4. Guidance that fenfluramine should not be used in patients with pre-existing severe valve disease in PL section 2. Guidance that doctors should perform echocardiogram monitoring prior to starting fenfluramine, during treatment, and after discontinuation in PL section 2. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription-only medicine, restricted medical prescription.
Suicidal ideation and behavior	**Routine risk communication:** SmPC section 4.4. PL section 2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance on monitoring of patients for signs of suicidal behavior and ideation which should be reported to the doctor immediately in SmPC section 4.4. Also warning in PL section 2 to patients with prior history of suicidal thoughts or behaviors to contact their healthcare professional. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription-only medicine, restricted medical prescription.

Table Part V–1: Routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Growth retardation	**Routine risk communication:** SmPC section 4.2, SmPC section 4.4 and SmPC section 4.8 (associated with weight loss). PL section 4 (associated with weight loss). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for weight and height monitoring in SmPC section 4.4. Legal status: Prescription-only medicine, restricted medical prescription
Long-term safety	**Routine risk communication:** None. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription-only medicine, restricted medical prescription.
Off-label use (wider pediatric epilepsies; obesity)	**Routine risk communication:** SmPC section 4.1, SmPC section 4.2, and SmPC section 4.4. PL section 1. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Guidance that Fintepla should be initiated and supervised by physicians with experience in the treatment of epilepsy in SmPC section 4.2. Guidance in SmPC section 4.2 and SmPC section 4.4 on off-label use: Fintepla must not be prescribed or used for weight management. Please refer to the CAP for further details. Guidance in PL section 2 that Fintepla must not be taken by anybody other than the patient for whom it is prescribed. Advice in SmPC section 6.4 that Fintepla must be stored securely. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription-only medicine, restricted medical prescription.

CAP=controlled access programme; PAH=pulmonary arterial hypertension; PL=package leaflet; SmPC=summary of product characteristics

V.2 Additional Risk Minimization Measures

V.2.1 Controlled access program

UCB is required to implement a CAP (EU-RMP Annex 6) to prevent off-label use for weight management in obese patients, and to inform of the need for periodic cardiac monitoring in patients taking Fintepla due to the important risks of PAH and VHD.

The aim of the program is to ensure that only Fintepla prescriptions from a register of health care professionals trained to not prescribe off-label for weight management and to perform periodic cardiac monitoring, will be fulfilled.

Neurologists will initiate Fintepla therapy but, in some Member States, for many patients, maintenance prescriptions will be written by a local general practitioner or family physician under the supervision of the responsible neurologist. This is to cover patients who may live a considerable distance from the neurologist.

Pharmacists will be informed about their role in the CAP (EU-RMP Annex 6).

V.2.2 Educational materials

Educational materials for healthcare professionals (initial prescribing Neuropediatrician or Neurologist)

List of addressed safety concerns:

- Valvular heart disease
- Pulmonary arterial hypertension
- Off-label use of fenfluramine for weight management

Rationale for the additional risk minimization activity:

This guide provides information on the safety of fenfluramine and information on the detection, careful monitoring, and/or proper management of selected safety concerns. Regarding the important risks of PAH and VHD, as well as the potential for off-label use of fenfluramine for weight management, the educational material stresses the importance of risk minimization measures. The materials provided to prescribing physicians will also advise them to encourage patients/carers to enroll in the fenfluramine registry to collect long-term safety data.

Target audience:

The materials will be directed to individual target audience as listed below, and will be adapted accordingly:

- The prescribing physician (Neuropediatrician or Neurologist)
- The Patient/Carer (via the prescribing Physician)

Plans to evaluate the effectiveness of the interventions and criteria for success:

The MAH will assess the adherence of prescribers to the risk minimization measures using a measurement of effectiveness survey (EU-RMP Annex 3). The study objectives will be to assess the awareness, knowledge and self-reported compliance of physicians prescribing fenfluramine to the educational material.

This will be a cross-sectional survey of physicians having prescribed fenfluramine at least once.

Criteria for success include:

- ≥80% of physicians distributing the patient/carer educational material
- ≥80% of physicians reporting awareness

- ≥80% of physicians reporting knowledge
- ≥80% of physicians reporting compliance

Educational materials for Patient/Carer

List of addressed safety concerns:

- Valvular heart disease
- Pulmonary arterial hypertension

Rationale for the additional risk minimization activity:

To inform parents and carers about the main risks associated with fenfluramine treatment, educate parents and carers on the necessity of echocardiograph monitoring, and the detection and management of selected safety concerns.

Target audience:

Parents/carers of patients with Dravet syndrome and LGS.

Planned distribution path:

Parents/carers will receive the educational materials from the prescribing physician.

Objectives:

- To educate parents/carers about the detection and proper management of selected safety concerns associated with fenfluramine.
- To encourage participation in the fenfluramine registry to collect long-term safety data.
- To inform patients about the importance of regular cardiac monitoring (ECHOs)
- Plans to evaluate the effectiveness of the interventions and criteria for success.

The distribution of the Parent/Carer Guide to patients and carers by prescribers will be assessed in the measurement of effectiveness survey (EU-RMP Annex 3).

V.3 Summary of risk minimization measures

Table Part V–2 provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pulmonary arterial hypertension	**Routine risk minimization measures:** • SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • A specific targeted follow-up questionnaire for potential cases of PAH is utilized in the

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• PL section 2 and PL section 4. • Contraindications to fenfluramine treatment in SmPC section 4.3. • Direction for echocardiogram assessment to confirm absence of pulmonary hypertension prior to fenfluramine initiation in SmPC section 4.4. • Direction for echocardiogram monitoring during use of fenfluramine and following discontinuation are included in SmPC section 4.4. • Recommendations for actions to take with fenfluramine if PAH is detected on echocardiogram in SmPC section 4.4 • Guidance that fenfluramine should not be used in patients with PAH in PL section 2. • Guidance that doctors should perform echocardiogram monitoring prior to starting fenfluramine and during treatment in PL section 2. • Guidance on signs of heart problems which should be reported to the doctor immediately in PL section 2. • Legal status: Prescription-only medicine,	post-marketing setting (EU RMP Annex 4) **Additional Pharmacovigilance activities:** • EP0218: A Registry of Patients Treated with Fenfluramine. *Final study report due date: Q1 2034* • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS. *Final study report due date: Q3 2025* • EP0219: A Drug Utilization Study of Fenfluramine In Europe. *Final study report due date: Q4 2027*

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
	restricted medical prescription. **Additional risk minimization measures:** • Guide for healthcare professionals. • Patient/carer guide. • CAP	
Valvular heart disease	**Routine risk minimization measures:** • SmPC section 4.3, SmPC section 4.4 and SmPC section 4.8. • PL section 2 and PL section 4. • Contraindications to fenfluramine treatment in SmPC section 4.3. • Direction for echocardiogram assessment to confirm absence of cardiac valve disease prior to fenfluramine initiation in SmPC section 4.4. • Direction for echocardiogram monitoring during use of fenfluramine and following discontinuation are included in SmPC section 4.4. • Recommendations for actions to take with fenfluramine if regurgitation is detected on echocardiogram in SmPC section 4.4.	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • A specific targeted follow-up questionnaire for potential cases of VHD is utilized in the post-marketing setting (EU-RMP Annex 4). **Additional Pharmacovigilance activities:** • EP0218: A Registry of Patients Treated with Fenfluramine. *Final study report due date: Q1 2034* • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS. *Final study report due date: Q3 2025* • EP0219: A Drug Utilization Study of Fenfluramine in Europe. *Final study report due date: Q4 2027*

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Guidance that fenfluramine should not be used in patients with valve disease in PL section 2. • Guidance that doctors should perform echocardiogram monitoring prior to starting fenfluramine and during treatment in PL section 2. • Guidance on signs of heart problems which should be reported to the doctor immediately in PL section 2. • Legal status: Prescription-only medicine, restricted medical prescription. **Additional risk minimization measures:** • Guide for healthcare professionals • Patient/carer guide • CAP	
Suicidal ideation and behavior	**Routine risk minimization measures:** • SmPC section 4.4 • PL section 2 • Guidance on monitoring of patients for signs of suicidal behavior and ideation which should be reported to the doctor immediately in SmPC section 4.4. • Warning in PL section 2 to patients with prior history of suicidal thoughts or	**Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • A specific targeted follow-up questionnaire for potential cases of '*suicidal ideation and behavior'* is utilized in the post-marketing setting (EU RMP Annex 4) **Additional Pharmacovigilance activities:** None

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
	behaviors to contact their healthcare professional. • Legal status: Prescription-only medicine, restricted **Additional risk minimization measures:** None	
Growth retardation	**Routine risk minimization measures:** • SmPC section 4.2, SmPC section 4.4 and SmPC section 4.8. • PL section 4. • Guidance for off-label use for weight loss in SmPC section 4.2. • Recommendations for weight and height monitoring in SmPC section 4.4. • Legal status: Prescription-only medicine, restricted medical prescription. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • EP0218: A Registry of Patients Treated with Fenfluramine. *Final study report due date: Q1 2034*
Long-term safety	**Routine risk minimization measures:** • Legal status: Prescription-only medicine, restricted. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:**

Table Part V–2: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
		• EP0218: A Registry of Patients Treated with Fenfluramine. *Final study report due date: Q1 2034*
Off-label use (in wider pediatric epilepsies; obesity	**Routine risk minimization measures:** • SmPC section 4.1, SmPC section 4.2 and SmPC section 4.4. • PL section 1 and PL section 2. • Legal status: Prescription-only medicine, restricted medical prescription. **Additional risk minimization measures:** • CAP • Guide for healthcare professionals	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Assessment of Fintepla sales patterns and patient exposure data. **Additional pharmacovigilance activities:** • EP0219: A Drug Utilization Study of Fenfluramine In Europe. *Final study report due date: Q4 2027* • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS. *Final study report due date: Q3 2025*

CAP=controlled access programme; LGS=Lennox-Gastaut syndrome; PAH=pulmonary arterial hypertension; PL=package leaflet; Q=calendar quarter; SmPC=summary of product characteristics; ZX008=fenfluramine hydrochloride

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

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 minimized, 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). Additionally, fenfluramine is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome as an add-on therapy to other antiepileptic medicines in patients 2-years of age and older. 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 minimize or further characterise the risks

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

Measures to minimize 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 (eg, with or without prescription) can help to minimize its risks.

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

In the case of Fintepla, these measures are supplemented with *additional risk minimization 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 minimize 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 (eg, on the long-term use of the medicine).

Table Part VI–1: List of important risks and missing information

List of important risks and missing information	
Important identified risks	Pulmonary arterial hypertension Valvular heart disease
Important potential risks	Suicidal ideation and behavior Growth retardation
Missing information	Long-term use Off-label use (in wider pediatric epilepsies; obesity)

II.B Summary of important risks

Summary of important identified risks

Important identified risk: Pulmonary arterial hypertension	
Evidence for linking the risk to the medicine	Based on historical experience with fenfluramine use in obese adults, and cases reported in the postmarketing setting with Fintepla in which PAH 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

Summary of important identified risks

Important identified risk: Pulmonary arterial hypertension	
	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-HT_{1B}, 5-HT_{2B} or 5-HT_{2A} receptors, nitric oxide deficiency, estrogen, and mutations in the BMPR2 gene.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.3, SmPC section 4.4., and SmPC section 4.8 • PL section 2 and PL section 4. • Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures** • Guide for healthcare professionals. • Patient/carer guide. • CAP
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • EP0218: A Registry of Patients Treated with Fenfluramine • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome • EP0219: A Drug Utilisation Study of Fenfluramine in Europe See Section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Valvular heart disease	
Evidence for linking the risk to the medicine	Based on historical experience with fenfluramine use in obese adults and cases reported in the postmarketing setting with Fintepla in which VHD was reported.
Risk factors and risk groups	Patients with pre-existing VHD.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.3, SmPC section 4.4 and SmPC section 4.8. • PL section 2 and PL section 4. • Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures** • Guide for healthcare professionals • Patient/carer guide

Summary of important identified risks

Important identified risk: Pulmonary arterial hypertension	
	• CAP
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • EP0218: A Registry of Subjects Treated with Fenfluramine • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome. • EP0219: A Drug Utilisation Study of Fenfluramine in Europe. See Section 2.3 of this summary for an overview of the post-authorisation development plan.

AEDs=anti-epileptic drugs; BMPR2=bone morphogenetic protein receptor type 2; CAP=controlled access programme; HIV=human immunodeficiency virus; 5-HT=5-hydroxytryptamine (serotonin); PAH=pulmonary arterial hypertension; PL=patient leaflet; SmPC=summary of product characteristics; VHD=valvular heart disease; ZX008=fenfluramine hydrochloride

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 1 of the risk factors for suicidal ideation and behavior 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 behavior.
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.4. • PL section 2. • Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None
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.

Summary of important identified risks

Important identified risk: Pulmonary arterial hypertension	
Risk minimization measures	**Routine risk minimization measures** • SmPC section 4.2, SmPC section 4.4 and SmPC section 4.8. • PL section 2. • Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • EP0218: A Registry of Patients Treated with Fenfluramine. See Section II.C of this summary for an overview of the post-authorisation development plan.

AEDs=anti-epileptic drugs; PL=patient leaflet; SmPC=summary of product characteristics.

Summary of missing information

Missing information: Long-term safety	
Risk minimization measures	**Routine risk minimization measures:** • Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures:** • None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • EP0218: A Registry of Patients Treated with Fenfluramine
Missing information: Off-label use (in wider pediatric epilepsies; obesity)	
Risk minimization measures	**Routine risk minimization measures**: • SmPC section 4.1, SmPC section 4.2 and SmPC section 4.4. • PL section 1 and PL section 2. Legal status: prescription-only medicine, restricted medical prescription. **Additional risk minimization measures:** • CAP to address potential off-label use for weight management. • Guide for healthcare professionals
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • EP0219: A Drug Utilisation Study of Fenfluramine in Europe.

Summary of important identified risks

Important identified risk: Pulmonary arterial hypertension	
	• EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome.

CAP=controlled access program; PL=patient leaflet; SmPC=summary of product characteristics; ZX008=fenfluramine hydrochloride.

II.C Postauthorization development plan

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

The following studies are conditions of the marketing authorisation:

- **EP0218: A Registry of Patients 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, with a focus on characterising and quantifying the important 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

- **EP0219: 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 2 years, in other rare paediatric epilepsies and for weight management. Data on the extent and frequency echocardiographic monitoring will also contribute to assess the effectiveness of risk minimisation measures.

- **EP0220: 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, as well as the distribution of the patient/carer educational material by the physicians.

PART VII ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Targeted questionnaire for suicidal ideation and behavior.

Targeted questionnaire for valvular heart disease and pulmonary arterial hypertension.

UCB Global DS database #: [case_num] **UCB LAM ID #:** [lam_case_num_cen_cu]

Questionnaire Completed By:

First and Last name: _____

Relationship to patient: _____

Address: _____

Tel: _____ Fax: _____

E-mail: _____

Patient information:

Patient initials: _____ Patient Gender: _____ Patient Date of Birth: _____

Fintepla Dosage regimen: _____

Indication of Use for Fintepla: _____

During of Treatment: _____

Medical History (please include all but especially any psychiatric diagnose/history):

_____

_____

_____

_____

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Prior to Taking Fintepla**	**While Taking Fintepla**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore or wish to fall asleep and not wake up. ***Have you thought about being dead or what it would be like to be dead?*** ***Have you wished you were dead or wished you could go to sleep and never wake up?*** ***Do you ever wish you weren't alive anymore?*** If yes, describe:	**Yes** ☐ **No** ☐ **Response Not Known**	**Yes** ☐ **No** ☐ **Response Not Known**

SUICIDAL IDEATION …continued

2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you thought about doing something to make yourself not alive anymore?*** ***Have you had any thoughts about killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐ **Response Not Known**	**Yes** ☐ **No** ☐ **Response Not Known**
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not specific plan). Includes person who would say *"I thought about taking an overdose, but I never made a plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)?*** ***What did you think about?*** If yes, describe:	**Yes** ☐ **No** ☐ **Response Not Known**	**Yes** ☐ **No** ☐ **Response Not Known**
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts, but I definitely will not do anything about them."* ***When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?*** ***This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.*** If yes, describe:	**Yes** ☐ **No** ☐ **Response Not Known**	**Yes** ☐ **No** ☐ **Response Not Known**
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you ever decided how or when you would make yourself not alive anymore/kill yourself?*** ***Have you ever planned out (worked out the details of) how you would do it?*** ***What was your plan?*** ***When you made this plan (or worked out the details), was any part of you thinking about actually doing it?*** If yes, describe:	**Yes** ☐ **No** ☐ **Response Not Known**	**Yes** ☐ **No** ☐ **Response Not Known**
INTENSITY OF IDEATION		
The following feature should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** ***Write response (options below):*** _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it is considered an actual suicide attempt. ***There does not have***	**Yes** ☐ **No** ☐

to be any injury or harm, just the potential for injury/ harm. If person pulls trigger while gun is in mouth, but gun is broken so no injury results, this is considered an attempt. ***Inferring Intent***: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent, but suicide can be inferred (e.g. gunshot to head, jumping from window of high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore?*** ***What did you do? Did you ever hurt yourself on purpose? Why did you do that?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to make yourself not alive anymore when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons, <u>not at all</u> to end your life or kill yourself (like to make yourself feel better, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Has subject engaged in Self-Injurious Behavior, intent unknown?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but someone or something stopped you before you actually did anything?*** ***What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to make yourself not alive anymore (end your life or kill yourself) but you changed your mind (stopped yourself) before you actually did anything?*** ***What did you do?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted attempts _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you done anything to get ready to make yourself not alive anymore (to end your life or kill yourself)- like giving things away, writing a goodbye note, getting things you need to kill yourself?*** If yes, describe:	
Suicidal Behavior: Suicidal behavior was present during the assessment period?	

Answer for Actual Attempts Only	Most Recent Attempt	Most Lethal Attempt	Initial/First Attempt
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third- degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Date:* _____ ___ *Enter Code:* _____	*Date:* _____ _ *Enter Code:* _____	*Date:* _____ *Enter Code:* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before you were run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code:* _____	*Enter Code:* _____	*Enter Code:* _____

UCB Global DS database #: [case_num] **UCB LAM ID #:** [lam_case_num_cen_cu]

Targeted follow-up questionnaire for valvular heart disease and pulmonary arterial hypertension

You have reported an event of possible valvular heart disease (VHD) and/or pulmonary arterial hypertension (PAH) for Fintepla (fenfluramine). This questionnaire is being sent to obtain valuable additional information about the reported case to thoroughly evaluate the relation to Fintepla exposure. By providing as detailed information as possible, you can make a valuable contribution to better the understanding of Fintepla.

Please refer to the local product label in your country for more information about Fintepla and the risks of VHD and PAH.

Cases of VHD and PAH have been reported for fenfluramine at higher doses when previously authorised to treat adult obesity, which in some cases were severe or even fatal. Therefore, periodic echocardiography must be performed in accordance with the local product label (i.e. Summary of Product Characteristics (SmPC)) of Fintepla and following-up on reported possible cases of VHD and PAH is of particular importance. Post-marketing data show that VHD and PAH also occur with doses used to treat Dravet syndrome and Lennox-Gastaut syndrome.

Echocardiograms (ECHO) are required:

- **Prior to starting Fintepla treatment, to exclude any pre-existing VHD or PAH**
- **Every 6 months during Fintepla treatment for the first 2 years**
- **Annually, after 2 years of Fintepla treatment**
- **Upon treatment discontinuation, 6 months after the last dose of Fintepla**
- **If an echocardiogram indicates pathological valvular changes, a follow-up echocardiogram should be considered at an earlier timeframe to evaluate whether the abnormality is persistent.**
- **If echocardiogram findings are suggestive of pulmonary arterial hypertension, a repeat echocardiogram should be performed as soon as possible and within 3 months to confirm these findings**

Echocardiograms indicative of pathological changes may require central adjudication by a UCB appointed expert provider. To anticipate this, we are asking for your consent for us to request ECHO images (patient's baseline, abnormal findings and two previous ECHO images as well as others, where needed) from the Imaging Facility for verification; the resultant report will be sent to you.

Do you consent for UCB to contact the Imaging Facility for the release of applicable ECHO images and share with expert provider?

(Select one): ☐ **Yes** ☐ **No**

If yes is selected, please provide contact details for the Imaging Facility:

Click or tap here to enter text.

Please note, that in order to complete our evaluation, a further follow-up request will be sent to you at a future date aligned with your patient's next ECHO to determine if subsequent routine ECHOs have presented VHD or PAH.

If an earlier ECHO is scheduled to confirm any observed pathological abnormalities, please contact us at AffiliateICSR@ucb.com quoting the UCB Global DS database number provided in this form.

Section 1: PATIENT INFORMATION

Patient Initials: Click or tap here to enter text.

Gender *(select one)*: ☐ **Male** ☐ **Female**

Pregnant? *(select **one**)*: ☐ **Yes** ☐ **No** ☐ **N/A**

Race/Ethnicity:

☐ **Asian** ☐**Australian Aboriginal/Torres Strait Islander** ☐ **Black** ☐ **Hispanic** ☐ **White**

☐ **Other (specify):** Click or tap here to enter text.

DOB *(MMM/YYYY)*: Click or tap to enter a date.

At time of the reported adverse event(s): Age: Click or tap here to enter text.**years**

Weight Click or tap here to enter text. **kg** **Height:**Click or tap here to enter text.**cm**

Section 2: ADVERSE EVENT(S) INFORMATION

#	ADVERSE EVENT(S)	Onset Date *(DD/MMM/YYYY)*	End Date *(DD/MMM/YYYY)*	Did the event result in any of the following? *(Select all that apply)*	Event Outcome *(Select one)*	Related to Fintepla? *(Select one)*
1	**Description:** Click or tap here to enter text. **Can you verify this event occurred as described?** *(Select one)* ☐Yes ☐ No	Click or tap to enter a date.	Click or tap to enter a date.	☐ **Death** ☐ **Life-threatening** ☐ **Hospitalization/ Prolonged Hosp** ☐ **Disability/Incapacity** ☐ **Congenital Anomaly/Birth Defect** ☐ ****Medically Significant** ☐ **None of the above; Non-Serious**	☐ **Resolved** ☐ **Resolved w/sequelae** ☐ **Resolving** ☐ **Not Resolved/ongoing** ☐ **Unknown**	☐ **Yes** ☐ **No** ☐**Unknown**
2	**Description:** Click or tap here to enter text. **Can you verify this event occurred as described?** *(Select one)* ☐Yes ☐ No	Click or tap to enter a date.	Click or tap to enter a date.	☐ **Death** ☐ **Life-threatening** ☐ **Hospitalization/ Prolonged Hosp** ☐ **Disability/Incapacity** ☐ **Congenital Anomaly/Birth Defect** ☐ ****Medically Significant** ☐ **None of the above; Non-Serious**	☐ **Resolved** ☐ **Resolved w/sequelae** ☐ **Resolving** ☐ **Not Resolved/ongoing** ☐ **Unknown**	☐ **Yes** ☐ **No** ☐**Unknown**
3	**Description:** Click or tap here to enter text. **Can you verify this event occurred as described?** *(Select one)* ☐Yes ☐ No	Click or tap to enter a date.	Click or tap to enter a date.	☐ **Death** ☐ **Life-threatening** ☐ **Hospitalization/ Prolonged Hosp** ☐ **Disability/Incapacity** ☐ **Congenital Anomaly/Birth Defect** ☐ ****Medically Significant** ☐ **None of the above; Non-Serious**	☐ **Resolved** ☐ **Resolved w/sequelae** ☐ **Resolving** ☐ **Not Resolved/ongoing** ☐ **Unknown**	☐ **Yes** ☐ **No** ☐**Unknown**

***Medically Significant indicates event was <u>not</u> fatal, life-threatening (it placed the subject at immediate risk of death), resulted in/prolonged hospitalization, disability/incapacity or congenital anomaly/birth defect, but based upon medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the aforementioned seriousness criteria.*

Was any treatment initiated for this/these adverse event(s)? *(Select one)* ☐ **Yes** ☐ **No**

If yes, specify: Click or tap here to enter text.

Has the patient had exposure to Fintepla prior to December 2020 (Marketing Authorisation); example, via clinical study or early access program)? *(Select one)* ☐**Yes** ☐**No** ☐ **Unknown**

If yes, did the patient have any adverse experience at that time? *(Select one)* ☐**Yes** ☐**No** ☐ **Unknown**

If yes, describe adverse experience:

Click or tap here to enter text.

What was the dose of Fintepla at the time of the event: Click or tap here to enter text.**mg/kg/day and** Click or tap here to enter text. **mg/day**

Was patient on concomitant stiripentol? ☐**Yes** ☐**No**

If yes, was stiripentol treatment discontinued due to this event? ☐**Yes** ☐**No**

Was Fintepla discontinued due to the onset of this event? *(Select one)* ☐**Yes** ☐**No**

Did the event abate after Fintepla discontinuation or dose reduction? *(Select one)* ☐**Yes** ☐**No** ☐**N/A**

If yes, did the event reoccur after Fintepla reintroduction or dose increase? *(Select one)* ☐**Yes** ☐**No** ☐**N/A**

If the event recurred, was the patient symptomatic? ☐**Yes** ☐**No**

If yes, describe symptoms (or signs): Click or tap here to enter text.

<u>Surveillance Echocardiography (ECHO)</u>:

Please provide all ECHO results, including baseline, in the table below.

For valvular findings - *use number to indicate finding: 1=absent/trace regurgitation; 2=mild regurgitation; 3=moderate regurgitation; 4=severe regurgitation; 5= choose from: valve thickening; restricted motion; or prolapse

For additional ECHO results – add information to section 9

Time of ECHO to treatment	**Findings**	**Signs/Symptoms**
Baseline ECHO (pre-treatment) **Date of ECHO:** Click or tap to enter a date. DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.

Follow-up ECHO (following **6 months** of treatment) **Date of ECHO:** Click or tap to enter a date. DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.
Follow-up ECHO (following **12 months** of treatment) **Date of ECHO:** Click or tap to enter a date. _____ DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.
follow-up ECHO (following **18 months** of treatment) **Date of ECHO:** Click or tap to enter a date. _____ DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.
ECHO following **6 months <u>after</u>** discontinuation (post treatment) **Date of ECHO:** Click or tap to enter a date. _____ DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.

For additional ECHO results		
ADDITIONAL ECHO ☐ During Treatment, Following Click or tap here to enter text. months **ON** treatment: — *OR* — ☐ After stop of drug Click or tap here to enter text. months **AFTER** discontinuation **Date of ECHO:** Click or tap to enter a date. DD/MMM/YYYY	☐ Aortic valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Mitral valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Tricuspid valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary valve: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5: select Choose an item. ☐ Pulmonary Arterial Hypertension ☐ Interventricular septal flattening ☐ Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. mmHg ☐ Other findings suggestive of PAH: Click or tap here to enter text. ☐ Any other cardiac findings: Click or tap here to enter text.	Did the patient have any symptoms/signs related to the abnormal ECHO finding? ☐Yes ☐No If yes – provide and include all abnormal physical examination findings: Click or tap here to enter text.

If the abnormal **findings** were suggestive of PAH or VHD, **was a specialist** (cardiologist or pulmonologist) **consulted**? *(Select one)* ☐**Yes, on** Click or tap here to enter text. (*DD/MMM/YYYY*) ☐**No** ☐**Unknown**	
If **No**, provide **reason**:	Click or tap here to enter text.
If Yes, please specify: Click or tap here to enter text.	Was a diagnosis of PAH confirmed: *(Select one)*: ☐ No ☐ Yes, **on** Click or tap to enter a date. (*DD/MMM/YYYY*) If Yes, provide relevant details: Click or tap here to enter text.
	Was a diagnosis of VHD confirmed: *(Select one)*: ☐ No ☐ Yes, **on** Click or tap to enter a date. (*DD/MMM/YYYY*) If Yes, provide relevant details: Click or tap here to enter text.

Did the VHD, PAH, or other cardiac valve abnormalities result in any of the following (check all that apply):

☐ **Medication or interventional therapy** ☐ **Hospitalization**
☐ **Discontinuation of Fintepla** ☐ **Death** ☐ **No action taken**

Section 3: MEDICAL HISTORY

Does the patient have any significant Medical History PRIOR to Fintepla start?

(Select one) ☐ **Yes** ☐ **No** ☐ **Unknown**

***If Yes**, select all that apply:*

Name of Medical Condition *(select all that apply)*	**Start Date** (*DD/MMM/YYYY*)	**End Date** (*DD/MMM/YYYY*) or **N/A** if ongoing
☐Bicuspid aortic valve	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Mitral valve prolapse	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**

☐Rheumatic heart disease	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Marfan's syndrome	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Sleep apnea	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Reversal of shunt with atrial septal defect	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Reversal of shunt with ventricular septal defect	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Reversal of shunt with patent foramen ovale	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Reversal of shunt with patent ductus arteriosus	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Aortic valve disease	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Mitral valve disease	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Hypertension	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Sickle cell disease	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Chronic obstructive pulmonary disease (COPD)	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Other medical conditions / risk factors *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Other medical conditions / risk factor (*specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**
☐Other medical conditions / risk factors *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐**N/A**

Section 4: FAMILY HISTORY

Does the patient have any significant Family History?
(Select one): ☐ **Yes** ☐ **No** ☐ **Unknown**

If **Yes**, *select all that apply in the table below*	*(Select all that apply)*		
☐ Family history of PAH	☐Maternal	☐ Paternal	☐Unknown
☐ Family history of pulmonary embolism	☐Maternal	☐ Paternal	☐Unknown
☐ Family history of VHD	☐Maternal	☐ Paternal	☐Unknown
☐ Family history of blood clotting disorder (specify): Click or tap here to enter text.	☐Maternal	☐ Paternal	☐Unknown

Section 5: FINTEPLA THERAPY INFORMATION

(Complete as much information as possible with dates/times the product was stopped and restarted if applicable; add information to section 9, if needed)

Indication for Fintepla Use: *(Select all that apply)*:
☐**Dravet Syndrome**
☐ **Lennox-Gastaut Syndrome**
☐**Other: specify:** Click or tap here to enter text.

Regimen #	Start / Restart Date of Fintepla (*DD/MMM/YYYY*)	Fintepla Dosage	Daily Exposure	End Date of Fintepla (*DD/MMM/YYYY N/A if ongoing*)	Regimen Duration (*# of Days*)	Lot Number and Expiration Date (*DD/MMM/YYYY*)	Patient's Weight and Height
1	Click or tap to enter a date.	Click or tap here to enter text. mg/kg/day	Click or tap here to enter text. mg/kg/day	Click or tap to enter a date. ☐ N/A	Click or tap here to enter text.	Lot #: Click or tap here to enter text. Exp Date: Click or tap here to enter text.	Weight Click or tap here to enter text. kg Height Click or tap here to enter text. cm
2	Click or tap to enter a date.	Click or tap here to enter text. mg/kg/day	Click or tap here to enter text. mg/kg/day	Click or tap to enter a date. ☐ N/A	Click or tap here to enter text.	Lot #: Click or tap here to enter text. Exp Date: Click or tap here to enter text.	Weight Click or tap here to enter text. kg Height Click or tap here to enter text. cm
3	Click or tap to enter a date.	Click or tap here to enter text. mg/kg/day	Click or tap here to enter text. mg/kg/day	Click or tap to enter a date. ☐ N/A	Click or tap here to enter text.	Lot #: Click or tap here to enter text. Exp Date: Click or tap here to enter text.	Weight Click or tap here to enter text. kg Height Click or tap here to enter text. cm
4	Click or tap to enter a date.	Click or tap here to enter text. mg/kg/day	Click or tap here to enter text. mg/kg/day	Click or tap to enter a date. ☐ N/A	Click or tap here to enter text.	Lot #: Click or tap here to enter text. Exp Date: Click or tap here to enter text.	Weight Click or tap here to enter text. kg Height Click or tap here to enter text. cm

Section 6: CONCOMITANT AND OTHER SUSPECT MEDICATIONS

(add information to section 9, if needed)

#	**Anti-Epileptic Drugs** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *DD/MMM/YYYY)* or **N/A** if ongoing	**Duration** *(# of days)*	**Dose**	**Units**	**Frequency**	**Did this product contribute to the event(s)?**	**Was this medication used to treat the event(s)?**
1	☐ **Stiripentol**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
2	☐ **Clobazam**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
3	☐ **Valproate**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
4	☐ **Cannabidiol**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
5	**Other** *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
#	**Strong Inhibitors of CYP1A2 and CYP2D6** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *DD/MMM/YYYY)* or **N/A** if ongoing	**Duration** *(# of days)*	**Dose**	**Units**	**Frequency**	**Did this product contribute to the adverse event?**	**Was this medication used to treat the event?**
1	☐ **Ciprofloxacin**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
2	☐ **Enoxacin**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
3	☐ **Fluvoxamine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
4	☐ **Oltipraz**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

5	☐ **Roficoxib**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
6	☐ **Zafirlukast**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
7	☐ **Bai-zhi (Angelica dahurica)**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
8	☐ **Bupropion**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
9	☐ **Dacomitinib**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
10	☐ **Fluoxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
11	☐ **Paroxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
12	☐ **Quinidine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
13	**Other** *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

#	**(Strong-moderate) Inducers of CYP1A2 and CYP2B6** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *DD/MMM/YYYY)* or **N/A** if ongoing	**Duration** *(# of days)*	**Dose**	**Units**	**Frequency**	**Did this product contribute to the adverse event?**	**Was this medication used to treat the event?**
1	☐ **Carbamazepine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
2	☐ **Rifampin**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

3	☐ **Phenytoin**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
4	☐ **Teriflunomide**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
5	☐ **Efavirenz**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
6	☐ **Ritonavir**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
7	☐ **Lopinavir and ritonavir**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
8	**Other** *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

#	**Selective Serotonin reuptake inhibitors (SSRIs)** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *DD/MMM/YYYY)* or **N/A** if ongoing	**Duration** *(# of days)*	**Dose**	**Units**	**Frequency**	**Did this product contribute to the adverse event?** *(Select one)*	**Was this medication used to treat the event?** *(Select one)*
1	☐ **Paroxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
2	☐ **Fluoxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
3	☐ **Citalopram**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
4	☐ **Escitalopram**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
5	☐ **Sertraline**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

6	☐ **Fluvoxamine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
7	☐ **Vilazodone**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
8	☐ **Vortioxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
9	☐ **Dapoxetine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
#	**Other Product /Dietary Supplement Name** *(select all that apply)*	**Start Date** (*DD/MMM/YYYY*)	**End Date** *DD/MMM/YYYY*) or **N/A** if ongoing	**Duration** *(# of days)*	**Dose**	**Units**	**Frequency**	**Did this product contribute to the adverse event?** *(Select one)*	**Was this medication used to treat the event?** *(Select one)*
1	☐ **Ergotamine**	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**
2	**Other** *(specify)*: Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	☐ **Yes** ☐ **No**	☐ **Yes** ☐ **No**

Section 7: RECREATIONAL EXPOSURES

(add information to section 9, if needed)

	Recreational Exposure(s)? *(Select one)*: ☐ **Yes** ☐ **No** ☐ **Unknown** *If* **Yes**, *select all that apply in the table below - add information to section 9, if needed*				
#	**Product / Substance Name** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *(DD/MMM/YYYY)* or **N/A** if *ongoing*	**Duration** *(# of days)*	**Did this product contribute to the adverse event?** *(Select one)*
1	☐ Alcohol	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
2	☐ Tobacco	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
3	☐ Marijuana	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
4	☐ MDMA (ecstasy)	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
5	☐ Other (*please specify*): Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
6	☐ Other (*please specify*) :Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐ **Unknown**
	Other pertinent Exposure(s), including Environmental Exposure(s)? *(Select one)*: ☐ **Yes** ☐ **No** ☐ **Unknown** *If* **Yes**, *please specify the type of exposure in the table below - add information to section 9, if needed*				
#	**Product / Substance Name** *(Select all that apply)*	**Start Date** *(DD/MMM/YYYY)*	**End Date** *(DD/MMM/YYYY)* or **N/A** if *ongoing*	**Duration** *(# of days)*	**Did this product contribute to the adverse event?** *(Select one)*
1	☐ Radiation	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐**Unknown**
2	☐ Other (*please specify*) :Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐**Unknown**
3	☐ Other (*please specify*) :Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date. ☐ **N/A**	Click or tap here to enter text.	☐ **Yes** ☐ **No** ☐**Unknown**

Section 8: RELEVANT DIAGNOSTIC TESTS AND LABORATORY DATA

8.1. Tests or Labs Performed for the Event

	Were any relevant tests or labs performed for the event(s)? *(Select one)*: ☐ **Yes** ☐ **No** ☐ **Unknown** *If* **Yes**, *describe below - add information to section 9, if needed*		
#	**Name of the Test** *(specify)*	**Date** *DD/MMM/YYYY*	**Result** *(select one)*:
1	Click or tap here to enter text.	Click or tap to enter a date.	☐ **Normal** ☐ **Abnormal** ☐ **Unknown** *If* **Abnormal**, *please describe*:Click or tap here to enter text.

2	Click or tap here to enter text.	Click or tap to enter a date.	☐ Normal ☐ Abnormal ☐ Unknown *If* Abnormal, *please describe:* Click or tap here to enter text.

#	Name of the Lab *(specify)*	Normal		Baseline		First Abnormal		Most Recent Abnormal		Resolution	
		Range	Units	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*
1	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
2	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.

8.2. Laboratory Markers Relevant to Hepatic and Renal Impairment

(add information to section 9, if needed)

#	Hepatic Marker *(select all that apply)*	Normal		Baseline		First Abnormal		Most Recent Abnormal		Resolution	
		Range	Units	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*
1	☐ Serum Albumin	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
2	☐ Serum Total Bilirubin	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
3	☐ Prothrombin Time	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
4	☐ AST (aspartate aminotransferase)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
5	☐ ALT (alanine aminotransferase)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
6	☐ ALP (alkaline phosphatase)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
7	☐ Other (*specify*) :Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.

#	Renal Marker *(select all that apply)*	Normal		Baseline		First Abnormal		Most Recent Abnormal		Resolution	
		Range	Units	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*	Value	Date *DD/MMM/YYYY*
1	☐ Creatinine Clearance	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
2	☐ Serum Creatinine	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.

3	☐ BUN (blood urea nitrogen)	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.
4	☐ Other (*specify*) :Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.	Click or tap here to enter text.	Click or tap to enter a date.

Section 9: PLEASE PROVIDE ANY ADDITIONAL INFORMATION YOU FEEL WILL ASSIST US IN OUR EVALUATION OF THIS REPORT: (e.g., relevant medical history, risk factors, concomitant illnesses, concomitant medications, including start and stop dates as applicable)

Click or tap here to enter text.

If unable to provide the above information, please provide us with the patient's treating physician and/or primary care physician so that we may further pursue our obligation to obtain follow-up information regarding these events:

Treating Physician: _____

Address: _____ **Phone:** _____

Primary Care Physician: _____

Address: _____ **Phone:** _____

Thank you for taking the time to provide this information.

Please sign below

Name _____ **Title** _____

Please Print

Relationship to the patient: _____

Signature_____**Date** _____

Privacy Notice ***UCB will process your personal data as well as patient personal and health related data according to the EU Data Protection Regulation 2016/679 (GDPR) and the United Kingdom General Data Protection Regulation to manage adverse events reporting, monitoring the safety of its products and comply with our legal obligations. We may engage local UCB affiliates and third parties who provide services to us (for example, IT hosting providers and vendors proving echo images verifications) which may involve their processing the personal data. Personal data may be also provided to regulators (for example the European Medicines Agency and, in the UK, MHRA) and law enforcement agencies. We may also publish information about adverse events that may include personal data (such as case studies and summaries); in this case, we will remove identifiers from reports so that no individual can easily be recognized. We may transfer personal data to third countries, including countries (like the US) which do not provide the same legal protections for the personal data as in EU/UK. Prior to any such transfer, we will ensure that recipients offer an adequate level of protection or there is a legal instrument providing appropriate safeguards for your personal data. In particular, disclosures to other UCB group companies will be based on UCB's Binding Corporate Rules ("BCRs"), available at https://www.ucb.com/UCB_BCRs.pdf. Disclosures to third party service providers will be based on transfer contracts (including the Standard Contractual Clauses) or other transfer mechanisms approved under applicable data protection laws. The personal data will be stored for the time required to achieve the objectives specified above, in compliance with the legislation in force, and to meet our legal obligations. For adverse events related to approved medicinal products, this period will be at least the period of the market authorization plus 10 years. To exercise your rights, you can contact UCB also by postal letter at: UCB S.A., Allée de la recherche 60, 1070 Anderlecht Belgium. You can also contact our Global Data Protection Officer by email at:*** dataprivacy@ucb.com***.***

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

Key messages of the additional risk minimization measures

Healthcare professional educational materials

- The Summary of Product Characteristics
- Guide for prescribing Neuropediatrician or Neurologist: (outline provided below)

  Main objectives:

  – To briefly inform physicians about the historical background on fenfluramine and its market withdrawal due to the risks VHD and PAH.

  – To emphasize that the currently approved indication has to be strictly adhered to and access is therefore controlled via a register for prescribers ensuring proper training before prescribing (Fintepla CAP).

  – To inform physicians about the conditions of the Fintepla CAP (that are agreed on national level).

  – To instruct physicians about the detection, monitoring, and/or proper management of VHD and PAH associated with fenfluramine.

  – The materials provided to prescribing physicians will also advise them to encourage patients/carers to enroll in the fenfluramine registry to collect long-term safety data.

Patient educational materials

- Patient information leaflet
- Patient/carer guide: (outline provided below)

  Main objectives:

  – To educate patients about the detection and proper management of VHD and PAH associated with fenfluramine.

  – To inform patients about the importance of regular cardiac monitoring (ECHOs).

  – To encourage participation in the fenfluramine registry to collect long-term safety data.

Controlled Access Programme

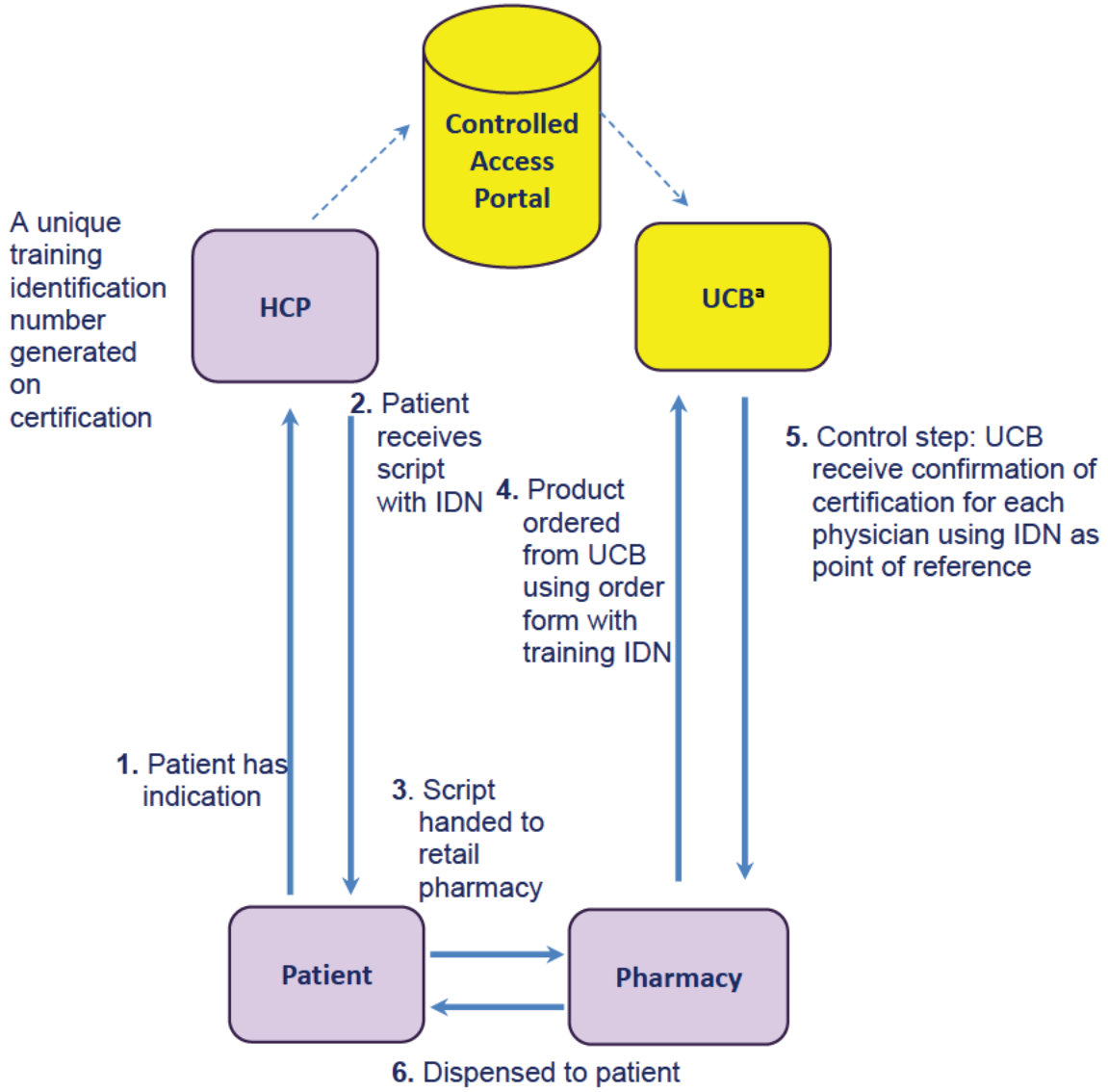
UCB is required to implement a CAP in order to prevent off-label use for weight management and to ensure that periodic echocardiogram monitoring is performed accordingly.

The aim of the programme is to prevent off-label use for weight management in obese patients, and to inform of the need for periodic cardiac monitoring in patients taking Fintepla due to the risks of VHD and PAH.

Neurologists or neuropediatricians will initiate Fintepla therapy. In some Member States, for many patients, *maintenance* prescriptions will be written by a local practitioner (here called secondary physician) under the supervision of the responsible neurologist/neuropediatrician. This is because many patients will live a considerable distance from the neurologist.

Prior to launch of Fintepla in each Member State, the details of the CAP must be agreed with the National Competent Authorities.

The Fintepla CAP is summarised below:



HCP=Healthcare professional; IDN=identification number.
[a]UCB Distribution center can be represented by a contracted third-party distributor.

Controlled Access Programme Process

The neurologist/neuropediatrician identifies a patient, with established Dravet syndrome or LGS, as suitable for treatment with Fintepla.

The neurologist/neuropediatrician is informed by the SmPC, direct letter, promotional and educational materials or face-to-face discussion that in order to prescribe Fintepla it is necessary for them to be included in a register (the Fintepla Controlled Access Portal) and receive a unique Training Identification Number (IDN), stored on the portal, that confirms that they must not prescribe Fintepla off-label for use in weight management and that echocardiogram monitoring needs to be performed according to the SmPC instructions. Training and registration on the Fintepla CAP will be provided on-line, on paper or face-to-face.

The secondary physician writing the maintenance prescription, requests training, as above, and gains their own unique Training IDN.

The prescriber (the initiating prescriber or the secondary physician writing a repeat prescription) writes the prescription and adds their unique training number to the prescription.

The patient/carer gives the prescription to the pharmacist.

The pharmacy orders Fintepla from the distributor entering the IDN to enable cross-checking of the doctor's identification against their training status.

The Fintepla Controlled Access Portal reconciles the Training IDN with a valid training entry and the distributor will fulfil the order.

The pharmacist receives and dispenses the medicine to the patient.

Pharmacist education and awareness

Information about the pharmacists' role in the CAP. When pharmacists attempt to fulfil an order, they will be directed by the UCB (or third-party logistics entity) to the CAP portal. The pharmacists will be asked to provide the IDN to allow the platform to check whether the prescriber has been trained.