

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Fintepla 2.2 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.2 mg of fenfluramine (as fenfluramine hydrochloride).

Excipient(s) with known effect

Glucose (maize): 0.627 mg/ml

Sodium ethyl para-hydroxybenzoate (E 215): 0.23 mg/ml

Sodium methyl para-hydroxybenzoate (E 219): 2.3 mg/ml

Sulfur dioxide (E 220): 0.000009 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, colourless, slightly viscous liquid, with a pH of 5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

4.2 Posology and method of administration

Fintepla should be initiated and supervised by physicians with experience in the treatment of epilepsy.

Fintepla is prescribed and dispensed according to the Fintepla controlled access programme (see section 4.4).

Posology

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

Table 1. Dosage recommendations for Dravet Syndrome

	<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)

* 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.

If the calculated dose is 3.0 ml or less, the green printed 3 ml syringe should be used.
If the calculated dose is more than 3.0 ml, the purple printed 6 ml syringe should be used.
The calculated dose should be rounded to the nearest graduated increment.

Table 2. Dosage recommendations for Lennox-Gastaut Syndrome

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)
Maximal recommended dose	26 mg (13 mg twice daily i.e. 6.0 ml twice daily)

**The dosage should be increased as tolerated to the recommended maintenance dosage (i.e., Day 14).

If the calculated dose is 3.0 ml or less, the green printed 3 ml syringe should be used.
If the calculated dose is more than 3.0 ml, the purple printed 6 ml syringe should be used.
The calculated dose should be rounded to the nearest graduated increment.

Discontinuation of treatment

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

Special populations

Patients with renal impairment

Generally, no dose adjustment is recommended when Fintepla is administered to patients with mild to severe renal impairment, however, a slower titration may be considered. If adverse reactions are reported, a dose reduction may be needed. (see section 5.2)

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

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

Patients with hepatic impairment

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

There are limited clinical data on the use of Fintepla with stiripentol in patients with mild impaired hepatic function (see section 5.2).

A slower titration may be considered in patients with hepatic impairment. If adverse reactions are reported, a dose reduction may be needed. (see section 5.2).

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.

Elderly

There are no data on the use of Fintepla in elderly patients.

Paediatric population

The safety and efficacy of Fintepla in children below 2 years of age has not yet been established. No data are available.

Method of administration

Fintepla is to be administered orally.

Fintepla may be taken with or without food.

Fintepla is compatible with commercially available gastric and nasogastric feeding tubes (see section 6.6).

Fintepla contains a very limited amount of digestible carbohydrates and is compatible with a ketogenic diet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Aortic or mitral valvular heart disease.

Pulmonary arterial hypertension.

Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome.

4.4 Special warnings and precautions for use

Aortic or mitral valvular heart disease and pulmonary arterial hypertension

Because of reported cases of valvular heart disease that may have been caused by fenfluramine at higher doses used to treat adult obesity, cardiac monitoring must be performed using echocardiography. Patients with valvular heart disease or pulmonary arterial hypertension were excluded from the controlled clinical studies of fenfluramine for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. No valvular heart disease was observed during these studies.

Prior to starting treatment, patients must undergo an echocardiogram to establish a baseline prior to initiating treatment (see section 4.3) and exclude any pre-existing valvular heart disease or pulmonary hypertension.

Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter. 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 pathological abnormalities on the echocardiogram are observed, it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist.

Once treatment is discontinued for any reasons, a final echocardiogram should be conducted 3-6 months after the last dose of treatment with fenfluramine.

If treatment is stopped because of aortic or mitral valvular heart disease, appropriate monitoring and follow-up should be provided in accordance with local guidelines for the treatment of aortic or mitral valvular heart disease.

With past use in higher doses to treat adult obesity, fenfluramine was reported to be associated with pulmonary arterial hypertension. Pulmonary arterial hypertension was not observed in the clinical programme, but post-marketing data show that it can also occur with doses used to treat epilepsy (see section 4.8)

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. If the echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as “intermediate probability” by the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines, it should lead to a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer, and cardiologist. If the echocardiogram finding, after confirmation, suggests of a high probability of pulmonary arterial hypertension, as defined by the 2015 ESC and ERS Guidelines, it is recommended fenfluramine treatment should be stopped.

Decreased appetite and weight loss

Fenfluramine can cause decreased appetite and weight loss (see section 4.8). An additive effect on decreased appetite can occur when fenfluramine is combined with other anti-epileptic medicines, for example stiripentol. The decrease in weight appears to be dose related. Most subjects resumed weight gain over time while continuing treatment. The patient's weight should be monitored. A benefit risk evaluation should be undertaken prior to commencing treatment with fenfluramine in patients with a history of anorexia nervosa or bulimia nervosa.

Fintepla controlled access programme

A controlled access programme has been created to 1) prevent off-label use in weight management in obese patients and 2) confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla.

Somnolence

Fenfluramine can cause somnolence.

Other central nervous system depressants, including alcohol, could potentiate the somnolence effect of fenfluramine (see sections 4.5 and 4.7).

Suicidal behaviour and ideation

Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials with anti-epileptic medicines that did not include fenfluramine has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known, and the available data do not exclude the

possibility of an increased risk for fenfluramine. Patients and caregivers of patients should be advised to seek medical advice should any signs of suicidal behaviour and ideation emerge.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhoea).

If concomitant treatment with fenfluramine and other serotonergic agents that may affect the serotonergic systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Increased seizure frequency

As with other anti-epileptic medicines, a clinically relevant increase in seizure frequency may occur during treatment with fenfluramine, which may require adjustment in the dose of fenfluramine and/or concomitant anti-epileptic medicines, or discontinuation of fenfluramine, should the benefit-risk be negative.

Cyproheptadine

Cyproheptadine is a potent serotonin receptor antagonist and may therefore decrease the efficacy of fenfluramine. If cyproheptadine is added to treatment with fenfluramine, patients should be monitored for worsening of seizures. If fenfluramine treatment is initiated in a patient taking cyproheptadine, fenfluramine's efficacy may be reduced.

Glaucoma

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Discontinue therapy in patients with acute decreases in visual acuity. Consider discontinuation if there is ocular pain and another cause cannot be determined.

Effect of CYP1A2 and CYP2B6 inducers

Co-administration with strong CYP1A2 inducers or CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of fenfluramine (see section 4.5). If co-administration of a strong CYP1A2 or CYP2B6 inducer with fenfluramine is considered necessary, the patient should be monitored for reduced efficacy and a dose increase of fenfluramine could be considered provided that it does not exceed twice the maximum daily dose (52 mg/day) (see section 4.2). If a strong CYP1A2 or CYP2B6 inducer is discontinued during maintenance treatment with fenfluramine, consider gradual reduction of the fenfluramine dosage to the dose administered prior to initiating the inducer (see section 4.2).

Effect of CYP1A2 or CYP2D6 inhibitors

Initiation of concomitant treatment with a strong CYP1A2 or CYP2D6 inhibitor may result in higher exposure and, therefore, adverse events should be monitored, and a dose reduction may be needed in some patients.

Coadministration of a single 0.35 mg/kg dose of fenfluramine with fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg once daily) in healthy volunteers increased the AUC_{0-t} of fenfluramine by a ratio of 2.1-fold and the C_{max} by a ratio of 1.2-fold, and decreased the AUC_{0-t} of norfenfluramine by a ratio of 1.3-fold and the C_{max} by a ratio of 1.4-fold, as compared to fenfluramine administered alone.

Coadministration of a single 0.35 mg/kg dose of fenfluramine with paroxetine (a strong CYP2D6 inhibitor) at steady state (30 mg once daily) in healthy volunteers increased the AUC_{0-t} of fenfluramine by a ratio of 1.8-fold and the C_{max} by a ratio of 1.1-fold, and decreased the AUC_{0-t} of norfenfluramine by a ratio of 1.2-fold and the C_{max} by a ratio of 1.3-fold, as compared to fenfluramine administered alone.

Excipients

This medicinal product contains sodium ethyl para-hydroxybenzoate (E 215) and sodium methyl para-hydroxybenzoate (E 219) which may cause allergic reactions (possibly delayed).

It also contains sulfur dioxide (E 220) which may rarely cause severe hypersensitivity reactions and bronchospasm.

Patients with rare glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per the maximum daily dose of 12 ml, that is to say essentially 'sodium-free'.

This medicinal product contains glucose which may be harmful to the teeth.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Pharmacodynamic interactions with other central nervous system depressants increase the risk of aggravated central nervous system depression. Examples of such depressants are other serotonergic agents (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); agents that impair metabolism of serotonin such as MAOIs; or antipsychotics that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.4).

Pharmacokinetic interactions

Clinical studies

Effect of steady state stiripentol plus clobazam and/or valproate on fenfluramine

At steady state in the Phase 3 studies, the co-administration of 0.2 mg/kg twice daily (0.4 mg/kg/day), maximum 17 mg/day, fenfluramine with a standard anti-epileptic medicine regimen of stiripentol plus clobazam and/or valproate, resulted in a 130% increase in fenfluramine AUC₀₋₂₄ and a 60% decrease in norfenfluramine AUC₀₋₂₄, as compared to 0.35 mg/kg twice daily (0.7 mg/kg/day), maximum 26 mg/day, fenfluramine without stiripentol (see section 4.2).

Effect of steady state cannabidiol on fenfluramine

Co-administration of a single 0.35 mg/kg dose of fenfluramine with repeated doses of cannabidiol increased the AUC_{0-INF} of fenfluramine by 59% and the C_{max} by 10%, and decreased the AUC_{0-INF} of norfenfluramine by 22% and the C_{max} by 33%, as compared to fenfluramine administered alone.

Co-administration of a single 0.35 mg/kg dose of fenfluramine, with repeated doses of cannabidiol, did not affect the pharmacokinetics of cannabidiol, as compared to cannabidiol alone. No dose adjustment is necessary when fenfluramine is co-administered with cannabidiol.

Effect of rifampicin (a strong inducer of CYP3A and 2C19 and a moderate inducer of CYP1A2, 2B6, 2C8 and 2C9), or strong CYP1A2 or CYP2B6 inducers

Rifampicin induces multiple CYP enzymes which metabolize fenfluramine and norfenfluramine. Co-administration of a single 0.35 mg/kg dose of fenfluramine with rifampicin at steady state (600 mg once daily) in healthy volunteers decreased the AUC_{0-t} of fenfluramine by 58% and the C_{max} by 40%, and decreased the AUC_{0-t} of norfenfluramine by 50%, and increased the C_{max} of norfenfluramine by 13%, as compared to fenfluramine administered alone. An increase in fenfluramine dose may be necessary when coadministered with *rifampicin* or a strong CYP1A2 or CYP2B6 inducer (see section 4.4).

Effect of CYP1A2 or CYP2D6 inhibitors

Co-administration of a single 0.35 mg/kg dose of fenfluramine with fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg once daily) in healthy volunteers increased the AUC_{0-t} of fenfluramine by a ratio of 2.1-fold and the C_{max} by a ratio of 1.2-fold, and decreased the AUC_{0-t} of norfenfluramine by a ratio of 1.3-fold and the C_{max} by a ratio of 1.4-fold, as compared to fenfluramine administered alone.

Co-administration of a single 0.35 mg/kg dose of fenfluramine with paroxetine (a strong CYP2D6 inhibitor) at steady state (30 mg once daily) in healthy volunteers increased the AUC_{0-t} of fenfluramine by a ratio of 1.8-fold and the C_{max} by a ratio of 1.1-fold, and decreased the AUC_{0-t} of norfenfluramine by a ratio of 1.2-fold and the C_{max} by a ratio of 1.3-fold, as compared to fenfluramine administered alone.

In vitro studies

Effect of fenfluramine on other medicinal products

Co-administration of a single 0.7 mg/kg dose of fenfluramine, with a single dose of a stiripentol, clobazam, and valproic acid combination, did not affect the pharmacokinetics of stiripentol, nor the pharmacokinetics of clobazam or its N-desmethyl-metabolite norclobazam, nor the pharmacokinetics of valproic acid, as compared to the stiripentol, clobazam, and valproic acid combination alone.

Effect of fenfluramine on CYP2D6 substrates

In vitro studies indicate that fenfluramine may inhibit CYP2D6. It has been reported that steady-state desipramine concentrations increase approximately 2-fold with concomitant administration of fenfluramine. Co-administration of fenfluramine with CYP2D6 substrates may increase their plasma concentrations.

Effect of fenfluramine on CYP2B6 and CYP3A4 substrates

In vitro studies indicate that fenfluramine may induce CYP2B6 and may induce intestinal CYP3A4. Co-administration of fenfluramine with CYP2B6 substrates or CYP3A4 substrates may decrease their plasma concentrations.

Effect of fenfluramine on MATE1 substrates

In vitro studies indicate that norfenfluramine (major and pharmacologically active metabolite) may inhibit MATE1 at clinically relevant concentrations. Co-administration of fenfluramine with MATE1 substrates may increase their plasma concentrations.

4.6 Fertility, pregnancy, and lactation

Pregnancy

There are limited data (less than 300 pregnancy outcomes) from the use of fenfluramine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity in the absence of paternal or maternal toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Fintepla during pregnancy.

Breast-feeding

It is unknown whether fenfluramine/metabolites are excreted in human milk.

Available pharmacokinetic data in animals have shown excretion of fenfluramine/metabolites in milk (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fintepla therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No effects of fenfluramine on human fertility up to clinical doses of 104 mg/day were noted. However, animal studies suggest that Fintepla may possibly affect female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fintepla has moderate influence on the ability to drive and use machines because it may cause somnolence and fatigue. Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile for Dravet Syndrome

The most commonly reported adverse reactions are decreased appetite (34.7%), diarrhoea (19.9%), upper respiratory tract infection (18.1%), echocardiogram abnormal* (18.1%), fatigue (18.1%), pyrexia (17.6%), blood glucose decreased (14.4%) and somnolence (13.0%).

** Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic.*

Summary of the safety profile for Lennox-Gastaut Syndrome

The most commonly reported adverse reactions are decreased appetite (27.8%), fatigue (18.8%), upper respiratory tract infection (15.9%), somnolence (13.6%), diarrhoea (11.9%) and vomiting (10.8%).

Tabulated list of adverse reactions

Adverse reactions reported with fenfluramine in placebo-controlled clinical studies and from post-marketing surveillance are listed in the tables below by System Organ Class and frequency. Frequencies are defined as very common ($\geq 1/10$) or common ($\geq 1/100$ to $< 1/10$) or not known (cannot be estimated from the available data).

Table 3: Adverse reactions for Dravet Syndrome

MedDRA System Organ Class	Very common	Common	Not known
Infections and infestations	Upper respiratory tract infection	Bronchitis	
Metabolism and nutrition disorders	Decreased appetite		
Psychiatric disorders		Abnormal behaviour Aggression Agitation Insomnia Mood swings	
Nervous system disorders	Somnolence	Ataxia Hypotonia Lethargy Seizure Status epilepticus Tremor	
Respiratory, thoracic and mediastinal disorders			Pulmonary arterial hypertension
Gastrointestinal disorders	Diarrhoea	Constipation Salivary Hypersecretion	
General disorders and administration site conditions	Pyrexia Fatigue		
Investigations	Blood glucose decreased Echocardiogram abnormal*	Weight decreased Blood prolactin increased	

* Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation, which are considered physiologic.

Table 4: Adverse reactions for Lennox-Gastaut Syndrome

MedDRA System Organ Class	Very common	Common
Infections and infestations	Upper respiratory tract infection	Bronchitis Influenza Pneumonia
Metabolism and nutrition disorders	Decreased appetite	
Psychiatric disorders		Aggression
Nervous system disorders	Somnolence	Seizure Status epilepticus Lethargy Tremor
Gastrointestinal disorders	Diarrhoea Vomiting	Constipation Salivary hypersecretion
General disorders and administrative site conditions	Fatigue	
Investigations		Blood prolactin increased Weight decreased

Injury, poisoning and procedural complications		Fall
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Description of selected adverse reactions

Decreased appetite and weight loss

Fenfluramine can cause decreased appetite and weight loss. In the controlled trials of children and young adults with Dravet syndrome 34.7% of fenfluramine-treated patients had an adverse reaction of decreased appetite, compared to 7.6% of patients on placebo, and approximately 18.9% of fenfluramine-treated patients had a decrease in weight $\geq 7\%$ from their baseline weight, compared to 2.4% of patients on placebo. In the controlled clinical trials of children and adults with Lennox-Gastaut syndrome, 27.8% of fenfluramine-treated patients had an adverse reaction of decreased appetite, compared to 11.5% of patients on placebo, and approximately 4% of fenfluramine-treated patients had a decrease in weight of $\geq 7\%$ from their baseline weight, compared to 0% of patients on placebo. The decreases in appetite and weight appeared to be dose related. Most subjects resumed weight gain over time while continuing fenfluramine treatment.

Status epilepticus and seizures

In the Dravet syndrome phase 3 clinical trials, the observed frequency of status epilepticus was 1.5% in the placebo group and 5.1% in the combined fenfluramine group. In the LGS phase 3 clinical trial, the observed frequency of status epilepticus was 1.1% in the placebo group and 1.1% in the fenfluramine group. There were no discontinuations due to status epilepticus in the Dravet syndrome and the LGS phase 3 clinical trials.

In the controlled trials in patients with Dravet syndrome seizures were reported less frequently in the fenfluramine treated patients (5.1%) than in patients on placebo (9.8%). However, seizures assessed as related to the study drug were more commonly reported in fenfluramine treated patients than placebo, 2.8% of fenfluramine-treated patients compared to 1.5% of patients on placebo. In the LGS trial, seizures were reported with a similar frequency in the fenfluramine treated patients (6.8%) and patients on placebo (6.9%). However, seizures assessed as related to the study drug were more commonly reported in fenfluramine treated patients than placebo, 6.3% of fenfluramine-treated patients compared to 1.1% of patients on placebo.

The mean days to onset of seizure events in the LGS phase 3 trial after starting treatment was 26.3 days in the fenfluramine 0.2 mg/kg/day group, 31.3 days in the fenfluramine 0.7 mg/kg/day and 31.3 days in the placebo group.

Echocardiographic safety assessments

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for 341 Dravet syndrome patients and 263 Lennox-Gastaut syndrome patients. No patient developed valvular heart disease or pulmonary arterial hypertension in the placebo-controlled studies or during the open-label extension studies with exposure of up to 3 years. In the Dravet syndrome double-blind studies, trace mitral valve regurgitation was reported in 17.9% of patients in the fenfluramine 0.2 mg/kg/day group (n=7/39), 23.3% in the fenfluramine 0.4 mg/kg/day group (n=10/43), 22.5% in the fenfluramine 0.7 mg/kg/day group (n=9/40), and in 9.5% in the placebo group (n=8/84). Mild mitral valve regurgitation was reported in 2.3% of patients in the fenfluramine 0.4 mg/kg/day group (n=1/43). Trace aortic valve regurgitation was reported in 7.9% of patients in the fenfluramine 0.7 mg/kg/day group (n=3/40). In the Lennox-Gastaut syndrome double-blind study, trace mitral valve regurgitation was reported in 14.8% of patients in the fenfluramine 0.2 mg/kg/day group (n=13/89), 17.6% in the fenfluramine 0.7 mg/kg/day group (n=15/87), (and 22.1% in the placebo group (n=19/87). Mild mitral valve regurgitation was reported in 1.1% of patients in the fenfluramine 0.7 mg/kg/day group (n=1/87).

Trace aortic valve regurgitation was reported in 5.6% of patients in the fenfluramine 0.2 mg/kg/day group (n=5/89) and 2.3% in the placebo group (n=2/87). One 11-year-old patient in the fenfluramine 0.2 mg/kg/day group exhibited mild aortic valve regurgitation. No abnormalities in valve morphology were observed, and upon a diagnostic evaluation via transoesophageal echocardiogram, the finding was downgraded to absent. Trace and mild mitral regurgitation and trace aortic regurgitation are all non-pathologic findings as defined by the 2015 ESC and ERS Guidelines. Where trace mitral or aortic regurgitation were observed, the results were often transient. Pulmonary arterial hypertension in a child associated with fenfluramine (10.12 mg/day) for Dravet syndrome has been reported post-marketing. The patient discontinued fenfluramine and the reaction resolved post-discontinuation (see section 4.4).

Lethargy, somnolence, and fatigue

In the controlled trials in subjects with Dravet syndrome, lethargy was commonly reported in 9.7%, and somnolence and fatigue/asthenia were very commonly reported in 13.0% and 18.1%, respectively in the fenfluramine treatment groups combined. In the controlled study with Lennox-Gastaut syndrome, lethargy was commonly reported in 4% of subjects. Fatigue/asthenia and somnolence were very commonly reported in 18.8% and 13.6% subjects, respectively. The majority of the adverse reactions of lethargy, somnolence, and fatigue/asthenia were reported in the first 2 weeks of treatment with fenfluramine and were mild or moderate in severity. Discontinuation due to lethargy, somnolence, and fatigue/asthenia was rare and, in most cases, these adverse events resolved or improved with ongoing treatment. In the controlled trials with Dravet syndrome, 0.8% and 1.6% subjects in the fenfluramine treatment groups combined discontinued due to lethargy and somnolence, respectively. In the LGS study, 1.7% subjects in the fenfluramine treatment group discontinued due to somnolence.

Gastrointestinal disorders

In the Phase 3 LGS controlled trial in children and young adults, diarrhoea (11.9%) and vomiting (10.8%) were observed more frequently in the combined fenfluramine groups than in the placebo group (4.6% and 5.7%, respectively) during the 14-week titration and maintenance periods. The mean time to onset of diarrhoea in the fenfluramine groups was 25.0 and 26.1 days in the 0.2 mg/kg/day and 0.8 mg/kg/day groups respectively versus 46.0 days in the placebo group while the mean time to onset of vomiting in the fenfluramine groups was 29.8 and 29.1 days in the 0.2 mg/kg/day and 0.8 mg/kg/day groups respectively versus 42.8 days in the placebo group.

In the LGS controlled trial through the open-label trial, diarrhoea and constipation were observed more frequently in the higher dose groups. The mean time to onset of diarrhoea was 215.7 days, 95.2 days, and 79.6 days in the $>0 - <0.4$ mg/kg/day, $0.4 - <0.6$ mg/kg/day, and ≥ 0.6 mg/kg/day mean daily dose groups respectively while the mean time to onset of constipation was 113.0 days, 173.7 days, and 140.1 days in the $>0 - <0.4$ mg/kg/day, $0.4 - <0.6$ mg/kg/day, and ≥ 0.6 mg/kg/day mean daily dose groups respectively.

All events reported for diarrhoea and constipation were mild or moderate in severity.

Infections and infestations disorders

In the Phase 3 LGS controlled trial in children and young adults, upper respiratory tract infection (7.4%) was observed more frequently in the combined fenfluramine groups than in the placebo group (3.4%) during the 14 week titration and maintenance periods. The mean time to onset of upper respiratory tract infection in the fenfluramine groups was 42.9 days and 40.8 days in the 0.2 mg/kg/day and 0.8 mg/kg/day groups respectively versus 46.7 days in the placebo group.

A higher frequency of infections was reported in the active arm among 2–6-year-old age group in the LGS controlled study. The combined incidences of upper respiratory tract infections (including streptococcal pharyngitis, pharyngotonsillitis, rhinitis, sinusitis and viral upper respiratory tract infection) was most commonly reported in 14.2% of subjects in the fenfluramine treatment group. Bronchitis (2.3%), influenza (2.3%), otitis media (1.1%), and pneumonia (2.3%) were commonly reported. Most of these infections were reported for 2 or more subjects in the fenfluramine treatment group and were not reported in the placebo group. In the LGS controlled trial through the open-label trial, nasopharyngitis, upper respiratory tract infection, gastroenteritis viral, and pneumonia were observed more frequently in the higher dose groups. The mean time to onset of these events was 6.0 – 155.1 days, 107.1 – 212.5 days, and 155.7 – 320.7 days in the >0 - <0.4 mg/kg/day, 0.4 - <0.6 mg/kg/day, and ≥0.6 mg/kg/day mean daily dose groups respectively.

All events reported for nasopharyngitis, upper respiratory tract infection, gastroenteritis viral, were mild or moderate in severity. Two cases of severe pneumonia were reported in the 0.4 - < 0.6 mg/kg/day mean daily dose group during the open-label part of the trial.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Only limited data have been reported concerning clinical effects and management of overdose of fenfluramine. Agitation, drowsiness, confusion, flushing, tremor (or shivering), fever, sweating, abdominal pain, hyperventilation, and dilated non-reactive pupils were reported at much higher doses of fenfluramine than those included in the clinical trial program.

Vital functions should be monitored closely, and supportive treatment administered in case of convulsions, arrhythmias, or respiratory difficulties.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiepileptics, other antiepileptics; ATC code: N03AX26

Mechanism 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 not known.

Clinical efficacy

Dravet syndrome

Children and young adults with Dravet syndrome

The effectiveness of fenfluramine in children and young adults with Dravet syndrome was evaluated in three randomised, multicentre, placebo-controlled studies (1501, 1502, 1504).

Study 1 (n=119) and Study 3 (n=143) are the prospective, merged analyses of the first 119 patients enrolled (Study 1) and the remaining subsequent total of 143 enrolled patients (Study 3) from 2 identical double-blind, placebo-controlled studies, ZX008-1501 and ZX008-1502. Study 1501 and Study 1502 were conducted in parallel and the design was identical: 3-arm, multicentre, randomised, double-blind, parallel group, placebo-controlled studies consisting of a 6-week baseline period followed by a 2-week titration period and a 12-week maintenance period for a total of 14-weeks treatment. Patients taking concomitant stiripentol were not enrolled in these studies. Eligible patients were randomised 1:1:1 to one of two doses of fenfluramine (0.7 mg/kg/day or 0.2 mg/kg/day, maximum 26 mg/day) or placebo. The mean (standard deviation) age of patients enrolled was 9.0 (4.7) years in Study 1 and was 9.3 (4.7) years in Study 3, with a range of 2 to 18 years. The majority of patients were ≥ 6 years of age (73.9% in Study 1 and 74.6% in Study 3). All enrolled patients were inadequately controlled on at least one anti-epileptic medicine, with or without vagal nerve stimulation and/or ketogenic diet, the most frequently used concomitant anti-epileptic medicines ($\geq 25\%$ overall) being valproate, clobazam, topiramate and levetiracetam.

In Study 1, the median baseline convulsive seizure frequency per 28 days was 34.0, 17.5, and 21.2 in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively. In Study 3, the median baseline convulsive seizure frequency per 28 days was 12.7, 18.0, and 13.0 in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively.

Table 5. Dravet syndrome: Study 1 and Study 3 results of primary and selected secondary efficacy endpoints

		Study 1			Study 3		
		Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day	Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day
Convulsive Seizure Frequency	N	40	39	40	48	46	48
	Baseline. Median (min, max)	34.0 (3.3, 147.3)	17.5 (4.8, 623.5)	21.2 (4.9, 127.0)	12.7 (4.0, 229.3)	18.0 (4.0, 1464.0)	13.0 (2.7, 2700.7)
Maintenance period	N	39	39	40	48	46	48
	At end of maintenance period. Median (min, max)	25.7 (3.6, 204.7)	17.1 (0.0, 194.3)	4.9 (0, 105.5)	10.6 (1.0, 139.0)	7.6 (0.0, 2006.8)	3.2 (0.0, 3651.7)
	Reduction in mean monthly baseline- adjusted Convulsive Seizure Frequency compared to Placebo	-	36.7% p=0.016	67.3% p<0.001	-	49.3% p<0.0001	65.7% p<0.0001
% reduction in convulsive seizures Maintenance period	Number (%) of patients with $\geq 50\%$ reduction in monthly convulsive seizures - change	4 (10.3%)	17 (43.6%) ES=33.3% RR: 4.25	29 (72.5%) ES=62.2% RR: 7.07	4 (8.3%)	21 (45.7%) ES=37.3% RR: 5.48	33 (68.8%) ES=60.4% RR: 8.25

		Study 1			Study 3		
		Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day	Placebo	Fenfluramine 0.2 mg/kg/day	Fenfluramine 0.7 mg/kg/day
	from baseline Effect size ¹ Relative Risk						
	Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline Effect size ¹ Relative Risk	2 (5.1%)	10 (25.6%) ES=20.5% RR: 5.00	21 (52.5%) ES=47.4% RR: 10.24	2 (4.2%)	9 (19.6%) ES=15.4% RR: 4.70	23 (47.9%) ES=43.7% RR: 11.50
	Number (%) of patients with ≥100% reduction in monthly convulsive seizures - change from baseline Effect size ¹	0 (0%)	6 (15.4%) ES=15.4%	6 (15.0%) ES=15.0%	0 (0%)	1 (2.2%)	10 (20.8%)
	Longest seizure-free interval (median)	9.5 days	15.0 days p=0.035	25.0 days p<0.001	10.0 days	18.5 days p=0.0002	30 days p<0.0001
	Titration + maintenance period						

¹ Effect size (ES) (Risk difference) calculated as proportion of Active-Placebo; RR: Relative Risk

Study 2 (previously known as 1504) (N=87) was a 2-arm, multicentre, randomised, double-blind, parallel group, placebo-controlled study consisting of a 6-week baseline period followed by a 3-week titration period and a 12-week maintenance period for a total of 15 weeks treatment. Eligible patients were randomised 1:1 to fenfluramine 0.4 mg/kg/day (maximum 17 mg/day) or placebo added to their stable standard of care regimen of stiripentol (plus clobazam and/or valproate) and possibly other anti-epileptic medicines. The mean (standard deviation) age of patients enrolled in Study 2 was 9.1 (4.80) years, with a range of 2 to 19 years. The majority of patients were ≥6 years of age (72.4%) and the minority <6 years (27.6%), male (57.5%) and, where reported, white (59.8%). All enrolled subjects were inadequately controlled on at least one anti-epileptic medicine, which included stiripentol, with or without vagal nerve stimulation and/or ketogenic diet. The median baseline convulsive seizure frequency per 28 days was 10.7 and 14.3 in the placebo and fenfluramine 0.4 mg/kg/day groups, respectively.

Table 6. Dravet syndrome: Study 2 (previously known as Study ZX008-1504) results of primary and selected secondary efficacy endpoints

		Study 2	
		Placebo + stiripentol	Fenfluramine 0.4 mg/kg/day + stiripentol
Convulsive Seizure Frequency	N	44	43
	Baseline. Median (min, max)	10.7 (2.7, 162.7)	14.3 (2.7, 213.3)
Maintenance period	N	44	42
	At end of maintenance period. Median (min, max)	11.4 (0.7, 169.3)	3.9 (0.0, 518.0)
	Reduction in mean monthly baseline-adjusted Convulsive Seizure Frequency compared to Placebo	-	54.9 % p<0.001
% reduction in convulsive seizures	Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline Effect size ¹ Relative Risk	4 (9.1%)	23 (54.8%) ES=45.7 RR: 6.02
	Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline Effect size ¹ Relative Risk	2 (4.5%)	17 (40.5%) ES=36.0% RR: 8.90
	Number (%) of patients with ≥100% reduction in monthly convulsive seizures - change from baseline Effect size ¹	0 (0%)	2 (4.8%) ES=4.8%
Longest seizure-free interval (median)		13.0 days	22.0 days p=0.004
Titration + maintenance period			

¹ Effect size (ES) (Risk difference) calculated as proportion of Active-Placebo; RR: Relative Risk

Adults

The Dravet syndrome population in Study 1 and Study 2 was predominantly paediatric patients, with only 7 adult patients who were 18-19 years old (3.4%), and therefore limited efficacy and safety data were obtained in the adult Dravet syndrome population.

Open-label data

Dravet syndrome patients who participated in Study 1 and Study 2 could participate in an open-label extension study (Study 5). The primary objective of the open-label study was long-term effectiveness and safety of fenfluramine at doses of 0.2 to 0.7 mg/kg/day, whereby the dose of fenfluramine could be titrated to optimize treatment. Data are reported for 330 patients who participated in the open-label study and received fenfluramine for up to 3 years (median treatment period: 631 days; range: 7-1086).

A total of 23% of patients discontinued study participation during the open-label extension treatment period, including 15% due to lack of efficacy and 1% due to adverse events.

Lennox-Gastaut syndrome

Children and adults with Lennox-Gastaut syndrome

The effectiveness of fenfluramine for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 to 35 years of age was evaluated in a randomized, double-blind, placebo-controlled study (Study 4 Part 1).

Study 4 Part 1 compared a 0.7 mg/kg/day (N=87) and a 0.2 mg/kg/day (N=89) dose (up to a maximum dose per day of 26 mg/kg) of fenfluramine with placebo. Patients had a diagnosis of Lennox-Gastaut syndrome and were inadequately controlled on at least one anti-epileptic medicine, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable anti-epileptic medicine therapy. Drop seizures included: generalized tonic-clonic, secondarily generalized tonic-clonic, tonic, atonic, or tonic-atonic seizures that were confirmed to result in drops. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of fenfluramine remained stable.

In Study 4 Part 1, 99% of patients were taking between 1 and 4 concomitant anti-epileptic medicines. The most frequently used concomitant anti-epileptic medicines (in at least 25% of patients) were clobazam (45.2%), lamotrigine (33.5%), and valproate (55.9%).

The primary efficacy endpoint in Study 4 Part 1 was percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period) in the fenfluramine 0.7 mg/kg/day group compared to the placebo group. Key secondary endpoints included the proportion of patients who achieve a $\geq 50\%$ reduction from baseline in drop seizure frequency per 28 days for the fenfluramine 0.7 mg/kg/day group compared to the placebo group and proportion of patients who achieve improvement (minimally, much, or very much improved) in the Clinical Global Impression – Improvement (CGI-I) as assessed by the Principal Investigator for the fenfluramine 0.7 mg/kg/day group compared to the placebo group.

In Study 4 Part 1, the median percent change from baseline (reduction) in the frequency of drop seizures per 28 days was significantly greater for the fenfluramine 0.7 mg/kg/day group compared with the placebo group (Table 6). A reduction in drop seizures was observed within 2 weeks of initiating treatment with fenfluramine, and the effect remained consistent over the 14-week treatment period.

Among subjects with ≥ 124 drop seizures per 28 days during Baseline, the reduction in DSF were -19.98%, -7.37%, -11.21% for subjects in the fenfluramine 0.7 mg/kg/day group, 0.2 mg/kg/day group, and placebo group respectively.

Table 7 Lennox-Gastaut syndrome: results of selected endpoints in Study 4 Part 1 (Maintenance Period)

	Placebo (N = 87)	Fenfluramine 0.7 mg/kg/day (N = 87)
Primary Endpoint: Percentage Change from BL in DSF During M		
DSF Summary Statistics ^a		
Median at BL	53.00	82.00
Median during M	47.33	55.73
Median Percentage Change from BL During M	-7.28	-27.16

	Placebo (N = 87)	Fenfluramine 0.7 mg/kg/day (N = 87)
Nonparametric Model ^b		
p-value for comparison with placebo	—	0.0018
HL Estimate for Median Difference (A-P)		
Estimate (Std Err)	—	-20 (5.795)
95% CI	—	-31.61, -8.89
Key Secondary Endpoint: Percentage of Patients with ≥ 50% Reduction from BL in DSF (50% Responder Rate) During M		
≥ 50% reduction in DSF, n (%)	11 (12.6)	27 (31.4)
p-value for comparison with placebo ^c		0.0044
Key Secondary Endpoint: Percentage of Patients with Improvement^d on the CGI-I Investigator Rating at End of M		
Subjects with score 1, 2, or 3, n (%)	27 (33.8)	39 (48.8)
p-value vs placebo ^e		0.0567

ANCOVA = analysis of covariance; A-P = active group–placebo group; BL = Baseline Period; CGI I = Clinical Global Impression – Improvement; CI = confidence interval; DSF = drop seizure frequency per 28 days; HL = Hodges-Lehmann; Std Err = standard error; T+M = Titration and Maintenance Periods

- BL, T+M, and percentage change from BL in M values for seizure frequency per 28 days are presented in original scale.
- Results are based on a nonparametric ANCOVA model with treatment group (3 levels) and weight strata (< 37.5 kg, ≥ 37.5 kg) as factors, rank of BL seizure frequency as a covariate, and rank of percentage change from BL in seizure frequency during treatment (M) as response
- Based on a logistic regression model that included a categorical response variable (achieved percentage point reduction, yes or no), weight group strata (< 37.5 kg, ≥ 37.5 kg), and Baseline DSF as a covariate.
- Minimally, much, or very much improved
- Based on a Cochran-Mantel-Haenszel test comparing active treatment with placebo, after adjusting for weight strata

The median percent reduction from baseline in drop seizure frequency per 28 days for the lower dose of fenfluramine (0.2 mg/kg/day) during the Maintenance Period did not reach statistical significance compared to placebo (Median change between 0.2 group of patients and placebo in % change from baseline during Maintenance Period -11.48 [95% CI -26.61, 3.31]).

The seizure type with the greatest median percentage change from Baseline in the fenfluramine 0.7 mg/kg/day group relative to the placebo group was generalised tonic-clonic seizures (-45.7% fenfluramine 0.7 mg/kg/day [n=38] versus 3.7% placebo [n=38]).

Lennox-Gastaut patients who completed Study 4 Part 1 could participate in Part 2, an open-label, 52-week, flexible-dose extension study. The primary objective of Study 4 Part 2 was to assess the long-term safety and tolerability of fenfluramine at doses of 0.2 mg/kg/day to 0.7 mg/kg/day. All patients received fenfluramine 0.2 mg/kg/day for 1 month, then the dose was titrated to optimize treatment.

Among the 172 LGS subjects treated with Fintepla for ≥ 12 months, 46.5% had received a mean daily dose of 0.4 to <0.6 mg/kg/day, 33.7% received a mean daily dose ≥ 0.6 mg/kg/day, 19.8% received a mean daily dose of >0 to <0.4 mg/kg/day.

Data are reported for 247 patients who enrolled in Study 4 Part 2 and received fenfluramine for a median duration of 364 days (range: 19-542 days). A total of 143 subjects had completed the study, 19 subjects were ongoing, and 85 subjects had withdrawn. The most common reason for discontinuation was lack of efficacy (55 [22.3%]), adverse event (13 [5.3%]), and withdrawal by subject (13 [5.3%]).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Fintepla in one or more subsets of the paediatric population in Dravet syndrome (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The pharmacokinetics of fenfluramine and norfenfluramine were studied in healthy subjects, in paediatric patients with Dravet syndrome, and in paediatric and adult patients with Lennox-Gastaut syndrome.

Absorption

Fenfluramine has a time to maximum plasma concentration (T_{max}) in the range of 3 to 5 hours at steady state. The absolute bioavailability of fenfluramine is approximately 68%-83%. There was no effect of food on the pharmacokinetics of fenfluramine or norfenfluramine.

For fenfluramine, the C_{max} occurs ~3 h following a single oral dose in healthy volunteers and is 28.6 ng/ml following a dose of 0.35 mg/kg and 59.3 ng/ml following a dose of 0.7 mg/kg fenfluramine. The AUC_{inf} is 673 ng × h/ml and 1660 ng × h/ml following 0.35 mg/kg and 0.7 mg/kg, respectively. For norfenfluramine, the C_{max} occurs ~12 h following a single oral dose in healthy volunteers and is 11.7 ng/ml and 16.1 ng/ml following a dose of 0.35 mg/kg or 0.7 mg/kg, respectively. The AUC_{inf} is 798 ng × h/ml and ~800 ng × h/ml following 0.35 mg/kg and 0.7 mg/kg, respectively. C_{max} and AUC_{inf} of fenfluramine appear dose proportional over the 0.35 to 0.7 mg/kg dose range in healthy volunteers. The C_{max} and AUC_{inf} of norfenfluramine are less than dose proportional over the 0.35 to 0.7 mg/kg dose range in healthy volunteers. The AUC_{inf} increase was 0.5-fold for the 0.7 mg/kg dose compared to the 0.35 mg/kg dose. The C_{max} increase was 0.7-fold for the 0.7 mg/kg dose compared to the 0.35 mg/kg dose.

In paediatric Dravet syndrome patients following fenfluramine dosing of 0.2 mg/kg/day, administered twice daily, steady state exposure (AUC_{0-24}) is 371 ng*h/ml for fenfluramine and 222 ng*h/ml for norfenfluramine. In paediatric patients following fenfluramine dosing of 0.7 mg/kg/day, administered twice daily with a maximum of 26 mg/day; steady state AUC_{0-24} is 1400 ng*h/ml for fenfluramine and 869 ng*h/ml for norfenfluramine following a dose of 0.7 mg/kg/day, administered twice daily. $C_{max,ss}$ was 68.6 ng/ml for fenfluramine and 37.8 ng/ml for norfenfluramine. When stiripentol is given concomitantly, the steady state AUC_{0-24} is 1030 ng*h/ml for fenfluramine and 139 ng*h/ml for norfenfluramine following a dose of 0.2 mg/kg/day, administered twice daily; the steady state AUC_{0-24} is 3240 ng*h/ml for fenfluramine and 364 ng*h/ml for norfenfluramine following a dose of 0.35 mg/kg/day, administered twice daily.

In paediatric and adult patients with Lennox-Gastaut syndrome who receive Fintepla 0.7 mg/kg/day, administered twice daily, up to a total daily dose of 26 mg fenfluramine, steady-state systemic exposure (C_{max} and AUC_{0-24h}) of fenfluramine is slightly lower on average but not considered to be meaningfully different than in patients with Dravet syndrome.

The plasma half-life of fenfluramine and norfenfluramine indicates that approximately 94% of steady-state would be reached in approximately 4 days for fenfluramine and 5 days for norfenfluramine (4 half-lives). In healthy subjects, the C_{max} accumulation ratio is 3.7-fold for fenfluramine and 6.4-fold for norfenfluramine and the AUC_{0-24} accumulation ratio is 2.6-fold for fenfluramine and 3.7-fold for norfenfluramine.

Distribution

Fenfluramine is 50% bound to human plasma proteins in vitro and binding is independent of fenfluramine concentrations. The geometric mean (CV%) volume of distribution (V_z/F) of fenfluramine is 11.9 (16.5%) L/kg following oral administration of fenfluramine in healthy subjects.

Biotransformation

Over 75% of fenfluramine is metabolised to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6. Norfenfluramine is then deaminated and oxidized to form inactive metabolites. The extent to which these inactive metabolites are present in plasma and urine is unknown. The involvement of enzymes other than CYPs (e.g. UGTs) in the metabolism of norfenfluramine is unknown, but literature data indicate that norfenfluramine may be glucuronidated to a significant extent.

Transporters

Fenfluramine and norfenfluramine were not *in vitro* substrates of P-glycoprotein, BCRP, OATP1B1, OATP1B3, OATP1A2, OATP2B1, OCT1, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

Elimination

Most of an orally administered dose of fenfluramine (>90%) is excreted in the urine mainly as metabolite; less than 5% is found in faeces. The geometric mean (CV%) clearance (CL/F) of fenfluramine is 6.9 L/h (29%) and the half-life is 20 hours following oral administration of fenfluramine in healthy subjects. The elimination half-life of norfenfluramine is ~30 h.

Special populations

Genetic polymorphisms

No impact of genotype in CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP3A4 on fenfluramine or norfenfluramine PK was observed.

Renal impairment

Renal elimination is the predominant route of elimination of fenfluramine, with more than 90% of the administered dose eliminated in the urine as parent or metabolites. In a study comparing the pharmacokinetics of a single dose of 0.35 mg/kg fenfluramine in subjects with severe renal impairment (determined by modification of diet in renal disease estimated glomerular filtration rate < 30 ml/min/1.73m²) and matched healthy volunteers, C_{max} and AUC_{0-t} of fenfluramine increased by 20% and 87%, respectively, in severe renal impairment. These increases in fenfluramine exposures are not clinically significant. Small and insignificant changes in AUC_{0-t} and C_{max} of norfenfluramine were observed in subjects with severe renal impairment. 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.

Hepatic impairment

In a study comparing the pharmacokinetics of a single dose of 0.35 mg/kg fenfluramine in subjects with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively), AUC_{0-t} of fenfluramine increased by 95% in subjects with mild hepatic impairment, 113% in subjects with moderate hepatic impairment, and 185% in subjects with severe hepatic impairment relative to matched subjects with normal liver function. Increases in C_{max} of fenfluramine ranged from 19% to 29% in hepatic impairment. Systemic exposures of norfenfluramine either increased slightly by up to 18% (AUC_{0-t}) or decreased by up to 45% (C_{max}) in subjects with hepatic impairment. In subjects with mild, moderate, and severe hepatic impairment, the mean plasma elimination half-life of fenfluramine increased to 34.5 hours, 41.1 hours, and 54.6 hours, respectively, compared to 22.8 hours in subjects with normal hepatic function. The corresponding mean plasma elimination half-life of norfenfluramine was 54.0 hours, 72.5 hours, and 69.0 hours, respectively, compared to 30.2 hours in subjects with normal hepatic function. The differences in exposures in mild and moderate hepatic impairment are not considered to be clinically meaningful. Dosage of fenfluramine should be reduced in patients with severe hepatic impairment. [see section 4.2, Posology and method of administration for special populations]

The retrospective analysis of steady-state exposures of fenfluramine and norfenfluramine in Study 2, Cohort 2 (n=12) indicated no clinically meaningful changes in the absence or presence of stable doses of stiripentol in patients with Dravet syndrome in the Phase 3 trials who were categorized with mild hepatic impairment as compared to those with normal hepatic function (AST/ALT and BILI \leq ULN). Fenfluramine is not recommended for use in patients with moderate and severe hepatic impairment treated with stiripentol.

Body weight

Drug clearance and PK exposure of fenfluramine and norfenfluramine are consistent across a broad range of BMI (12.3 to 35 kg/m²).

Gender

The pharmacokinetics of fenfluramine and norfenfluramine were consistent between males and females.

Race

The evaluation was limited by the small sample size of non-white subjects that no conclusion on the effect of race on the pharmacokinetics can be made. The genetic polymorphs of the enzymes that metabolize fenfluramine are similar across races, only their frequency differs. Thus, although the mean exposure may differ slightly depending on race, the range of exposure would be expected to be similar.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In a lactation study, rats were dosed orally with radiolabeled dexfenfluramine at 1.2 mg/kg, and samples of plasma and milk were collected over 24 hours following the dose. Both dexfenfluramine and nordexfenfluramine were found in milk at 2 hours after dosing and levels declined over 24 hours. No dexfenfluramine was found in the milk at 24 hours. Nordexfenfluramine was present in small amounts at 24 hours. The radioactivity milk:plasma ratio was 9 ± 2 at 2 hours and 5 ± 1 at 24 hours. Based on a bodyweight comparison, the human equivalent dose (0.2 mg/kg dexfenfluramine) is less than the maximum recommended human dose of Fintepla.

Reproduction and development

Fenfluramine and norfenfluramine crossed the placenta in pregnant rats and rabbits. Plasma exposures were higher in rat foetuses than in the dams, while plasma exposures in rabbits were comparable between does and foetuses; however the effects in human foetuses are unknown.

In an embryofoetal development study in rats, decreased foetal body weight and increased incidences of external and skeletal malformations were observed at the high dose level in association with maternal toxicity. No foetal abnormalities were noted at exposures at least five-fold the plasma AUC in humans administered the maximum recommended therapeutic dose of Fintepla.

No fenfluramine-related external, visceral or skeletal malformations or variations were determined in an embryofoetal development study in rabbits but increased post-implantation losses were evident at all doses secondarily to fenfluramine maternal toxicity (body weight loss and decreased food consumption). Additional clinical signs of dilated pupils and increased respiration rate and tremors were observed. Plasma exposures (AUC) in rabbits were below those in humans at the maximum recommended therapeutic dose of Fintepla.

In a pre- and post-natal study in rats, maternal toxicity was associated with an increase in stillbirths at the high dose. No adverse effects on the F₀ and F₁ generations were confirmed at five-fold higher

plasma exposures (AUC) than in humans at the maximum recommended therapeutic dose of Fintepla. In the first generation of offspring, there were no effects on overall reproductive function.

Fenfluramine did not affect the reproductive performance of male rats. In female rats, a reduction in the fertility index (defined by the proportion of matings that resulted in pregnancies) was observed at maternally toxic doses that correlated with less corpora lutea, significantly fewer implantation sites and a higher percentage of pre- and post-implantation losses. No effects on the fertility index were noticed at plasma exposures (AUC) approximately equivalent to those in humans at the maximum recommended therapeutic dose of Fintepla.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium ethyl para-hydroxybenzoate (E 215)
Sodium methyl para-hydroxybenzoate (E 219)
Sucralose (E 955)
Hydroxyethylcellulose (E 1525)
Monosodium phosphate (E 339)
Disodium phosphate (E 339)
Cherry flavouring powder:
 Acacia (E 414)
 Glucose (maize)
 Ethyl benzoate
 Natural flavouring preparations
 Natural flavouring substances
 Flavouring substances
 Maltodextrin (maize)
 Sulfur dioxide (E 220)
Potassium citrate (E 332)
Citric acid monohydrate (E 330)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

Shelf life after first opening

This medicinal product should be used within 3 months of first opening the bottle.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.

6.5 Nature and contents of container

Fintepla is presented in a white High Density Polyethylene (HDPE) bottle with a child-resistant, tamper-evident cap packaged in a carton, a Low Density Polyethylene (LDPE) press-in bottle adaptor, and Polypropylene (PP)/HDPE oral syringes. The oral syringe included in the pack should be used to administer the prescribed dose.

Presentations:

Bottle containing 60 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.

Bottle containing 120 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.

Bottle containing 250 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.

Bottle containing 360 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Inserting the bottle adaptor:

When the bottle is first opened the bottle adaptor must be pushed into the bottle.

Wash and dry hands.

Remove the bottle adaptor packaging.

Place the bottle on a flat, firm surface.

Open the bottle.

Hold the bottle firmly.

Align the bottle adaptor with the open top of the bottle.

Push the bottle adaptor into the bottle using the palm of the hand.

The bottle adaptor should be flush with the top of the bottle.

The bottle adaptor should not be removed after each use.

The bottle cap can be screwed onto the bottle with the bottle adaptor in place.

Cleaning the syringe:

Separate the plunger from the syringe to rinse each part.

Rinse the oral syringe with clean water and allow it to air dry after each use.

Rinse the inside of the syringe and the plunger.

The syringe and plunger can be cleaned in a dishwasher.

Clean water can be pulled into the syringe with the plunger and pushed out several times to clean the syringe.

The syringe and plunger must be completely dry before the next use.

Feeding tubes

Fintepla oral solution is compatible with most enteral feeding tubes.

To flush the feeding tube, fill the syringe used for dosing with water and flush the tube. Do this 3 times.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.,
Allée de la Recherche 60,
B-1070 Bruxelles,
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1491/001
EU/1/20/1491/002
EU/1/20/1491/003
EU/1/20/1491/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Ltd,
Millmount Site, Block 7,
City North Business Campus,
Stamullen,
Co. Meath,
K32 YD60
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of Fintepla in each Member State (MS), the marketing authorisation holder (MAH) must agree about the content and format of the educational materials (EM) and the controlled access programme (CAP) including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authorities (NCA).

The MAH shall ensure that, in each MS where Fintepla is marketed, a **CAP** is implemented to prevent off-label use for weight management in obese patients, since the benefit-risk ratio in this population is known to be negative.

In addition, the CAP shall be implemented to confirm that prescribing physicians have been informed of the need for periodic cardiac monitoring in patients taking Fintepla due to the important potential risk of valvular heart disease and important identified risk of pulmonary arterial hypertension.

The MAH shall ensure that in each MS where Fintepla is marketed, all healthcare professionals who are expected to prescribe the product are aware of the CAP and are provided with the educational package consisting of:

- Summary of product characteristics (SmPC)
- HCP guide

The educational material for healthcare professionals (**HCP guide**) shall address the following risks:

- Valvular heart disease (VHD)
- Pulmonary arterial hypertension (PAH)
- Off-label use for weight management

The HCP guide shall contain the following key messages:

- Brief information about the historical background on fenfluramine and its market withdrawal due to the risks of VHD and PAH.
- Emphasis that the currently approved indication has to be strictly adhered to and access is therefore controlled ensuring proper information of physicians before prescribing.
- Informing physicians about the conditions of the Fintepla Controlled Access Programme (that are agreed on national level).
- Instruction on detection, monitoring, and/or proper management of VHD and PAH associated with fenfluramine.
- Advice to encourage patients/carers to enrol patients in the fenfluramine registry to collect long-term safety data.

The educational material for patients and/or caregivers should address the following risks:

- Valvular heart disease (VHD)
- Pulmonary arterial hypertension (PAH)

The **patient/carer guide** shall contain the following key messages:

- Information about the importance of periodic cardiac monitoring (ECHOs)
- Education about the detection and proper management of VHD and PAH associated with fenfluramine.

- Encouragement to participate in the fenfluramine registry to collect long-term safety data.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
<p>Fintepla Registry on long-term safety The MAH shall perform an observational registry to provide data on long-term safety of fenfluramine in routine practice, with a focus on characterising and quantifying the important potential risk of VHD and important identified risk of PAH (primary objective), and growth retardation (secondary objective). In addition, data on the frequency of echocardiographic monitoring will contribute to assess the effectiveness of risk minimisation measures.</p>	<p>Final report: Q1 2034</p>

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

Fintepla 2.2 mg/ml oral solution
fenfluramine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2.2 mg fenfluramine (as hydrochloride).

3. LIST OF EXCIPIENTS

Excipients: E 215, E 219, Cherry flavouring (glucose, E 220).

4. PHARMACEUTICAL FORM AND CONTENTS

oral solution

Bottle of 60 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 120 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 250 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 360 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of first opening the bottle.

Date of first bottle opening __ / __ / ____

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1491/001 60 ml oral solution
EU/1/20/1491/002 120 ml oral solution
EU/1/20/1491/003 250 ml oral solution
EU/1/20/1491/004 360 ml oral solution

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fintepla

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle

1. NAME OF THE MEDICINAL PRODUCT

Fintepla 2.2 mg/ml oral solution
fenfluramine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2.2 mg fenfluramine (as hydrochloride).

3. LIST OF EXCIPIENTS

Excipients: E 215, E 219, Cherry flavouring (glucose, E 220).

4. PHARMACEUTICAL FORM AND CONTENTS

oral solution

Bottle of 60 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 120 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 250 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes
Bottle of 360 ml, bottle adaptor, two 3 ml oral syringes, and two 6 ml oral syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 3 months of first opening the bottle.

Date of first bottle opening __ / __ / ____

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1491/001 60 ml oral solution
EU/1/20/1491/002 120 ml oral solution
EU/1/20/1491/003 250 ml oral solution
EU/1/20/1491/004 360 ml oral solution

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fintepla

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Fintepla 2.2 mg/ml oral solution fenfluramine

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you or your child may experience. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child starts taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you or your child only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours or your child's.
- If you or your child experience any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fintepla is and what it is used for
2. What you need to know before you take Fintepla
3. How to take Fintepla
4. Possible side effects
5. How to store Fintepla
6. Contents of the pack and other information

1. What Fintepla is and what it is used for

Fintepla contains the active substance fenfluramine.

Fintepla is used to treat seizures (fits) in patients aged 2 years and over who have either a type of epilepsy called Dravet syndrome or one called Lennox-Gastaut syndrome. It can help to reduce the number and severity of seizures.

It is not completely known how Fintepla works. However, it is thought to work by increasing the activity in the brain of a natural substance called serotonin and the sigma 1 receptor, and this may reduce seizures.

2. What you need to know before you or your child takes Fintepla

Do not take Fintepla if:

- you or your child are allergic to fenfluramine or any of the other ingredients of this medicine (listed in section 6)
- you or your child have a heart problem such as 'valve disease' or 'pulmonary arterial hypertension' (high pressure in the arteries of the lungs)
- you or your child have taken medicines called monoamine oxidase inhibitors in the last 2 weeks.

Do not take Fintepla if any of the above apply to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking Fintepla.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Fintepla if:

- you or your child have glaucoma

- you or your child have had thoughts about harming or killing yourself
- you or your child are taking a medicine called cyproheptadine, which is used to treat allergies or to improve appetite.

If any of the above applies to you or your child (or you are not sure), talk to your doctor, pharmacist or nurse before taking Fintepla.

Tests and checks

Before you or your child start taking Fintepla your doctor must check the heart with an echocardiogram (ECHO). The doctor will check that the valves in the heart work properly and the pressure in the artery between the heart and lungs is not too high. Once you or your child has started taking Fintepla, you will have an echocardiogram check every 6 months for the first 2 years and then once a year. If Fintepla treatment is stopped, you or your child will need to have an echocardiogram 6 months after the last dose.

Your doctor should also check your weight before and during your treatment as Fintepla can cause you to lose weight.

‘Serotonin syndrome’

Tell your doctor or pharmacist before taking Fintepla if you or your child are taking medicines which can increase the levels of serotonin in your brain. This is because taking these medicines and Fintepla can cause serotonin syndrome, which is a life-threatening condition. Medicines that can increase serotonin levels include:

- ‘triptans’ (such as sumatriptan) – used for migraine
- MAOI medicines – used for depression
- SSRI or SNRI medicines – used for depression and anxiety.

Look out for the signs of serotonin syndrome which include:

- being agitated, seeing things which are not there (hallucinations) or passing out
- heart and circulation problems such as fast heartbeat, blood pressure going up and down, high body temperature, sweating
- twitching muscles and being uncoordinated
- feeling or being sick and diarrhoea.

Tell your doctor straight away if you notice any of the serious side effects above.

Other medicines and Fintepla

Tell your doctor or pharmacist if you or your child are taking, have recently taken, or might take any other medicines. This is because Fintepla can affect the way some other medicines work. Also, some other medicines can affect the way Fintepla works.

Fintepla can make you or your child feel sleepy. You or your child may be even more sleepy if you take other medicines such as anti-depressants or alcohol at the same time as Fintepla.

In particular, tell your doctor or pharmacist if you or your child are taking, have recently taken, or might take:

- stiripentol, a medicine for epilepsy, as your dose of Fintepla may need to be reduced
- ‘triptans’, MAOI, SNRI or SSRI medicines – see above under ‘Serotonin syndrome’
- carbamazepine, primidone, rifampicin, phenobarbital and other barbiturates, phenytoin, and efavirenz, as your dose of Fintepla may need to be increased.

Also speak with your doctor or pharmacist if you or your child smoke as the dose of Fintepla may need to be increased.

Pregnancy and breast-feeding

If you or your child are pregnant, think you or your child might be pregnant, or are planning to have a baby or are breast-feeding, ask your doctor for advice before taking this medicine.

Driving and using machines

Talk to your doctor about driving, using machines, or if you or your child undertake activities such as cycling or other sports, because you or your child may feel sleepy after taking this medicine.

Fintepla contains sodium ethyl p-hydroxybenzoate (E 215) and sodium methyl p-hydroxybenzoate (E 219)

This may cause allergic reactions (possibly delayed).

Fintepla contains sulfur dioxide (E 220)

This may rarely cause hypersensitivity reactions and bronchospasm.

Fintepla contains glucose

This may be harmful to the teeth.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Fintepla contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 12 ml, that is to say essentially 'sodium-free'.

3. How to take Fintepla

Always take this medicine exactly as your doctor, pharmacist or nurse has told you. Check with them if you are not sure.

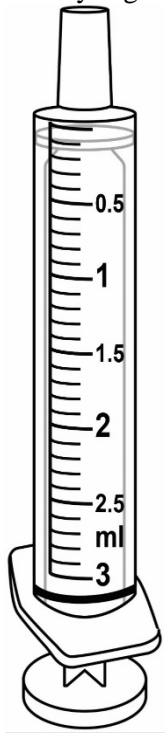
How much to take

- You will be told how many ml to take for each dose.
- Take the medicine twice a day.
- Your doctor will start you or your child on a low dose. This can then be gradually increased depending on how well the medicine works and how it affects you or your child.
- The maximum amount you can take is 6 ml twice a day.
- If you are taking stiripentol, the maximum amount you can take is 4 ml twice a day.
- Do not take more than the prescribed dose as it may cause serious side effects.

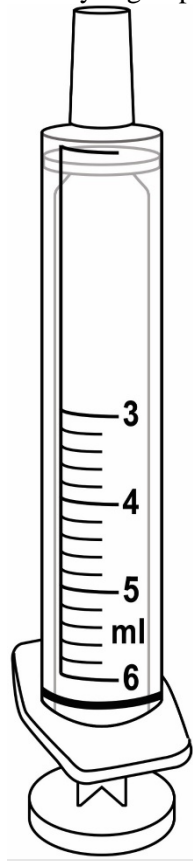
Taking this medicine

- Take this medicine by mouth.
- Take the medicine with food or between meals.
- Fintepla oral solution is compatible with a ketogenic diet.
- The medicine is a liquid. Use the oral syringes provided to measure your dose, as explained below.
- Use the green 3 ml syringe for doses up to 3.0 ml.
- Use the purple 6 ml syringe for doses between 3.2 ml and 6.0 ml.
- Fintepla oral solution is compatible with most enteral feeding tubes.
- To flush the feeding tube, fill the syringe used for dosing with water and flush the tube. Do this 3 times.

3 ml syringe - green



6 ml syringe - purple





Write on the carton the date you first opened the bottle.

You must attach the bottle adaptor the first time you open the bottle. The following instructions tell you how to attach the adaptor.

Inserting the bottle adaptor:

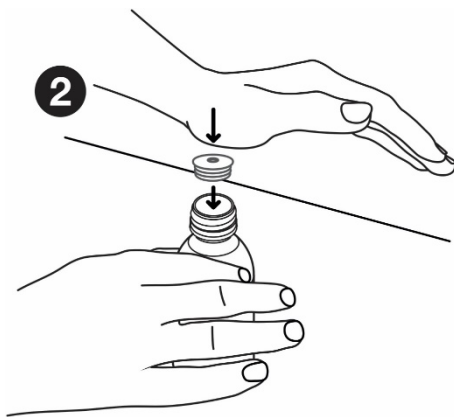
When the bottle is first opened the bottle adaptor must be pushed into the bottle.

Wash and dry your hands.

Remove the bottle adaptor from its packaging.

Place the bottle on a flat, firm surface.

Open the bottle.



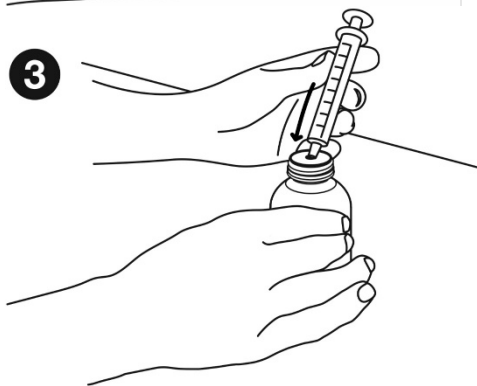
Hold the bottle firmly.

Line up the bottle adaptor with the open top of the bottle.

Push the bottle adaptor into the bottle with your palm until the adaptor is flush with the top of the bottle.

Leave in the bottle adaptor after using the medicine.

Screw the bottle cap onto the bottle with the bottle adaptor left in.

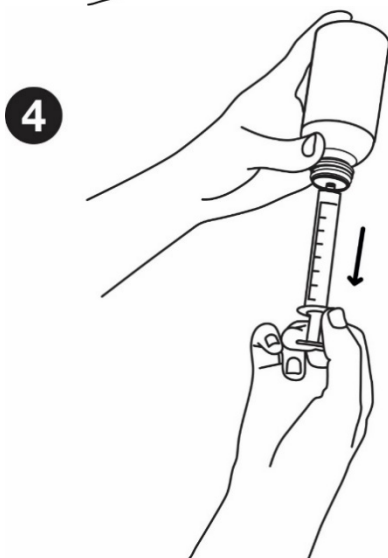


Taking the medicine:

Before you measure out the dose, make sure the plunger is pushed all the way into the oral syringe.

Hold the bottle of medicine firmly on a hard, flat surface.

Push the tip of the oral syringe into the bottle adaptor until it cannot be pushed further.



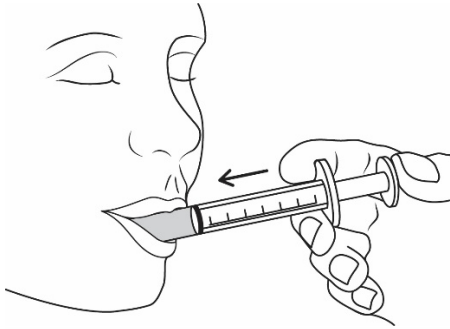
Hold the oral syringe and bottle together and turn upside down.

Slowly pull the plunger to draw up the right dose.

Hold the oral syringe and bottle together and then turn over.

Holding the bottle firmly, gently pull the oral syringe out of the bottle adaptor.

5

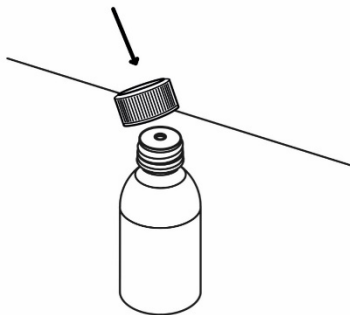


Place the tip of the oral syringe against the inside of the patient's cheek.

Gently push the plunger until it is fully pressed. There will be a small volume left in the tip of the syringe. This is normal.

Do not squirt the medicine into the back of the throat as this may cause choking.

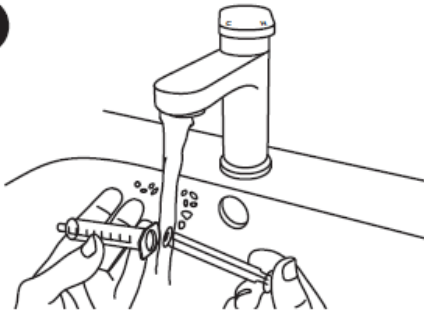
6



Place the cap back on the bottle and turn until it stops.

Always leave the adaptor in place in the bottle.

7



Cleaning the syringe:

Rinse the oral syringe with clean water and allow it to air dry after each use.

Rinse the inside of the syringe and the plunger.

Clean water can be pulled into the syringe with the plunger and pushed out several times to clean the syringe.

It is okay to separate the plunger from the syringe to rinse each part.

It is safe to clean the syringe and plunger in a dishwasher.

The syringe and plunger must be completely dry before the next use.

If you or your child take more Fintepla than you or your child should

Talk to a doctor or go to a hospital straight away. Take the medicine bottle with you. The following effects may happen: being agitated, sleepy or confused, being flushed or hot, shivering and sweating.

If you or your child forget to take Fintepla

- Take it as soon as you remember it. However, if it is nearly time to take the next dose, skip the missed dose.
- Do not take a double dose to make up for a forgotten dose.

If you or your child stop taking Fintepla

Do not stop taking Fintepla without talking to your doctor. If your doctor decides to stop this medicine, the doctor will ask you or your child to slowly lower the amount taken each day. Slowly lowering the dose will reduce the risk of having a seizure and status epilepticus.

Six months after the last dose of Fintepla, you or your child will need to have an echocardiogram.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Dravet Syndrome

Very common: may affect more than 1 in 10 people

- Upper respiratory tract infection
- decreased appetite
- somnolence
- diarrhoea
- high temperature
- feeling tired, sleepy or weak
- lower blood sugar
- abnormal echocardiogram

Common: may affect up to 1 in 10 people

- bronchitis
- abnormal behaviour
- rapid mood changes
- aggression
- agitation
- insomnia
- trembling of the hands, arms or legs
- having problem with coordination of movements, walking and balance
- decreased muscle tone
- seizures
- long-lasting seizures (status epilepticus)
- lethargy
- weight loss
- constipation
- salivary hypersecretion
- increased blood prolactin

Not known (frequency cannot be estimated from the available data):

- high blood pressure in the arteries of the lungs (pulmonary arterial hypertension)

Lennox-Gastaut Syndrome

Very common: may affect more than 1 in 10 people

- diarrhoea
- vomiting
- upper respiratory tract infection
- feeling tired, sleepy or weak
- somnolence
- loss of appetite

Common: may affect up to 1 in 10 people

- aggression
- constipation
- salivary hypersecretion
- bronchitis
- influenza
- pneumonia
- falling
- weight loss
- seizures

- long-lasting seizures (status epilepticus)
- lethargy
- trembling of the hands, arms or legs
- increased blood prolactin

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above.

Reporting of side effects

If you experience any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fintepla

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and bottle label after EXP. The expiry date refers to the last day of that month.
- Do not refrigerate or freeze.
- Use within 3 months of first opening the bottle.
- Wash the syringe after each use.
- If you lose or damage a syringe, or cannot read the dose markings on a syringe, use another oral syringe provided in your pack, or speak to your pharmacist.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Fintepla contains

The active substance is called fenfluramine. Each ml contains 2.2 mg of fenfluramine (as fenfluramine hydrochloride).

The other ingredients are:

- Sodium ethyl para-hydroxybenzoate (E 215)
- Sodium methyl para-hydroxybenzoate (E 219)
- Sucralose (E 955)
- Hydroxyethylcellulose (E 1525)
- Monosodium phosphate (E 339)
- Disodium phosphate (E 339)
- Cherry flavouring powder:
 - Acacia (E 414)
 - Glucose (maize)
 - Ethyl benzoate
 - Natural flavouring preparations
 - Natural flavouring substances
 - Flavouring substances
 - Maltodextrin (maize)
 - Sulphur dioxide (E 220)
- Potassium citrate (E 332)
- Citric acid monohydrate (E 330)
- Water for injections

What Fintepla looks like and contents of the pack

- Fintepla oral solution is supplied as a clear, colourless, cherry-flavoured slightly viscous liquid.

- The solution is available in a white bottle with a childresistant, tamperevident cap.
- Each carton contains either:
 - Bottle containing 60 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.
 - Bottle containing 120 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.
 - Bottle containing 250 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.
 - Bottle containing 360 ml oral solution, a bottle adaptor, two 3 ml oral syringes with 0.1 ml graduations, and two 6 ml syringes with 0.2 ml graduations.
- Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

UCB Pharma S.A.,
Allée de la Recherche 60,
B-1070 Bruxelles,
Belgium

Manufacturer:

Millmount Healthcare Ltd,
Millmount Site, Block 7,
City North Business Campus,
Stamullen,
Co. Meath,
K32 YD60
Ireland

For any information about this medicine, please contact the local representative of Marketing Authorisation Holder:

België/Belgique/Belgien

UCB Pharma S.A./NV
Tél/Tel: + 32 / (0)2 559 92 00

Lietuva

UAB Medfiles
Tel: +370 5 246 16 40

България

Ю СИ БИ България ЕООД
Тел.: + 359 (0) 2 962 30 49

Luxembourg/Luxemburg

UCB Pharma SA/NV
Tél/Tel: + 32 / (0)2 559 92 00 (Belgique/Belgien)

Česká republika

UCB s.r.o.
Tel: + 420 221 773 411

Magyarország

UCB Magyarország Kft.
Tel.: + 36-(1) 391 0060

Danmark

UCB Nordic A/S
Tlf: + 45 / 32 46 24 00

Malta

Pharmasud Ltd.
Tel: + 356 / 21 37 64 36

Deutschland

UCB Pharma GmbH
Tel: + 49 /(0) 2173 48 4848

Nederland

UCB Pharma B.V.
Tel.: + 31 / (0)76-573 11 40

Eesti

OÜ Medfiles
Tel: +372 730 5415

Norge

UCB Nordic A/S
Tlf: + 47 / 67 16 5880

Ελλάδα

UCB A.E.
Τηλ: + 30 / 2109974000

España

UCB Pharma, S.A.
Tel: + 34 / 91 570 34 44

France

UCB Pharma S.A.
Tél: + 33 / (0)1 47 29 44 35

Hrvatska

Medis Adria d.o.o.
Tel: +385 (0) 1 230 34 46

Ireland

UCB (Pharma) Ireland Ltd.
Tel: + 353 / (0)1-46 37 395

Ísland

Vistor hf.
Simi: + 354 535 7000

Italia

UCB Pharma S.p.A.
Tel: + 39 / 02 300 791

Κύπρος

Lifepharm (Z.A.M.) Ltd
Τηλ: + 357 22 056300

Latvija

Medfiles SIA
Tel: . +371 67 370 250

Österreich

UCB Pharma GmbH
Tel: + 43-(0)1 291 80 00

Polska

UCB Pharma Sp. z o.o. / VEDIM Sp. z o.o.
Tel: + 48 22 696 99 20

Portugal

UCB Pharma (Produtos Farmacêuticos), Lda
Tel: + 351 21 302 5300

România

UCB Pharma Romania S.R.L.
Tel: + 40 21 300 29 04

Slovenija

Medis, d.o.o.
Tel: + 386 1 589 69 00

Slovenská republika

UCB s.r.o., organizačná zložka
Tel: + 421 (0) 2 5920 2020

Suomi/Finland

UCB Pharma Oy Finland
Puh/Tel: + 358 9 2514 4221

Sverige

UCB Nordic A/S Tel: + 46 / (0) 40 294 900

United Kingdom (Northern Ireland)

UCB (Pharma) Ireland Ltd.
Tel : + 353 / (0)1-46 37 395

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for fenfluramine, the scientific conclusions of PRAC are as follows:

Given the known risk of VHD/PAH at higher doses of fenfluramine used in the past to treat adult obesity, the first probable case of pulmonary arterial hypertension in a child treated with lower doses of fenfluramine (10.12 mg/day) for Dravet syndrome (index case) is of particular importance. VHD/PAH represent very important potential risks of fenfluramine for the treatment of DS and LGS. Taking into account the serotonergic stimulation of cardiac valve tissue as a plausible mechanism of action and the known association between VHD/PAH and higher doses of fenfluramine used as an appetite suppressant, the PRAC considers that this single case warrants an update of the product information to provide clinicians with the most up-to-date evidence on this important risk. The product information of products containing fenfluramine should be amended accordingly.

In view of available data including 18 post-marketing reports of aggression/anger with a positive de-challenge and 19 post-marketing reports with a plausible onset latency a causal relation between fenfluramine and aggression is at least possible. Aggression was recently added to the ADR table for DS (variation EMEA/H/C/003933/II/018). The MAH proposes to add 'aggression' to the ADR table for LGS with the frequency unknown. However, as aggression was reported in 1.1 % in fenfluramine-treated participants in clinical trials, it should be assigned to the frequency category common.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for fenfluramine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing fenfluramine is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.