

**EU-RISK MANAGEMENT PLAN FOR FINTEPLA
(FENFLURAMINE)**

2.2 MG/ML ORAL SOLUTION

Version 3.1

Date: 18 Apr 2024

20240418-rmp-v3.1 RTN-003754

ADMINISTRATIVE INFORMATION ON THE RISK MANAGEMENT PLAN

Risk Management Plan (RMP) Version number: 3.1

Data lock point for this RMP: 24 Jun 2023

Date of final sign off: 18 Apr 2024

Rationale for submitting an updated RMP: As part of request for supplementary information by European Medicine Agency's (EMA's) Pharmacovigilance Risk Assessment committee (PRAC) in the frame of Type II variation (procedure number: EMEA/H/C/003933/II/0022/G) and PSUSA procedure EMEA/H/C/PSUSA/00010907/202306.

Summary of significant changes in this RMP:

Exposure from clinical data source presented in Part II SIII was corrected.

Pulmonary arterial hypertension (PAH) was reclassified to important identified risk throughout the applicable sections based on a comprehensive review including fenfluramine's post-marketing data and as requested EMA as part of fenfluramine PSUSA procedure EMEA/H/C/PSUSA/00010907/202306

Corrections as requested by PRAC including deletion of 'dogs' from the bullet on carcinogenicity study in Part II SII and deletion of study EP0212 from Part III, Part V, and Part VI were done.

Other RMP versions under evaluation: None

Details of currently approved RMP(s):

Version number: 2.16

Approved with procedure: EMEA/H/C/003933/II/0017

Date of approval (opinion date): 31 Aug 2023

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 module.

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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
BMP2	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
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
PBRER	periodic benefit-risk evaluation report
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 expected 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 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.

Table 1: Product overview

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: <i>Paediatric (children aged 2 years and older) and adult populations</i> <u>Posology</u> <i>Paediatric (children aged 2 years and older) and adult populations</i> Table 1. Dosage recommendations for Dravet Syndrome <table><tr><td></td><td><u>without</u> stiripentol</td><td><u>with</u> stiripentol</td></tr><tr><td>Starting dose – first week</td><td colspan="2">0.1 mg/kg taken twice daily (0.2 mg/kg/day)</td></tr><tr><td>Day 7 - second week*</td><td>0.2 mg/kg twice daily (0.4 mg/kg/day)</td><td>Maintenance dose 0.2 mg/kg twice daily (0.4 mg/kg/day)</td></tr><tr><td>Day 14 - Further titration as applicable*</td><td>0.35 mg/kg twice daily (0.7 mg/kg/day)</td><td>Not applicable</td></tr><tr><td>Maximal recommended dose</td><td>26 mg (13 mg twice daily i.e. 6.0 mL twice daily)</td><td>17 mg (8.6 mg twice daily i.e. 4.0 mL twice daily)</td></tr></table> <p>* For patients who are tolerating fenfluramine and require a further reduction of seizures. For patients requiring more rapid titration, the dose may be increased every 4 days.</p> <p>If the calculated dose is 3.0 mL or less, the green printed 3 mL syringe should be used.</p> <p>If the calculated dose is more than 3.0 mL, the purple printed 6 mL syringe should be used.</p> <p>The calculated dose should be rounded to the nearest graduated increment.</p> Table 2. Dosage recommendations for Lennox-Gastaut Syndrome <table><tr><td>Starting dose – first week</td><td>0.1 mg/kg taken twice daily (0.2 mg/kg/day)</td></tr><tr><td>Day 7 - second week**</td><td>0.2 mg/kg twice daily (0.4 mg/kg/day)</td></tr><tr><td>Day 14 - maintenance dose**</td><td>0.35 mg/kg twice daily (0.7 mg/kg/day)</td></tr></table>		<u>without</u> stiripentol	<u>with</u> stiripentol	Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)		Day 7 - second week*	0.2 mg/kg twice daily (0.4 mg/kg/day)	Maintenance dose 0.2 mg/kg twice daily (0.4 mg/kg/day)	Day 14 - Further titration as applicable*	0.35 mg/kg twice daily (0.7 mg/kg/day)	Not applicable	Maximal recommended dose	26 mg (13 mg twice daily i.e. 6.0 mL twice daily)	17 mg (8.6 mg twice daily i.e. 4.0 mL twice daily)	Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)	Day 7 - second week**	0.2 mg/kg twice daily (0.4 mg/kg/day)	Day 14 - maintenance dose**	0.35 mg/kg twice daily (0.7 mg/kg/day)
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Table 1: Product overview

	<p>Maximal recommended dose</p> <p>26 mg (13 mg twice daily i.e. 6.0 mL twice daily)</p>
	<p><i>** The dosage should be increased as tolerated to the recommended maintenance dosage (ie, Day 14). For patients requiring more rapid titration, the dose may be increased every 4 day</i></p> <p>If the calculated dose is 3.0 mL or less, the green printed 3 mL syringe should be used.</p> <p>If the calculated dose is more than 3.0 mL, the purple printed 6 mL syringe should be used.</p> <p>The calculated dose should be rounded to the nearest graduated increment.</p> <p><u><i>Discontinuation of treatment</i></u></p> <p>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.</p> <p><u><i>Special populations</i></u></p> <p><i>Patients with renal impairment</i></p> <p>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.</p> <p>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.</p> <p>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</p> <p><i>Patients with hepatic impairment</i></p> <p>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.</p> <p>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.</p>

Table 1: Product overview

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

EEA=European economic area; EU=European union; 5-HT=5-hydroxytryptamine (serotonin); RMP=risk management plan

PART II: SAFETY SPECIFICATION

PART II: MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

1 DRAVET SYNDROME

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 one 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).

1.2 Prevalence

In December 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 [EMA/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 1–1](#) 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 1–1: 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
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.

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); 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).

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).

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.

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).

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.

2 LENNOX-GASTAUT SYNDROME

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).

2.2 Prevalence

The European prevalence sources used by the sponsor, in 2004, are summarized below in [Table 2–1](#). 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 2–1: 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
Waalder 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 two additional European prevalence sources, regarding LGS specifically, were identified since 2004 (the date when a public summary of orphan designation for rufinamide was published [EMA/122307/2004 Rev.1]) ([Table 2–2](#)). 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 2–2: Summary of European Prevalence Data on LGS Identified Post 2004

Prevalence Source	Region	Years	Age Range (years)	Point prevalence (per 10,000)
Syvetsen et al, 2015	Norway	1999-2014	All ages	0.3
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 2–3](#)

Table 2–3: 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).

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). 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).

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 two 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 two 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.

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).

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 2018, Strzelczyk 2021, Mastrangelo 2017, Asadi-Pooya 2018). Some develop autistic features and most require specialized educational settings (Crumrine 2011; Arzimanoglou 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 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 1](#).

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
Toxicity	<p>Single and Repeat-Dose Studies</p> <p>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.</p> <ul style="list-style-type: none"> • Mice <p>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</p>	<p>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.</p> <p>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.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>study in CByB6F1/Tg rasH2 hemizygous (transgenic) mice.</p> <p>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 $\geq 120\text{mg/kg/day}$ in males and $\geq 80\text{mg/kg/day}$ in females. Poor or variable body weight gains or losses were observed at $\geq 40\text{mg/kg/day}$ in males through Day 14 and $\geq 80\text{mg/kg/day}$ in females through Day 8. Clinical pathology changes included increased neutrophils at $\geq 80\text{mg/kg/day}$ in females only; decreased white blood cell counts and red blood cell mass at $\geq 80\text{mg/kg/day}$ in males and $\geq 120\text{mg/kg/day}$ in females; Target organ effects were observed at Day 15 termination in the thymus, pancreas, and liver at $\geq 40\text{mg/kg/day}$ reaching a level of adversity in the thymus only at $\geq 80\text{mg/kg/day}$. Based on the study results, the NOAEL was considered to be 40mg/kg/day.</p> <p>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.</p> <ul style="list-style-type: none"> Rats <p>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.</p> <p>In a GLP 13-week repeat-dose toxicity at dose levels of 0, 3.5, 5.0, 8.0, 13, and 20mg/kg/day, fenfluramine HCl was well tolerated at all dose levels and the NOAEL was identified as 20mg/kg/day.</p> <p>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.</p>	<p>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.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>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.</p> <ul style="list-style-type: none"> • Dogs <p>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.</p> <p>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.</p> <p>There were no fenfluramine HCl-related microscopic changes in the brain or cardiac valves (both mitral and aortic) in mice, rats and dogs.</p>	
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	<p>Two carcinogenicity studies in mice and rat with fenfluramine HCl were conducted by legacy Zogenix.</p> <p>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</p>	Non-clinical data revealed no special hazard for humans based on conventional carcinogenic studies.

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>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.</p> <p>A GLP 2-year carcinogenicity study in rats at dose levels of 0, 1, 2.5, and 8mg/kg/day was also conducted.</p> <p>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.</p> <p>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.</p>	
<p>Reproductive and Developmental Studies</p>	<p>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.</p> <p>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, salivation and pale extremities. In rabbits, the clinical observations included tremors, convulsions, dilated pupils, increased respiratory rate and laboured breathing.</p> <ul style="list-style-type: none"> <p>Fertility and early embryonic development to implantation study in rats</p> <p>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),</p> 	<p>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.</p> <p>The findings associated with toxicity in animals are not clinically relevant.</p> <p>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.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>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.</p> <ul style="list-style-type: none"> 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 losses at all doses. There were no fenfluramine HCl-related 	<p>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.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>external, visceral, or skeletal malformations or variations. Based on the significant maternal body weight loss and reduction in food consumption at all dose levels, the maternal NOAEL was not identified..</p> <ul style="list-style-type: none"> Developmental and Perinatal/Postnatal Reproduction in Rats <p>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.</p>	
Juvenile Toxicity Studies	<p>Two juvenile toxicity studies in rats were conducted by legacy Zogenix</p> <ul style="list-style-type: none"> Dose Range study <p>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.</p> <ul style="list-style-type: none"> 10-week toxicity study <p>A GLP 10-week study in juvenile rats (PND 7 through 76) was conducted at dose levels of 0,</p>	<p>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.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>3.5, 9, and 20mg/kg/day orally. The primary 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 ($\geq 9\text{mg/kg/day}$) 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.</p> <p>There were no fenfluramine HCl-related microscopic changes in the brain or cardiac valves (both mitral and aortic).</p>	
Safety Pharmacology	<p>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.</p> <p>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).</p> <p>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.</p> <p>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</p>	<p>Safety pharmacology studies have not identified any safety concerns.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>females at 9 and 20mg/kg/day. These findings 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).</p> <p>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).</p>	
Other toxicity-related information or data		
Cardiotoxicity	<p>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).</p> <p>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).</p>	<p>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</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
		<p>to 4.4 percentage points), and mitral regurgitation rates of 1.8% vs 1.2% for unexposed (95% confidence interval, 1.0 to 2.1 percentage points).</p> <p>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.</p>
<p>Neurotoxicity (neuropathology)</p>	<p>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.</p> <p>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.</p>	<p>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.</p> <p>Fenfluramine is not expected to have a negative impact on cognition in humans.</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
	<p>Together, these data show that fenfluramine is not neurotoxic as measured by appropriate 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.</p> <p>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).</p>	
Pulmonary Arterial Hypertension	<p>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 (Dempsey, 2013) in the development of the condition.</p>	<p>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</p>

Table 1: Summary of important nonclinical safety findings

Study type	Key safety finding from nonclinical studies	Relevance to human usage
		<p>dexfenfluramine used (Brenot, 1993).</p> <p>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.</p>

AE=adverse event; BID=bis in die (twice/day [dosing]); BRIEF=behavior rating instrument of executive function; BRIEF-P=BRIEF--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 24 Jun 2023 (the data lock point [DLP] of the EU-RMP), 1180 unique study participants have been randomized in the legacy Zogenix/UCB-sponsored clinical studies with ZX008 (fenfluramine developmental name). Of the 1180 study participants, 351 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 1180 total individuals, 829 patients diagnosed with Dravet or LGS received ZX008 in ZX008 studies (ZX008-1501, ZX008-1502, ZX008-1503, ZX008-1504, ZX008-1601, ZX008-1602, ZX008-1800).

[Table 1](#) provides the estimated cumulative number of participants exposed to investigational medicinal product (fenfluramine), Placebo and Blinded Study Drug in Phase 1-4 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.

Table 1: Estimated cumulative study participants exposure in fenfluramine Phase 1-4 clinical studies

Treatment	Participants dosed with Fenfluramine	Participants dosed with Placebo	Participants dosed with Blinded Study Drug
Pediatric and Adult Dravet Syndrome or LGS	829	105	0
Adult volunteers	351	60	0

LGS=Lennox-Gastaut syndrome

Note: A study participant can be counted under both the fenfluramine and placebo columns if they received both treatments.

Cut-off date: 24 Jun 2023.

Cumulative summary tabulations from completed and ongoing clinical studies of the demographic data are presented by age group in [Table 2](#), by sex in [Table 3](#), and by racial/ethnic group in [Table 4](#). If a study participant is exposed to more than 1 treatment, including placebo, the study participant is counted once for each treatment.

Table 2: Cumulative study participant exposure to investigational drug from ongoing and completed clinical studies by age group

	Pediatric (<18)	Adult (≥18)	Total
Pediatric and Adult Dravet Syndrome or LGS	674	155	829
Adult volunteers	0	351	351

LGS=Lennox-Gastaut syndrome.

Cut-off date: 24 Jun 2023.

Table 3: Cumulative study participant exposure to investigational drug from ongoing and completed clinical studies by sex

	Male	Female	Total
Pediatric and Adult Dravet Syndrome or LGS	451	378	829
Adult volunteers	241	110	351

LGS=Lennox-Gastaut syndrome.

Cut-off date: 24 Jun 2023.

Table 4: Cumulative study participant exposure to investigational drug from ongoing and completed clinical studies by racial/ethnic group

Clinical Study	American Indian or Alaska Native	Asian	Black/ African American	Native Hawaiian or Other Pacific Islander	NR	Other ^a	Unk	White	Total
Pediatric and Adult Dravet Syndrome or LGS	P	76	20	P	86	19	PP	614	829
Adult volunteers	P	35	56	P	0	11	0	245	351

LGS=Lennox-Gastaut syndrome; NR=not reported; Unk=unknown.

Data from completed clinical studies as of 24 Jun 2023.

^aOther column captures participants reporting more than one ethnic/racial group or reporting Multiracial.

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

1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

The main exclusion criteria in pivotal clinical studies in Dravet syndrome and LGS within the ZX008 development program are discussed in [Table 1–1](#). Exclusion criteria applied to ensure standardization of the study population (rather than safety-related exclusion criteria) are not presented.

Table 1–1: 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 potential 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.

Table 1–1: Exclusion criteria in pivotal clinical studies within the development program

Is it considered to be included as missing information?	No
Rationale	The anorectic effect of fenfluramine is known and would not be safe to study against a background of anorexia nervosa or bulimia, two 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 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	<p>Legacy Zogenix sponsored Study ZX008-1903, investigating the effects of hepatic insufficiency on the pharmacokinetics of fenfluramine.</p> <p>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.</p> <p>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.</p>
<p>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</p>	
Reason for exclusion	<p>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:</p> <ul style="list-style-type: none"> • 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 1–1: Exclusion criteria in pivotal clinical studies within the development program

Rationale	<ul style="list-style-type: none"> • 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 norfenfluramine 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.
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Table 1–1: 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 1–1: 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.
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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.

2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

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.

3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Table 3–1 provides an example of overview of exposure in special population typically under-represented in clinical trial development programs.

Table 3–1: Exposure of special populations included or not in clinical trial development programs

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

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant women	Not included in the clinical development program
Breastfeeding woman	
<p>Patients with relevant comorbidities:</p> <ul style="list-style-type: none"> Patients with hepatic impairment 	<p>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 1).</p> <p>Asymptomatic study participants with mild hepatic impairment (elevated liver enzymes <3xULN and/or elevated bilirubin <2xULN) were not excluded from the clinical development program.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Monitoring of patients should be considered</p>
<p>Patients with relevant comorbidities:</p> <ul style="list-style-type: none"> Patients with renal impairment 	<p>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.</p>

Table 3–1: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with relevant comorbidities: <ul style="list-style-type: none"> Patients with cardiovascular impairment 	Patients with cardiovascular impairment were not included in the clinical development program (Section 1).
Patients with relevant comorbidities: <ul style="list-style-type: none"> Immunocompromised patients 	There were no exclusion criteria for immunocompromised patients
Patients with relevant comorbidities: <ul style="list-style-type: none"> 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	<p>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.</p> <p>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 CDKL5 deficiency disorder.</p>

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

PART II: MODULE SV: POSTAUTHORIZATION EXPERIENCE

1 POST-AUTHORISATION EXPOSURE

1.1 Method used to calculate exposure

As highlighted in the Pharmacovigilance Risk Assessment Committee (PRAC) preliminary assessment report (AR) for PSUR No.4 (EMA/H/C/PSUSA/00010907/202212), the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) Index has recently been 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.

Patient-years = $\frac{\text{total amount of product distributed [in mg]}}{\text{DDD}}$

365.25 days in year

0.25 is added to account for leap years.

1.2 Exposure

The total amount of product sold since first approval (International Birth Date [IBD] 25 Jun 2020) to the DLP (24 Jun 2023) was cci mg, as derived from the UCB sales data. According to the methodology described above, patient exposure to fenfluramine is estimated at approximately cci patient-years cumulatively.

The breakdown of exposure by region are presented in [Table 1–1](#).

Table 1–1: Estimated Exposure Data from Post-Marketing Sources

Region	Cumulative (Jun 2020 to Jun 2023) (Patient-years)
EU	
cci	

Table 1–1: Estimated Exposure Data from Post-Marketing Sources

Region	Cumulative (Jun 2020 to Jun 2023) (Patient-years)
CCI	
EEA	
CCI	
Europe (non-EU/non-EEA)	
CCI	
Asia Pacific Nations	
CCI	
Rest of the World	
PPD	
Total in Patient Years	CCI

EEA=European economic area; EU=European union; ROW=rest of world.

Note: Sales data are only available on a month-to-month basis, so the sales data used for the calculation includes data from 01 Jan 2020 to 30 Jun 2023

US Risk Evaluation and Mitigation Strategy

In the US, all patients who have received fenfluramine must be enrolled in the US Risk Evaluation and Mitigation Strategy (REMS) program. As of the DLP of this report (24 Jun 2023), cumulatively, a total of CCI patients have received treatment. The REMS exposure data are included in the cumulative exposure presented in [Table 1–2](#).

Table 1–2: Cumulative Exposure Data from US REMS

US REMS Gender	Cumulative (number of patients)
Male	CCI

Table 1–2: Cumulative Exposure Data from US REMS

US REMS Gender	Cumulative (number of patients)
Female	CCI
US REMS Previous exposure	
Naïve	CCI
Not Naïve	CCI
US REMS Age^a	
<18	CCI
≥18	CCI

REMS=Risk Evaluation and Mitigation Strategy.

^a Age at time of enrollment.

Cumulative: From the IBD to 24 Jun 2023

PART II: MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

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

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).

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:

1. 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 (\geq moderate mitral regurgitation or \geq 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 PBRER#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).

2. 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.

3. 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 (Dempsey 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 Phase 3 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

Stiripentol with or without clobazam (and/or valproate)

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.

4. Known risks that do not impact the risk-benefit profile:

- None

5. 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.

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

Table 1–1: 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.

Table 1–1: Risks considered important for inclusion in the list of safety concerns in the RMP

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 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, one 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	<p>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.</p> <p>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.</p>

Table 1–1: 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	<p>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.</p> <p>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.</p> <p>To prevent off-label use in weight management a CAP is required (See EU-RMP Part VII Annex 6).</p>
Use in patients with renal impairment	
Risk-benefit impact	<p>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.</p>
Use in patients with hepatic impairment	
Risk-benefit impact	<p>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.</p>

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.

2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

The European Pharmacovigilance and Risk Assessment Committee (PRAC) in the context of the recently finalized fenfluramine PSUSA procedure EMEA/H/C/PSUSA/00010907/202306 recommended to reclassify the important potential risk of ‘pulmonary arterial hypertension’ as an important identified risk. A comprehensive review of PAH was thus undertaken. Based on the

existing information, the historical body of information, biological plausibility of PAH cases reviewed, overlapping pharmacokinetic exposure from the epilepsy and weight loss dose ranges, and the presence of an index case in the pediatric population where the background risk of PAH is considered very rare; an association between fenfluramine and PAH could not be excluded. Pulmonary arterial hypertension was thus reclassified to an important identified risk.

3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

3.1 Presentation of important identified risks and important potential risks

3.1.1 Important identified risks

Table 3–1: Important identified risk: Pulmonary arterial hypertension

Potential mechanisms	Fenfluramine is 1 of over 16 different compounds that, based on case reports, has in the literature been associated with PAH. The clinical appearance and pathology of drug-induced PAH is indistinguishable from other forms of PAH. Since it is associated with compounds of varying structures and it occurs in a subset of individuals taking those drugs, the mechanism, or mechanisms, of drug-induced PAH has/have not been identified. Studies of fenfluramine-induced PAH have hypothesized that several factors may be responsible for the potential association and cause, including stimulation of 5-HT _{1B} , 5-HT _{2B} or 5-HT _{2A} receptors, nitric oxide deficiency, estrogen, and mutations in the BMPR2 gene (CTD Module 2.6.6.8.3).
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Table 3–1: Important identified risk: Pulmonary arterial hypertension

Evidence source(s) and strength of evidence	<p>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.</p> <p>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). As described below, no evidence of PAH has been identified in legacy Zogenix-sponsored clinical studies in 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 >3 years of exposure in some participants.</p>
Characterization of the risk	<p>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).</p> <p><u>Clinical study data</u></p> <p>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 36 months. There was no evidence of PAH during the entire ZX008 development program for DS or LGS.</p> <p><u>Postmarketing data</u></p> <p>In post-marketing data, new onset of PAH in a child with Dravet Syndrome, considered likely associated with fenfluramine (10.12mg/day) has been reported. The patient discontinued fenfluramine and the reaction resolved post-discontinuation.</p>

Table 3–1: Important identified risk: Pulmonary arterial hypertension

Risk factors and risk groups	<p>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).</p> <p>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.</p>
Preventability	<p>Effective measures to prevent fenfluramine-induced PAH are not known; however, it is contraindicated for use in patients with pre-existing PAH. 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. 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. A final echocardiogram should be conducted 3-6 months after the last dose of treatment with fenfluramine.</p>
Impact on risk-benefit balance of the product	<p>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). Also, due to the significant high morbidity and mortality associated with Dravet syndrome and LGS patients who are experiencing frequent convulsive seizures, establishing meaningful seizure reduction in these populations leads to an acceptable risk/benefit profile for fenfluramine.</p>
Public health impact	<p>Not yet established in the Dravet syndrome or LGS population as estimated exposure to fenfluramine in the post-marketing setting is limited.</p> <p>The public health impact is expected to be low, based on the low probability of developing PAH seen in obese adult patients treated with fenfluramine.</p>

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

3.1.2 Important potential risks

Table 3–2: Important potential risk: Valvular heart disease

Potential mechanism(s)	<p>In vitro and in vivo studies have been conducted to attempt to identify any association between fenfluramine and valvulopathy. 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 valvulopathy 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 valvulopathy remains hypothetical and unproven scientifically.</p> <p>Fenfluramine does not have a strong binding affinity for 5-HT_{2B}, but the fenfluramine metabolite, norfenfluramine, binds potently to the 5-HT_{2B} receptor, and therefore has been hypothesized to play a role in the reported fenfluramine-associated valvulopathy, rather than fenfluramine itself. These data suggest cardiac 5-HT_{2B} receptor activation by norfenfluramine may be the basis for any clinical effect on valves, but no single assay has been able to demonstrate whether a 5-HT_{2B} agonist will act as a valvulopathogen in vivo. Importantly, 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 Drug-Induced Valvular Heart Disease (DI-VHD) in humans (Norris and Milan, 2018). No case of valvulopathy has been identified in Dravet syndrome patients taking ZX008 for up to 3 years.</p>
Evidence source(s) and strength of evidence	<p>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).</p>

Table 3–2: Important potential risk: Valvular heart disease

	<p>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).</p> <p>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.</p> <p>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). Even today, though, 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).</p> <p>An examination of published studies of valve disease associated with active or very recent fenfluramine use is provided in the table below. The studies reviewed include only those studies involving at least 20 study participants. As shown, most of the available reports are derived from a case-control study design; the remainder include observational or referral study designs and 1 primary clinical trial design. A few notable features emerge. The rates of valve regurgitation reported for exposed vs. unexposed individuals are highly variable, and there is a trend of lower rates reported by studies with larger samples of exposed individuals. It can also be seen that lower rates are reported in studies published at later dates. These findings are consistent with temporal trends that often emerge following initial reports of an adverse drug effect. Early reports can focus on a small number of exposed individuals that may be subject to initial sampling or referral bias; Kimmel (1999) reviewed medical histories</p>
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Table 3–2: Important potential risk: Valvular heart disease

	<p>of 18 patients reported to have fen/phen-induced valvulopathy and found 4 (22%) had heart murmurs diagnosed prior to fenfluramine use, 2 (11%) had prior use of medications known to cause valvulopathy, and 1 (6%) had shortness of breath prior to starting fen/phen (Kimmel et al, 1999). This phenomenon is illustrated by comparing the high valve disease rates reported by Connolly et al., in 1997 with the substantially lower valve disease rates reported by the same investigator group (Teramae et al, 2000) in 2000, where the latter study is based on a much larger sized case series. A critical review of the studies in uncovers multiple methodological issues and sources of bias that could possibly affect their conclusions including study design, study sample, exposure and outcomes, no Baseline echocardiograms, lack of standardization for echocardiogram settings, unblinded echocardiogram readings, and inherent biases, as detailed in the CV ISS. Another important observation relates to the type of valve disease reported. Aside from the very initial case series by Connolly et al., most studies suggest that fenfluramine use may increase risk of regurgitation mainly for the aortic valve, with risk estimates that are negative or inconclusive for the other valves.</p> <p>Legacy Zogenix has reviewed publications of data from experimental animal models; 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 valvulopathy while others do not, and some report valvulopathy 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 valvulopathy.</p> <p>In summary, 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. In the ensuing years, multiple controlled investigations reported the rates of VHD were much lower than originally reported. 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.</p>																																																	
	<p>Overview of Published Studies of Valve Disease Associated with Fenfluramine in the Literature</p> <table><tr><th rowspan="2">Study</th><th rowspan="2">Year</th><th rowspan="2">No.</th><th rowspan="2">Drug: Treatment Duration (days)</th><th rowspan="2">Notes</th><th colspan="4">Valve Regurgitation, %</th></tr><tr><th>AR</th><th>MR</th><th>TR</th><th>PR</th></tr><tr><td colspan="9">Case Series or Observational Uncontrolled Cohort</td></tr><tr><td>Connolly et al.</td><td>1997</td><td>E: 24</td><td>Fen-Phen: 330±207</td><td>Non-blinded echo reading</td><td>E: 88%</td><td>E: 70%</td><td>E: 29%</td><td>n / a</td></tr><tr><td>Wadden et al.</td><td>1998</td><td>E: 20</td><td>Fen-Phen: 730</td><td>2 blinded echo readers</td><td>E: 25%</td><td>E: 10%</td><td>n/a</td><td>n / a</td></tr><tr><td>Fisher et al.</td><td>1998</td><td>E: 156</td><td>Fen Phen: 30 to 1800</td><td>Non-blind echo reading</td><td>E: 19%</td><td>E: 3%</td><td>E: 1%</td><td>n / a</td></tr></table>	Study	Year	No.	Drug: Treatment Duration (days)	Notes	Valve Regurgitation, %				AR	MR	TR	PR	Case Series or Observational Uncontrolled Cohort									Connolly et al.	1997	E: 24	Fen-Phen: 330±207	Non-blinded echo reading	E: 88%	E: 70%	E: 29%	n / a	Wadden et al.	1998	E: 20	Fen-Phen: 730	2 blinded echo readers	E: 25%	E: 10%	n/a	n / a	Fisher et al.	1998	E: 156	Fen Phen: 30 to 1800	Non-blind echo reading	E: 19%	E: 3%	E: 1%	n / a
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Table 3–2: Important potential risk: Valvular heart disease

	Lepor et al.	2000	E: 85	Fen-Phen: 321	2 blinded echo readers	E: 28%	E: 11%	E: 13%	n / a
	**Teramane et al.	2000	E: 191*	Dex/Fen± Phen: 30 to 720	Non-blind echo readers	E: 29%	E: 6%	E: 4%	n / a
	Dahl et al	2008	E: 5743	Dex/Fen: N/A	Semi-blinded echo readers	E: 15%	E: 5%	E: 5%	n / a
Case-Control									
	Jick et al.	1998	E: 9765	Dex/Fen: 136±106	1 blinded echo reader	0.09%	0.04		n / a
	Khan et al.	1998	E: 257 U: 239	Dex/Fen (±Phen): 226±240	2 semi-blinded echo readers	E: 23% U: 1.3%		n/a	n / a
	Palmieri et al.	2002	E: 19 U: 2505	Dex/Fen: N/A	All hypertensive; 2 blinded echo readers/study	E: 32% U: 6%	E: 11% U: 19%	n/a	n / a
	Ko et al.	2003	E: 36 U: 43	Dex/Fen: 154±203	All T2D; 1 blinded echo reader	E: 11% U: 0%	E: U: :	E: 0% U: 0%	n / a
Randomized Controlled Trials									
	Weissman et al.	1998	E: 718 U: 354	Dex vs Placebo: 72±23	Blinded echo readers	E: 5.4% U: 3.6%	E: U: : 1.2%	E: 4.8% U: 5.9%	n / a
<p>AR=aortic valve regurgitation; Dex=dexfenfluramine; E=exposed; echo=echocardiogram; Fen=fenfluramine; n/a=not applicable; MR=mitral valve regurgitation; NEJM=New England journal of medicine; Phen=phentermine; PR=pulmonary valve regurgitation; T2D=type II diabetes mellitus; TR=tricuspid valve regurgitation; U=unexposed.</p> <p>Retrospective studies attempting to define the incidence, prevalence, dose-relationship, time of onset and reversibility of the effect were subsequently published. One review article found that with improvement of scientific methods, including use of control groups, standardization of echocardiogram performance and readings, and improved understanding of the relatively new technology of color echocardiography, reported prevalence rates of fenfluramine-associated valvular regurgitation decreased (Figure 1) (Weissman et al, 2001).</p>									

Table 3–2: Important potential risk: Valvular heart disease

	<p>Figure 1 Prevalence of valvular regurgitation (using the FDA criteria) in patients on diet pills using large, published controlled studies with standardized Echo (Weissman et al, 2001)</p> <table><tr><th></th><th>FDA 1997</th><th>Kahn 1998</th><th>Weissman 1998</th><th>Jick 1998</th><th>Shively 1999</th><th>Gardin 2000</th><th>Jollis 2000</th></tr><tr><td>Treatment n =</td><td>284</td><td>233</td><td>667</td><td>8903</td><td>223</td><td>934</td><td>1137</td></tr><tr><td>Control n =</td><td>0</td><td>233</td><td>315</td><td>9281</td><td>189</td><td>539</td><td>672</td></tr></table> <p>Adapted from: Weissman, N.J. <i>Am. J. Med. Sci.</i> 2001; 321: 285-91</p>		FDA 1997	Kahn 1998	Weissman 1998	Jick 1998	Shively 1999	Gardin 2000	Jollis 2000	Treatment n =	284	233	667	8903	223	934	1137	Control n =	0	233	315	9281	189	539	672
	FDA 1997	Kahn 1998	Weissman 1998	Jick 1998	Shively 1999	Gardin 2000	Jollis 2000																		
Treatment n =	284	233	667	8903	223	934	1137																		
Control n =	0	233	315	9281	189	539	672																		
Characterization of the risk	<p>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).</p> <p><u>Clinical study data</u></p> <p>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. The results from the ZX008 clinical program strongly support the supposition that low dose fenfluramine when given to patients with Dravet syndrome and LGS does not encompass a high risk of valvulopathy.</p> <p><u>Postmarketing data</u></p> <p>To date, no change to the characterization of the risk has been identified from postmarketing sources regarding fenfluramine use and VHD.</p>																								
Risk factors and risk groups	<p>When evaluating the risk of valve disease in the setting of fenfluramine use, a few conclusions can be drawn from considering the evidence to date in a historical context. First, the magnitude and type of risk initially reported in 1997 was excessive (Weissman et al, 2001). Additionally, more recently published studies tend to report lower rates compared with earlier published studies; there is also a trend of lower rates reported by studies with larger compared to smaller samples of exposed individuals studied. Importantly, the risk of valve disease with fenfluramine prescribed at much lower doses than those used for adult weight loss, for any</p>																								

Table 3–2: Important potential risk: Valvular heart disease

	<p>duration of time, remains unknown. No participants in the ZX008 clinical program developed VHD, with some now being treated for over 3 years. For adults treated with fenfluramines at doses prescribed for weight loss and for durations longer than 3 to 6 months, and most commonly co-prescribed with phentermine, there appears to be a valve disease risk that primarily involves the aortic valve and that leads to a type of regurgitation that is predominantly mild, rarely reported as moderate, and never reported as severe in controlled studies. Furthermore, the presence of regurgitation has not been consistently associated with any obvious structural abnormality (Sachdev et al, 2002; Jollis et al, 2000). Interestingly, the risk of aortic valve regurgitation may well be more pronounced in persons with baseline cardiovascular risk factors, including elevated blood pressure and older age (Lepor et al, 2000; Palmieri et al, 2002; Kancherla et al, 1999). Reassuringly, however, a wealth of evidence indicates that any drug-induced valve disease tends to reverse after treatment discontinuation, or at the very least, stabilize (Dahl et al, 2008; Fleming and Boyd, 2007; Hensrud et al, 1999; Mast et al, 2001). Also reassuring is the fact that there have been no consistent reports of fenfluramine-associated heart failure, which is well recognized as the most clinically significant sequela of important valve disease (Cheng et al, 2019).</p>
Preventability	<p>Despite the lack of empirical evidence, the risk of VHD associated with fenfluramine use could be reduced by avoidance of use in patients with existing VHD and by use of fenfluramine at the lowest effective dose. Monitoring of patients using echocardiography will aid 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. Should an AE of VHD or progressive subclinical worsening be observed, published information indicates drug-induced valve disease tends to reverse after treatment discontinuation, or at the very least, stabilize.</p>
Impact on risk-benefit balance of the product	<p>Clinically significant VHD can result in volume overload of the ventricle and left ventricular cavity enlargement with systolic dysfunction. If untreated, over time, this eventually leads to heart failure. Since the voluntary recall of fenfluramine in 1997, there have been follow-up studies of patients with alleged fenfluramine-induced valvulopathy, which reported that regression or stability of VHD occurs in most of these patients. For instance, Hensrud et al, described regression of VHD after 6 months in 8 of 15 participants who had discontinued fen-phen, while no worsening was found in the remaining participants (Hensrud et al, 1999). In a large double-blind, placebo-controlled trial, 914 patients were followed 1 year after dexfenfluramine exposure of 3 months and compared to the placebo group, a greater proportion of patients previously treated with dexfenfluramine had a decrease in aortic regurgitation of at least 1 grade and there were no significant changes in mitral regurgitation or leaflet mobility and no progression of valvular regurgitation was found (Weissman et al, 2001).</p> <p>Close monitoring of all patients treated with fenfluramine through echocardiography can lead to early subclinical detection and treatment, significantly minimizing the likelihood of severe valvulopathy, and thus reducing the overall impact on the patient. Therefore, while the risk/benefit relationship for fenfluramine is considered unfavorable for the treatment of obesity in adults at 60 mg per day or greater,</p>

Table 3–2: Important potential risk: Valvular heart disease

	establishing seizure reduction in Dravet syndrome patients and in LGS 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 unknown.

AE=adverse event; CDC=centers for disease control; CV ISS=cardiovascular integrated summary of safety;
 DI-VHD=drug-induced valvular heart disease; TGF=transforming growth factor; tph1=tryptophan hydroxylase 1.

Table 3–3: Important potential risk: Suicidal ideation and behavior

Potential mechanisms	<p>Suicidal ideation and behavior are included in the label for AEDs; however, the exact mechanism is not known.</p> <p>Suicide attempts, both incident and recurrent, are associated with epileptic disorders with an unknown mechanism or etiology.</p>
Evidence source(s) and strength of evidence	<p>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.</p>

Table 3–3: Important potential risk: Suicidal ideation and behavior

<p>Characterization of the risk</p>	<p><u>Clinical study data</u></p> <p>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.</p> <p>In Study 3 (DS) (f. Study 2), 1 study participant was reported to exhibit non-suicidal self-injurious behavior. In the same study, a PP-year-old PPD study participant reported suicidal ideation. During the Screening visit for the study, PP mother reported that the study participant sometimes verbalized PP wished to be dead, without an implementation plan, as a way to show PP 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 changes in the 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 PPD 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.</p> <p>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).</p> <p>In Study 1601 (LGS), CCI</p> <p>Based on the overall C-SSRS results, ZX008 did not appear to increase the risk of suicidal thoughts and behavior.</p> <p><u>Postmarketing data</u></p> <p>To date, no change to the characterization of the risk has been identified from postmarketing sources regarding fenfluramine use and suicidal ideation and behavior.</p>
<p>Risk factors and risk groups</p>	<p>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.</p>

Table 3–3: 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 3–4: 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 serotonergic 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	<u>Clinical study data</u> 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 $\geq 7\%$ (18.9% vs 2.4%).

Table 3–4: Important potential risk: Growth retardation

	<p>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.</p> <p>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 $\geq 7\%$ 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 $\geq 10\%$.</p> <p>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.</p> <p>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 $\geq 7\%$ 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 $\geq 7\%$ of the Part 2 Baseline value, as expected. A body weight decrease of $\geq 7\%$ 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 $\geq 7\%$ 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 $\geq 10\%$ of the Part 2 Baseline.</p> <p>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 $\geq 7\%$ or $\geq 10\%$ 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 $\geq 7\%$ 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 $\geq 7\%$ loss in weight regained weight to within 7% of their OLE Baseline weight. Seven (43.8%) adult participants experienced a body weight loss of $\geq 7\%$ 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 $\geq 10\%$ at any visit remained with a $\geq 10\%$ weight loss at the last post-baseline assessment.</p>
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Table 3–4: Important potential risk: Growth retardation

	<u>Postmarketing data</u> To date, no change to the characterization of the risk 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 ZX000 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.

3.2 Presentation of the missing information

3.2.1 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.

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 study participants treated with fenfluramine.

3.2.2 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 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Pulmonary arterial hypertension
Important potential risks	Valvular heart disease 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)

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 PBRERs, 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 [Part VII Annex 4](#).

- **Other forms of routine pharmacovigilance activities:** None.

2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

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 two 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 4 years from fenfluramine earliest market entry..

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 $\geq 5\%$ 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 one 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:

- Protocol approved by PRAC: 12 Jan 2023.
- Start of data collection: market entry + 3 years: Q2 2024.
- End of data collection: + 12 months: Q1 2026.
- Final study report submission: 6 months: Q1 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 one 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 six 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 Current expected earliest date of market entry (Germany): 15 Feb 2021.

- 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 PBRERs.

For further details please see EU RMP [Part VII Annex 3](#)

2.2 EP0218: A Cardiovascular (CV) registry of Subjects Treated with Fenfluramine

Study short name and title

A Registry of Subjects Treated with Fenfluramine.

Rationale and study objectives

Pulmonary arterial hypertension has been identified as an important identified risk and valvular heart disease has been identified as an important potential risk for fenfluramine. 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 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 assess the effectiveness of risk minimization measures.

These above-mentioned objectives will be assessed in patients treated with fenfluramine approved indications as well as for all patients treated with fenfluramine enrolled in the registry

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 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 will be an observational prospective multi-country longitudinal cohort study (a registry) of study participants 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) in both European (potentially including Germany, Austria, Denmark, Italy, Spain and France) and non-European countries (potentially including US and Japan).

- The enrolment period will be three years from the registry start date in the first participating country.
- The study period will be ten years from the registry start date in the first participating country.
- Patients will be followed up until six 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 ten years.
- The maximum follow-up period in the registry for the last patient included will be seven 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 (see Section 9.2.2), 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 VHD and PAH observed in the registry against background risks. Background risks will be obtained via electronic healthcare databases in Europe to assess the incidence rate of 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 one case is observed in the registry.

The study period will be at most 10 years from the earliest fenfluramine patient market entry.

Study population

The study population will be study participants aged in accordance with the indication statement in the SmPC and treated with fenfluramine according to the product label. The study participants will be 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 neurologists with experience in the treatment of epilepsy).

Milestones

- Protocol approved by PRAC: 01 Sep 2022
- Start of data collection: 09 Jun 2023
- Progress reports: At the time of PBRER submissions
- Interim safety update reports: Estimated Q3 2026 (3 years +6 months from start of data collection). The appropriate date for the second interim report will be determined after the first report has been assessed.
- End of data collection: + 10 years: Q1 2033
- Final study report submission: Q1 2034

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

For further details please see EU RMP [Part VII Annex 3](#)

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 [Part VII Annex 3](#)

3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

The summary of ongoing and planned additional pharmacovigilance activities is provided in [Table 3–1](#).

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Status				
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
EP0218 A Registry of Subjects Treated with Fenfluramine	Primary objective: Assess the long-term cardiac safety of fenfluramine prescribed in	Valvular heart disease Pulmonary arterial hypertension	Protocol approval	01 Sep 2022
			Annual progress reports	PBRER ^a

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Status				
Ongoing	routine practice, with a focus on: 1. Incidence of cardiac valvular disease (\geq mild aortic regurgitation or \geq moderate mitral regurgitation) 2. Incidence of PAH Secondary objective: Assess the occurrence of growth retardation, if any, for study participants prescribed fenfluramine in routine practice.	Long-term safety Growth retardation	Interim safety reports	Interim safety reports: Estimated Q3 2026 (3 years +6 months from start of data collection). The appropriate date for the second interim report will be determined after the first report has been assessed.
			Final report	Q1 2034
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 Dravet syndrome if any. Secondary objectives: 1. Describe the dose, frequency, and duration of fenfluramine treatment	Off-label use (in wider pediatric epilepsies; obesity) Valvular heart disease Pulmonary arterial hypertension	Protocol approval	Protocol approved by PRAC on 12 Jan 2023
			Start of data collection (patient counts)	Market entry + 3 years: Q2 2024
			End of data collection	Q1 2026

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	<p>2. Describe the demographic characteristics (eg, age, sex, weight) of patients treated with fenfluramine in routine clinical practice</p> <p>3. Describe the extent and frequency of echocardiographic monitoring</p> <p>Exploratory objective: Identify and describe prescriptions of fenfluramine for weight management.</p>		Final report	Q1 2027
<p>EP0220</p> <p>A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome and LGS.</p> <p><i>Ongoing</i></p>	<p>Primary objectives:</p> <p>1. Assess the awareness and knowledge of physicians routinely prescribing fenfluramine regarding the educational material on echocardiogram follow-up</p>	Valvular heart disease	Protocol approval	Protocol approved by PRAC on 21 Jul 2022
		<p>Pulmonary arterial hypertension</p> <p>Off-label use in wider pediatric epilepsies; obesity</p>	Interim report	14 Jun 2023

Table 3–1: Ongoing and planned additional Pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	<p>2. Assess the self-reported compliance of physicians routinely prescribing fenfluramine with the recommendations provided in the educational materials</p> <p>Secondary objectives:</p> <p>1. Assess the physician reported distribution of educational material to patients/carers by physicians routinely prescribing fenfluramine on echocardiogram follow-up</p> <p>2. 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</p>		Final report	Q3 2025

^a Registry progress reports will be provided annually with the scheduled PBRER.

PAH=pulmonary arterial hypertension; PBRER=periodic benefit-risk evaluation report; PK=pharmacokinetics; ZX008=fenfluramine hydrochloride.

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.

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

Risk Minimization Plan

1 ROUTINE RISK MINIMIZATION MEASURES

Description of routine risk minimization measures by safety concern is presented in [Table 1–1](#).

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

Safety concern	Routine risk minimization activities
Pulmonary arterial hypertension	<p>Routine risk communication: SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8. PL section 2 and PL section 4.</p> <p>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 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.</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine, restricted medical prescription.</p>

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

Safety concern	Routine risk minimization activities
Valvular heart disease	<p>Routine risk communication: SmPC section 4.3, SmPC section 4.4 and SmPC section 4.8. PL section 2 and PL section 4.</p> <p>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 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 and during treatment in PL section 2.</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine, restricted medical prescription.</p>
Suicidal ideation and behavior	<p>Routine risk communication: SmPC section 4.4. PL section 2.</p> <p>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.</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine, restricted medical prescription.</p>

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

Safety concern	Routine risk minimization activities
Growth retardation	<p>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).</p> <p>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</p>
Long-term safety	<p>Routine risk communication: None.</p> <p>Routine risk minimization activities recommending specific clinical measures to address the risk: None.</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine, restricted medical prescription.</p>
Off-label use (wider pediatric epilepsies; obesity)	<p>Routine risk communication: SmPC section 4.1, SmPC section 4.2, and SmPC section 4.4. PL section 1.</p> <p>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.</p> <p>Other routine risk minimization measures beyond the Product Information: Legal status: Prescription-only medicine, restricted medical prescription.</p>

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

2 ADDITIONAL RISK MINIMIZATION MEASURES

2.1 Controlled access program

UCB is required to implement a CAP (EU-RMP [Part VII 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 [Part VII Annex 6](#)).

2.2 Educational materials

2.2.1 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 [Part VII 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:

- $\geq 80\%$ of physicians distributing the patient/carers educational material
- $\geq 80\%$ of physicians reporting awareness

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

2.2.2 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 [Part VII Annex 3](#)).

3 SUMMARY OF RISK MINIMIZATION MEASURES

[Table 3–1](#) provides a summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

Safety concern	Risk minimization measures	Pharmacovigilance activities
Pulmonary arterial hypertension	Routine risk minimization measures: <ul style="list-style-type: none"> • SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8. • PL section 2 and 	Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection: <ul style="list-style-type: none"> • A specific targeted follow-up questionnaire for potential cases of PAH is utilized in the

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

	<p>PL section 4.</p> <ul style="list-style-type: none"> • 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 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: 	<p>post-marketing setting</p> <p>Additional Pharmacovigilance activities:</p> <ul style="list-style-type: none"> • EP0218: A Registry of Subjects Treated with Fenfluramine. <p><i>Final study report due date: Q1 2034</i></p> <ul style="list-style-type: none"> • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome. <p><i>Final study report due date: Q3 2025</i></p> <ul style="list-style-type: none"> • EP0219: A Drug Utilization Study of Fenfluramine In Europe. <p><i>Final study report due date: Q1 2027</i></p>
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Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

	<p>Prescription-only medicine, restricted medical prescription.</p> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Guide for healthcare professionals. • Patient/carer guide. <p>CAP.</p>	
Valvular heart disease	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • 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 in SmPC section 4.4. • Recommendations for actions to take with fenfluramine if regurgitation is detected on echocardiogram in SmPC section 4.4. • Guidance that 	<p>Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • A specific targeted follow-up questionnaire for potential cases of VHD is utilized in the post-marketing setting (EU RMP Part VII Annex 4). <p>Additional Pharmacovigilance activities:</p> <ul style="list-style-type: none"> • EP0218: A Registry of Subjects Treated with Fenfluramine. <i>Final study report due date: Q1 2034</i> • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome. <i>Final study report due date: Q3 2025</i> • EP0219: A Drug Utilization Study of Fenfluramine in Europe. <i>Final study report due date: Q1 2027</i>

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

	<p>fenfluramine should not be used in patients with valve disease in PL section 2.</p> <ul style="list-style-type: none"> • 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. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • Guide for healthcare professionals • Patient/carer guide • CAP 	
Suicidal ideation and behavior	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • 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. 	<p>Routine Pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • A specific targeted follow-up questionnaire for potential cases of '<i>suicidal ideation and behavior</i>' is utilized in the post-marketing setting. <p>Additional Pharmacovigilance activities:</p> <p>None</p>

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

	<ul style="list-style-type: none"> Warning in PL section 2 to patients with prior history of suicidal thoughts or behaviors to contact their healthcare professional. Legal status: Prescription-only medicine, restricted <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> None. 	
Growth retardation	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> 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. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> None. 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None. <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> EP0218: A Registry of Subjects Treated with Fenfluramine. <p><i>Final study report due date: Q1 2034</i></p>
Long-term safety	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> Legal status: Prescription-only 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> None. <p>Additional pharmacovigilance</p>

Table 3–1: Summary table of pharmacovigilance activities and risk minimization activities

	<p>medicine, restricted.</p> <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • None. 	<p>activities:</p> <ul style="list-style-type: none"> • EP0218: A Registry of Subjects Treated with Fenfluramine. <p><i>Final study report due date: Q1 2034</i></p>
Off-label use (in wider pediatric epilepsies; obesity)	<p>Routine risk minimization measures:</p> <ul style="list-style-type: none"> • 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. <p>Additional risk minimization measures:</p> <ul style="list-style-type: none"> • CAP 	<p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • Assessment of Fintepla sales patterns and patient exposure data. <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • EP0219: A Drug Utilization Study of Fenfluramine In Europe. <p><i>Final study report due date: Q1 2027</i></p> <ul style="list-style-type: none"> • EP0220: A European Study of the Effectiveness of Risk Minimization Measures for Fenfluramine in Dravet Syndrome. <p><i>Final study report due date: Q3 2025</i></p>

CAP=controlled access programme; 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.

1 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>.

2 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.

2.1 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 1: List of important risks and missing information

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

2.2 Summary of important risks

Table 2: 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, 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 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	<p>Routine risk minimization measures</p> <ul style="list-style-type: none"> • 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. <p>Additional risk minimization measures</p> <ul style="list-style-type: none"> • Guide for healthcare professionals. • Patient/carer guide. • CAP.
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities</p> <ul style="list-style-type: none"> • EP0218: A Registry of Subjects with 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. <p>See Section 2.3 of this summary for an overview of the post-authorisation development plan.</p>

Table 3: Summary of important potential risks

Important potential risk: Valvular heart disease	
Evidence for linking the risk to the medicine	Based on historical experience with fenfluramine use in obese adults, in which VHD was reported.
Risk factors and risk groups	Patients with pre-existing VHD.
Risk minimization measures	<p>Routine risk minimization measures</p> <ul style="list-style-type: none"> • 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. <p>Additional risk minimization measures</p> <ul style="list-style-type: none"> • Guide for healthcare professionals. • Patient/carer guide.

Table 3: Summary of important potential risks

	<ul style="list-style-type: none"> • CAP.
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities</p> <ul style="list-style-type: none"> • 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. <p>See Section 2.3 of this summary for an overview of the post-authorisation development plan.</p>
Important potential risk: Suicidal ideation and behaviour	
Evidence for linking the risk to the medicine	Based on data from studies showing that epilepsy increases the risk for suicidal thoughts and ideation, and AEDs increase the risk of suicidal thoughts in people with epilepsy.
Risk factors and risk groups	Psychiatric illness is one of the risk factors for suicidal ideation and 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	<p>Routine risk minimization measures</p> <ul style="list-style-type: none"> • SmPC section 4.4. • PL section 2. • Legal status: prescription-only medicine, restricted medical prescription. <p>Additional risk minimization measures</p> <ul style="list-style-type: none"> • None.
Additional pharmacovigilance activities	<p>Additional pharmacovigilance activities</p> <p>None</p>
Important potential risk: Growth retardation	
Evidence for linking the risk to the medicine	Based on data from studies showing that fenfluramine can cause weight reduction which can impact physiological growth.
Risk factors and risk groups	Patients in the target population with a significant history of nutritional or growth problems or those treated with concurrent medications known to cause appetite or weight loss.
Risk minimization measures	<p>Routine risk minimization measures</p> <ul style="list-style-type: none"> • SmPC section 4.2, SmPC section 4.4 and SmPC section 4.8. • PL section 2.

Table 3: Summary of important potential risks

	<ul style="list-style-type: none"> Legal status: prescription-only medicine, restricted medical prescription. Additional risk minimization measures <ul style="list-style-type: none"> None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities <ul style="list-style-type: none"> EP0218: A Registry of Subjects Treated with Fenfluramine. 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.

Table 4: Summary of missing information

Missing information: Long-term safety	
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> Legal status: prescription-only medicine, restricted medical prescription. Additional risk minimization measures: <ul style="list-style-type: none"> None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none"> EP0218: A Registry of Subjects Treated with Fenfluramine.
Missing information: Off-label use (in wider pediatric epilepsies; obesity)	
Risk minimization measures	Routine risk minimization measures: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> CAP to address potential off-label use for weight management.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: <ul style="list-style-type: none"> EP0219: A Drug Utilisation Study of Fenfluramine in Europe. 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.

2.3 Postauthorization development plan

2.3.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

- **EP0218: A Registry of Subjects 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 potential risks of valvular heart disease and pulmonary arterial hypertension. In addition, the registry will provide data to characterise and quantify the important potential risk of growth retardation. Moreover, the data collected on the frequency of echocardiographic monitoring will also contribute to assess the effectiveness of risk minimisation measures.

2.3.2 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.


RMP 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.

	SUBTYPE	CLASSIFICATION	DOCUMENT NUMBER	VERSION	STATUS	EFFECTIVE DATE
	Associated Form	Drug Safety	sop-af-105182	1.0	Effective	30 Aug 2022
Fintepla® (fenfluramine) Suicidal Ideation follow-up form						


	Standard Medical Follow-up Query (SMFQ) - Fintepla® (fenfluramine) Suicidal Ideation follow-up form	Sop-af-105182 v1.0 Associated to sop-ai-014552 Page 1 of 4
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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														
<i>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.</i>	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. <i>Have you thought about being dead or what it would be like to be dead?</i> <i>Have you wished you were dead or wished you could go to sleep and never wake up?</i> <i>Do you ever wish you weren't alive anymore?</i> If yes, describe:	<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td colspan="2">Response Not Known</td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>	Response Not Known		<table border="0"> <tr> <td>Yes</td> <td>No</td> </tr> <tr> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td colspan="2">Response Not Known</td> </tr> </table>	Yes	No	<input type="checkbox"/>	<input type="checkbox"/>	Response Not Known	
Yes	No													
<input type="checkbox"/>	<input type="checkbox"/>													
Response Not Known														
Yes	No													
<input type="checkbox"/>	<input type="checkbox"/>													
Response Not Known														


Please use additional copies of this questionnaire if more room is needed to accommodate requested information


	SUBTYPE Associated Form	CLASSIFICATION Drug Safety	DOCUMENT NUMBER sop-af-105182	VERSION 1.0	STATUS Effective	EFFECTIVE DATE 30 Aug 2022
Fintepla® (fenfluramine) Suicidal Ideation follow-up form						

	Standard Medical Follow-up Query (SMFQ) - Fintepla® (fenfluramine) Suicidal Ideation follow-up form	Sop-af-105182 v1.0 Associated to sop-ai-014552 Page 2 of 4
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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. <i>Have you thought about doing something to make yourself not alive anymore?</i> <i>Have you had any thoughts about killing yourself?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Response Not Known	Yes No <input type="checkbox"/> <input type="checkbox"/> 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." <i>Have you thought about how you would do that or how you would make yourself not alive anymore (kill yourself)?</i> <i>What did you think about?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Response Not Known	Yes No <input type="checkbox"/> <input type="checkbox"/> 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 <u>some intent to act on such thoughts</u> , as opposed to "I have the thoughts, but I definitely will not do anything about them." <i>When you thought about making yourself not alive anymore (or killing yourself), did you think that this was something you might actually do?</i> <i>This is different from (as opposed to) having the thoughts but knowing you wouldn't do anything about it.</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Response Not Known	Yes No <input type="checkbox"/> <input type="checkbox"/> 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. <i>Have you ever decided how or when you would make yourself not alive anymore/kill yourself?</i> <i>Have you ever planned out (worked out the details of) how you would do it?</i> <i>What was your plan?</i> <i>When you made this plan (or worked out the details), was any part of you thinking about actually doing it?</i> If yes, describe:	Yes No <input type="checkbox"/> <input type="checkbox"/> Response Not Known	Yes No <input type="checkbox"/> <input type="checkbox"/> Response Not Known
INTENSITY OF IDEATION		
<i>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).</i> Most Severe Ideation: _____ <div style="display: flex; justify-content: space-between;"> Type # (1-5) Description of Ideation </div>	Most Severe	Most Severe
Frequency <i>How many times have you had these thoughts?</i> <i>Write response (options below):</i> _____ (1) Only one time (2) A few times (3) A lot (4) All the time (0) Don't know/Not applicable	_____	_____


Please use additional copies of this questionnaire if more room is needed to accommodate requested information


	SUBTYPE Associated Form	CLASSIFICATION Drug Safety	DOCUMENT NUMBER sop-af-105182	VERSION 1 . 0	STATUS Effective	EFFECTIVE DATE 30 Aug 2022
Fintepla® (fenfluramine) Suicidal Ideation follow-up form						

	Standard Medical Follow-up Query (SMFQ) - Fintepla® (fenfluramine) Suicidal Ideation follow-up form	Sop-af-105182 v1.0 Associated to sop-ai-014552 Page 3 of 4
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SUICIDAL BEHAVIOR (Check all that apply, so long as these are separate events; must ask about all types)	Lifetime
<p>Actual Attempt: A potentially self-injurious act committed with at least some wish to die, <i>as a result of act</i>. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> intent/desire to die associated with the act, then it is considered an actual suicide attempt. <i>There does not have to be any injury or harm</i>, 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.</p> <p>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.</p> <p><i>Did you ever <u>do anything</u> to try to kill yourself or make yourself not alive anymore?</i></p> <p><i>What did you do? Did you ever hurt yourself on purpose? Why did you do that?</i></p> <p><i>Did you _____ as a way to end your life?</i></p> <p><i>Did you want to die (even a little) when you _____?</i></p> <p><i>Were you trying to make yourself not alive anymore when you _____?</i></p> <p><i>Or did you think it was possible you could have died from _____?</i></p> <p><i>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)?</i> (Self-Injurious Behavior without suicidal intent)</p> <p>If yes, describe:</p> <p>Has subject engaged in Non-Suicidal Self-Injurious Behavior?</p> <p>Has subject engaged in Self-Injurious Behavior, intent unknown?</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p> <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p>
<p>Interrupted Attempt:</p> <p>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act (<i>if not for that, actual attempt would have occurred</i>).</p> <p>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.</p> <p><i>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?</i></p> <p><i>What did you do?</i></p> <p>If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of Attempts</p> <p>_____</p>
<p>Aborted Attempt:</p> <p>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.</p> <p><i>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?</i></p> <p><i>What did you do?</i></p> <p>If yes, describe:</p>	<p>Yes No</p> <p><input type="checkbox"/> <input type="checkbox"/></p> <p>Total # of aborted attempts</p> <p>_____</p>

Please use additional copies of this questionnaire if more room is needed to accommodate requested information

	SUBTYPE Associated Form	CLASSIFICATION Drug Safety	DOCUMENT NUMBER sop-af-105182	VERSION 1 . 0	STATUS Effective	EFFECTIVE DATE 30 Aug 2022
Fintepla® (fenfluramine) Suicidal Ideation follow-up form						


	Standard Medical Follow-up Query (SMFQ) - Fintepla® (fenfluramine) Suicidal Ideation follow-up form	Sop-af-105182 v1.0 Associated to sop-ai-014552 Page 4 of 4
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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). <i>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?</i> If yes, describe:	
Suicidal Behavior: Suicidal behavior was present during the assessment period?	

<i>Answer for Actual Attempts Only</i>	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; <i>medical</i> 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; <i>medical</i> 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	<i>Date:</i> <i>Enter Code:</i>	<i>Date:</i> <i>Enter Code:</i>	<i>Date:</i> <i>Enter Code:</i>
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	<i>Enter Code:</i> 	<i>Enter Code:</i> 	<i>Enter Code:</i>

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Please use additional copies of this questionnaire if more room is needed to accommodate requested information

	SUBTYPE Associated Form	CLASSIFICATION Drug Safety	DOCUMENT NUMBER sop-af-105182	VERSION 1 . 0	STATUS Effective	EFFECTIVE DATE 30 Aug 2022
Fintepla® (fenfluramine) Suicidal Ideation follow-up form						

Document Approvals
Approved Date: 30 Aug 2022


Approval Task Verdict: Approve	Name: Liz Urbina Role: Owner Approval Date of signature: 04-Aug-2022 16:42:13 GMT+0000
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Approval Task Verdict: Approve	Name: Catherine Wilputte Role: Management Approval Date of signature: 24-Aug-2022 14:23:22 GMT+0000
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Final Approval (QA, QP, RP, Legal) Task Verdict: Approve	Name: Bart Teeuw Role: Qualified/Responsible Person Approval Date of signature: 24-Aug-2022 15:05:45 GMT+0000
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Final Approval (QA, QP, RP, Legal) Task Verdict: Approve	Name: Sandra Van der Poel Role: Quality Approval Date of signature: 30-Aug-2022 12:52:32 GMT+0000
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	Standard Medical Follow-up Query (SMFQ) - Fintepla [®] (fenfluramine) Cardiovascular Event follow-up form <u>(Ex-US cases)</u>	Doc Number: sop-af-105293 Version: 3.0 Refer to: sop-ai-014552 Page 1 of 15
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UCB Global DS database #: [case_num]	UCB LAM ID #: [lam_case_num_cen_cu]
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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.

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 Summary of Product Characteristics (SmPC) of Fintepla and following-up on reported possible cases of VHD and PAH is of particular importance.

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.

	Standard Medical Follow-up Query (SMFQ) - Fintepla® (fenfluramine) Cardiovascular Event follow-up form (Ex-US cases)	Doc Number: sop-af-105293 Version: 3.0 Refer to: sop-ai-014552 Page 2 of 15
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If an earlier ECHO is scheduled to confirm any observed pathological abnormalities, please contact us at AffiliateCSR@ucb.com quoting the UCB reference 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 here to enter text.](#) _____

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 (continues on next page)

#	ADVERSE EVENT(S)	Onset Date (DD/MM/YYYY)	End Date (DD/MM/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) <input type="checkbox"/> Yes <input type="checkbox"/> No	Click or tap to enter a date. _____	Click or tap to enter a date. _____	<input type="checkbox"/> Death <input type="checkbox"/> Life-threatening <input type="checkbox"/> Hospitalization/ Prolonged Hospitalization <input type="checkbox"/> Disability/Incapacity <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> **Medically Significant <input type="checkbox"/> None of the above; Non-Serious	<input type="checkbox"/> Resolved <input type="checkbox"/> Resolved w/ sequelae <input type="checkbox"/> Resolving <input type="checkbox"/> Not Resolved/ongoing <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
2	Description: Click or tap here to enter text. _____ Can you verify this event occurred as described? (Select one) <input type="checkbox"/> Yes <input type="checkbox"/> No	Click or tap to enter a date. _____	Click or tap to enter a date. _____	<input type="checkbox"/> Death <input type="checkbox"/> Life-threatening <input type="checkbox"/> Hospitalization/ Prolonged Hospitalization <input type="checkbox"/> Disability/Incapacity <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> **Medically Significant <input type="checkbox"/> None of the above; Non-Serious	<input type="checkbox"/> Resolved <input type="checkbox"/> Resolved w/ sequelae <input type="checkbox"/> Resolving <input type="checkbox"/> Not Resolved/ongoing <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
3	Description: Click or tap here to enter text. _____ Can you verify this event occurred as described? (Select one) <input type="checkbox"/> Yes <input type="checkbox"/> No	Click or tap to enter a date. _____	Click or tap to enter a date. _____	<input type="checkbox"/> Death <input type="checkbox"/> Life-threatening <input type="checkbox"/> Hospitalization/ Prolonged Hospitalization <input type="checkbox"/> Disability/Incapacity <input type="checkbox"/> Congenital Anomaly/Birth Defect <input type="checkbox"/> **Medically Significant <input type="checkbox"/> None of the above; Non-Serious	<input type="checkbox"/> Resolved <input type="checkbox"/> Resolved w/ sequelae <input type="checkbox"/> Resolving <input type="checkbox"/> Not Resolved/ongoing <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown

****Medically Significant** indicates event was not 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

	Standard Medical Follow-up Query (SMFQ) - Fintepla[®] (fenfluramine) Cardiovascular Event follow-up form (Ex-US cases)	Doc Number: sop-af-105293 Version: 3.0 Refer to: sop-ai-014552
		Page 3 of 15

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.](#) _____


Surveillance Echocardiography (ECHO):

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 – click in the last row and add more as needed


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

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

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For additional ECHO results – use the last row and click on the + symbol in the bottom right corner to add more rows as needed		
<p>ADDITIONAL ECHO</p> <p><input type="checkbox"/> During</p> <p>Treatment: Click or tap here to enter text.</p> <p>Following _____ months ON treatment:</p> <p>--- OR ---</p> <p><input type="checkbox"/> After stop of drug Click or tap here to enter text. _____ months</p> <p>AFTER discontinuation</p> <p>Date of ECHO: Click or tap to enter a date.</p> <p>_____ (DD/MM/YYYY)</p>	<p><input type="checkbox"/> Aortic valve: <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5: select Choose an item. _____</p> <p><input type="checkbox"/> Mitral valve: <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5: select Choose an item. _____</p> <p><input type="checkbox"/> Tricuspid valve: <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5: select Choose an item. _____</p> <p><input type="checkbox"/> Pulmonary valve: <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5: select Choose an item. _____</p> <p><input type="checkbox"/> Pulmonary Arterial Hypertension</p> <p><input type="checkbox"/> Interventricular septal flattening</p> <p><input type="checkbox"/> Pulmonary artery systolic pressure (PASP) reading: Click or tap here to enter text. _____ mmHg</p> <p><input type="checkbox"/> Other findings suggestive of PAH: Click or tap here to enter text. _____</p> <p>_____</p> <p><input type="checkbox"/> Any other cardiac findings: Click or tap here to enter text. _____</p>	<p>Did the patient have any symptoms/signs related to the abnormal ECHO finding?</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>If yes - provide and include all abnormal physical examination findings:</p> <p>Click or tap here to enter text.</p> <p>_____</p>

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If the abnormal findings were suggestive of PAH or VHD, was a specialist (cardiologist or pulmonologist) consulted? (Select one) <input type="checkbox"/> Yes, on Click or tap here to enter text. <input type="checkbox"/> No <input type="checkbox"/> Unknown _____ (DD/MMM/YYYY)	
If No, provide reason:	Click or tap here to enter text.
If Yes, specify: Click or tap here to enter text. _____	Was a diagnosis of PAH confirmed: (Select one) <input type="checkbox"/> Yes, on Click or tap to enter a date. <input type="checkbox"/> No If Yes, provide relevant details: _____ (DD/MMM/YYYY) Click or tap here to enter text.
	Was a diagnosis of VHD confirmed: (Select one) <input type="checkbox"/> Yes, on Click or tap to enter a date. <input type="checkbox"/> No If Yes, provide relevant details: _____ (DD/MMM/YYYY) Click or tap here to enter text.
	Was a diagnosis of PAH confirmed: (Select one) <input type="checkbox"/> Yes, on Click or tap to enter a date. <input type="checkbox"/> No If Yes, provide relevant details: _____ (DD/MMM/YYYY) Click or tap here to enter text.
	Was a diagnosis of VHD confirmed: (Select one) <input type="checkbox"/> Yes, on Click or tap to enter a date. <input type="checkbox"/> No If Yes, provide relevant details: _____ (DD/MMM/YYYY) 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) <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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
<input type="checkbox"/> Bicuspid aortic valve	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Mitral valve prolapse	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Rheumatic heart disease	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Marfan's syndrome	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Sleep apnea	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Reversal of shunt with atrial septal defect	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Reversal of shunt with ventricular septal defect	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Reversal of shunt with patent foramen ovale	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Reversal of shunt with patent ductus arteriosus	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A

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<input type="checkbox"/> Aortic valve disease	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Mitral valve disease	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Hypertension	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Sickle cell disease	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> Chronic obstructive pulmonary disease (COPD)	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> 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. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> 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. _____ <input type="checkbox"/> N/A
<input type="checkbox"/> 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. _____ <input type="checkbox"/> N/A


Section 4: FAMILY HISTORY

Does the patient have any significant Family History? (Select one): <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
If Yes, select all that apply in the table below		(Select all that apply)
<input type="checkbox"/> Family history of PAH	<input type="checkbox"/> Maternal <input type="checkbox"/> Paternal <input type="checkbox"/> Unknown	
<input type="checkbox"/> Family history of pulmonary embolism	<input type="checkbox"/> Maternal <input type="checkbox"/> Paternal <input type="checkbox"/> Unknown	
<input type="checkbox"/> Family history of VHD	<input type="checkbox"/> Maternal <input type="checkbox"/> Paternal <input type="checkbox"/> Unknown	
<input type="checkbox"/> Family history of blood clotting disorder (specify): Click or tap here to enter text. _____ _____	<input type="checkbox"/> Maternal <input type="checkbox"/> Paternal <input type="checkbox"/> Unknown	


Section 5: FINTEPLA THERAPY INFORMATION

(Complete as much information as possible with dates/times the product was stopped and restarted if applicable; use the last row and click on the + symbol in the bottom right corner to add additional rows, if needed)

Indication for Fintepla Use: (Select all that apply): <input type="checkbox"/> Dravet Syndrome <input type="checkbox"/> Lennox-Gastaut Syndrome <input type="checkbox"/> 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. _____ <input type="checkbox"/> 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

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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. _____ <input type="checkbox"/> 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. 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. _____ <input type="checkbox"/> 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. text. _____	Weight Click or tap here to enter text. _____kg Height Click or tap here to enter text. _____cm
	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. _____ <input type="checkbox"/> 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. text. _____	Weight Click or tap here to enter text. _____kg Height Click or tap here to enter text. _____cm

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Section 6: CONCOMITANT AND OTHER SUSPECT MEDICATIONS

(Click on the last row in each section and click on the + symbol in the bottom right corner to add additional rows, 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	<input type="checkbox"/> Stiripentol	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
2	<input type="checkbox"/> Clobazam	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
3	<input type="checkbox"/> Valproate	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
4	<input type="checkbox"/> Cannabidiol	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
5 add lines if need	Other (specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Ciprofloxacin	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
2	<input type="checkbox"/> Enoxacin	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
3	<input type="checkbox"/> Fluvoxamine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
4	<input type="checkbox"/> Oltipraz	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
5	<input type="checkbox"/> Rofecoxib	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

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		enter a date. _____	enter a date. _____ <input type="checkbox"/> N/A	text. _____	enter text. _____	text. _____	text. _____		
6	<input type="checkbox"/> Zafirlukast	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
7	<input type="checkbox"/> Bai-zhi (Angelica dahurica)	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
8	<input type="checkbox"/> Bupropion	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
9	<input type="checkbox"/> Dacomitinib	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
10	<input type="checkbox"/> Fluoxetine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
11	<input type="checkbox"/> Paroxetine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
12	<input type="checkbox"/> Quinidine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
13 add lines if need	Other (specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Carbamazepine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
2	<input type="checkbox"/> Rifampin	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
3	<input type="checkbox"/> Phenytoin	Click or tap to enter a date. _____	Click or tap to enter a date. _____	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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

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			<input type="checkbox"/> N/A						
4	<input type="checkbox"/> Teriflunomide	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
5	<input type="checkbox"/> Efavirenz	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
6	<input type="checkbox"/> Ritonavir	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
7	<input type="checkbox"/> Lopinavir and ritonavir	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
9 add lines if need	Other (specify): Click or tap here to enter text.	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Paroxetine	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
2	<input type="checkbox"/> Fluoxetine	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
3	<input type="checkbox"/> Citalopram	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
4	<input type="checkbox"/> Escitalopram	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
5	<input type="checkbox"/> Sertraline	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
6	<input type="checkbox"/> Fluvoxamine	Click or tap to enter a date.	Click or tap to enter a date.	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.	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No

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7	<input type="checkbox"/> Vilazodone	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
8	<input type="checkbox"/> Vortioxetine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
9	<input type="checkbox"/> Dapoxetine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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	<input type="checkbox"/> Ergotamine	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
2 add lines if need	Other (specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> 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. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No



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Section 7: RECREATIONAL EXPOSURES


(Click on the last row in each section and click on the + symbol in the bottom right corner to add additional rows, if needed)

Recreational Exposure(s)? (Select one): <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If Yes, select all that apply in the table below. If more rows are needed, please copy this page					
#	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	<input type="checkbox"/> Alcohol	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
2	<input type="checkbox"/> Tobacco	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
3	<input type="checkbox"/> Marijuana	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
4	<input type="checkbox"/> MDMA (ecstasy)	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
5	<input type="checkbox"/> Other (please specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
6 add lines if need	<input type="checkbox"/> Other (please specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Other pertinent Exposure(s), including Environmental Exposure(s)? (Select one): <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If Yes, please specify the type of exposure in the table below. If more rows are needed, please add rows or copy this page					
#	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	<input type="checkbox"/> Radiation	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
2	<input type="checkbox"/> Other (please specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
3 add lines if need	<input type="checkbox"/> Other (please specify): Click or tap here to enter text. _____	Click or tap to enter a date. _____	Click or tap to enter a date. _____ <input type="checkbox"/> N/A	Click or tap here to enter text. _____	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> 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): <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown If Yes, describe below. If more rows are needed, click on the last row and click on the + symbol in the bottom right corner to add additional rows or copy this page						
#	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. _____	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal <input type="checkbox"/> Unknown If Abnormal, please describe: Click or tap here to enter text. _____			
2 add line-if need	Click or tap here to enter text. _____	Click or tap to enter a date. _____	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal <input type="checkbox"/> 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


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		Range	Units	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY
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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
2 add lines if need	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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____

8.2. Laboratory Markers Relevant to Hepatic and Renal Impairment

(Click on the last row in each section and click on the + symbol in the bottom right corner to add additional rows or copy this page, if needed)

#	Hepatic Marker (select all that apply)	Normal		Baseline		First Abnormal		Most Recent Abnormal		Resolution	
		Range	Units	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY
1	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
2	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
3	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
4	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
5	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
6	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
7 add lines if need	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
#	Renal Marker (select all that apply)	Normal		Baseline		First Abnormal		Most Recent Abnormal		Resolution	
		Range	Units	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY	Value	Date DD/MM/YY
1	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____

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		text. _____	enter text. _____	_____	_____	_____	_____	_____	_____	text. _____	_____
2	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
3	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____
4 add lines if need	<input type="checkbox"/> 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 here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here to enter a date. _____	Click or tap here to enter text. _____	Click or tap here 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

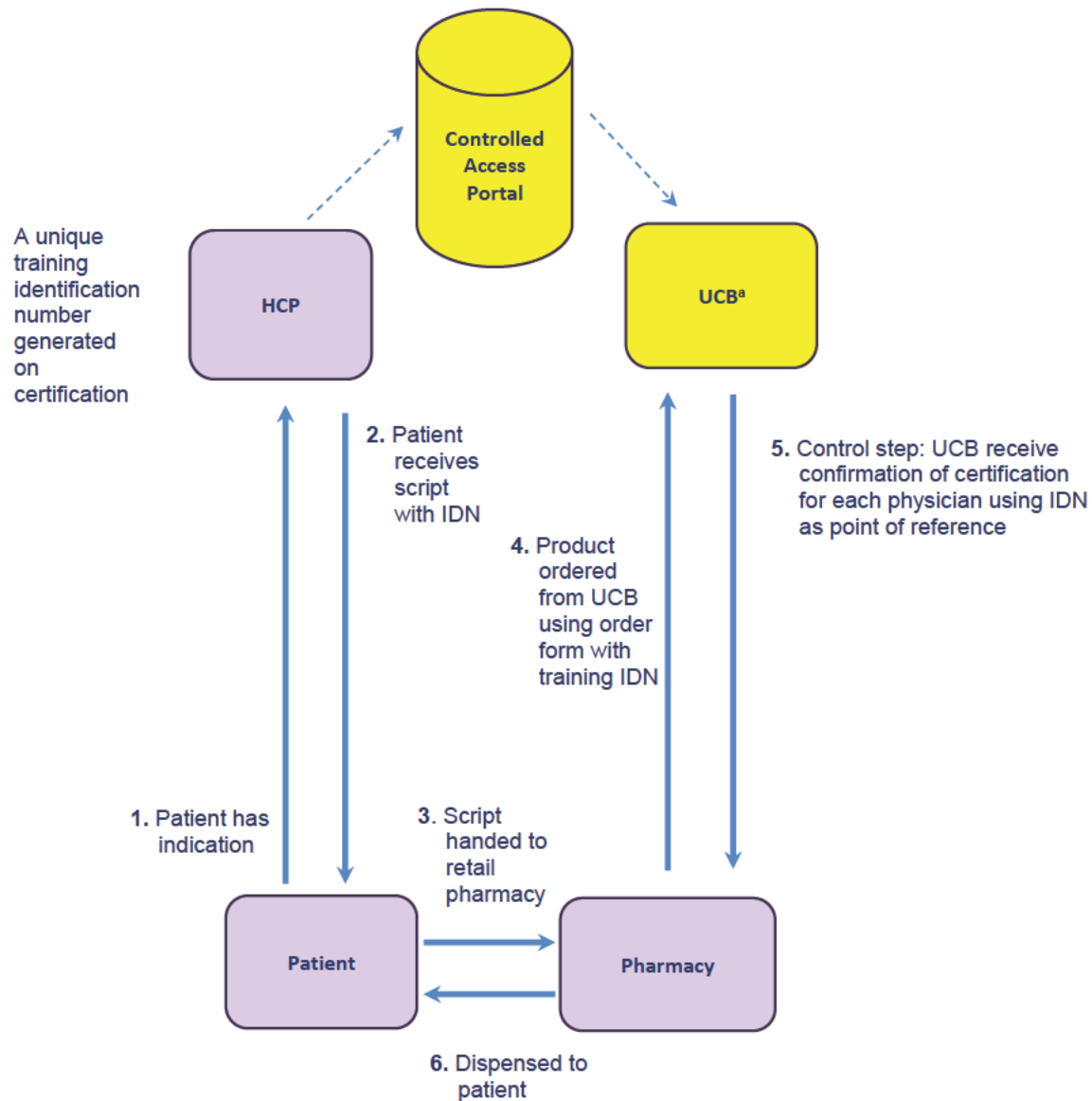
UCB is required to implement a CAP in order to prevent off-label use for weight management and to ensure that periodic echocardiogram monitoring is performed accordingly.

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 neuropsychiatrists 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/neuropsychiatrist. 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.

^aUCB 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.