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 2.5 mg 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

Children aged 2 years and older and adults

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

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

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

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

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

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

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

Always round the calculated dose up or down to the nearest graduation mark, following standard rounding conventions. For example, for a patient that needs a dose of 2.15 ml, the applied volume needs to be rounded up to 2.2 ml as the 3 ml syringe can only deliver 2.1 ml or 2.2 ml. Likewise a volume of 1.13 ml would need to be rounded down to a delivered volume of 1.1 ml. For a patient that needs a dose of 3.15 ml, the applied volume needs to be rounded up to 3.2 ml as the 6 ml syringe can only deliver 3.0 ml or 3.2 ml. Likewise a volume of 4.25 ml would need to be rounded down to a delivered volume of 4.2 ml.

If the calculated dose is 3 ml or less, the green printed 3 ml syringe should be used (with 0.1 ml graduation marks).
If the calculated dose is more than 3 ml, the purple printed 6 ml syringe should be used (with 0.2 ml graduation marks).

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

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

<table>
<tr><td></td><td colspan="3">Dosing without concomitant STP*</td><td colspan="2">Dosing with concomitant STP**</td></tr>
<tr><td>Weight category</td><td>Starting dose</td><td>Day 7-13</td><td>Day 14 and further</td><td>Starting dose</td><td>Day 7 and further</td></tr>
<tr><td></td><td>0.1 mg/kg twice daily</td><td>0.2 mg/kg twice daily</td><td>0.35 mg/kg twice daily</td><td>0.1 mg/kg twice daily</td><td>0.2 mg/kg twice daily</td></tr>
<tr><td>3-5 kg</td><td>0.1-0.2 ml</td><td>0.3-0.5 ml</td><td>0.5-0.8 ml</td><td>0.1-0.2 ml</td><td>0.3-0.5 ml</td></tr>
</table>

5-7 kg	0.2-0.3 ml	0.5-0.6 ml	0.8-1.1 ml	0.2-0.3 ml	0.5-0.6 ml
7-10 kg	0.3-0.5 ml	0.6-0.9 ml	1.1-1.6 ml	0.3-0.5 ml	0.6-0.9 ml
10-15 kg	0.5-0.7 ml	0.9-1.4 ml	1.6-2.4 ml	0.5-0.7 ml	0.9-1.4 ml
15-20 kg	0.7-0.9 ml	1.4-1.8 ml	2.4-3.2 ml	0.7-0.9 ml	1.4-1.8 ml
20-30 kg	0.9-1.4 ml	1.8-2.7 ml	3.2-4.8 ml	0.9-1.4 ml	1.8-2.7 ml
30-38 kg	1.4-1.7 ml	2.7-3.4 ml	4.8-6 ml (maximum dose)	1.4-1.7 ml	2.7-3.4 ml
38-43 kg	1.7-2 ml	3.4-4 ml	6 ml (maximum dose)	1.7-2 ml	3.4-4 ml (maximum dose)
43-55 kg	2-2.5 ml	4-5 ml	6 ml (maximum dose)	2-2.5 ml	4 ml (maximum dose)
55-65 kg	2.5-3 ml	5-6 ml (maximum dose)	6 ml (maximum dose)	2.5-3 ml	4 ml (maximum dose)
65-86 kg	3-4 ml	6 ml (maximum dose)	6 ml (maximum dose)	3-4 ml (maximum dose)	4 ml (maximum dose)
86-130 kg	4-6 ml (maximum dose)	6 ml (maximum dose)	6 ml (maximum dose)	4 ml (maximum dose)	4 ml (maximum dose)

*Without concomitant STP: The maximum dose 13 mg twice daily corresponds to 6 ml twice daily.
**With concomitant STP: The maximum dose of 8.6 mg twice daily corresponds to 4 ml twice daily.

Discontinuation of treatment

When discontinuing treatment, the dose should be decreased gradually. 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

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.

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

Fenfluramine can cause valvular heart disease and pulmonary arterial hypertension in patients treated for Dravet syndrome or Lennox-Gastaut syndrome (see section 4.8). Therefore, echocardiographic monitoring must be performed.

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. 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 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.

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.

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 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 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 medicinal products, serotonin syndrome, a potentially life-threatening condition, may occur with fenfluramine treatment, particularly with concomitant use of other serotonergic medicinal products (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); with medicinal products 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 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular

aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If concomitant treatment with fenfluramine and other serotonergic medicinal products that may affect the serotonergic systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy with Fintepla and/or other serotonergic medicinal products should be considered.

Increased seizure frequency

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 medicinal products (including SSRIs, SNRIs, tricyclic antidepressants, or triptans); medicinal products 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 AUC_{0-24} and a 60% decrease in norfenfluramine AUC_{0-24}, 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. Coadministration 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
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.

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 Ndesmethyl-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 fenfluramine 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

The most commonly reported adverse reactions are decreased appetite (31.9%), fatigue (17.6%), diarrhoea (16.7%), and somnolence (15%).

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 (≥1/10), common (≥1/100 to <1/10) or not known (cannot be estimated from the available data).

Table 3: Adverse reactions

MedDRA System Organ Class	Very common	Common	Not known
Infections and infestations		Bronchitis	
Metabolism and nutrition disorders	Decreased appetite		
Psychiatric disorders		Abnormal behaviour Aggression Agitation Insomnia Mood swings	Irritability
Nervous system disorders	Somnolence	Ataxia Hypotonia Lethargy Seizure Status epilepticus Tremor	Serotonin syndrome
Cardiac disorders			Valvular heart disease
Respiratory, thoracic and mediastinal disorders			Pulmonary arterial hypertension
Gastrointestinal disorders	Diarrhoea	Constipation Salivary Hypersecretion Vomiting	

Skin and subcutaneous tissue disorders		Rash	
General disorders and administration site conditions	Fatigue		
Investigations		Weight decreased Blood glucose decreased Blood prolactin increased	

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 7.4% of fenfluramine-treated patients had a decrease in weight, compared to 0.8% of patients on placebo. In the controlled clinical trials of children and adults with Lennox-Gastaut syndrome, 28.8% of fenfluramine-treated patients had an adverse reaction of decreased appetite, compared to 15.3% of patients on placebo, and approximately 8.1% of fenfluramine-treated patients had a decrease in weight, compared to 3.1% 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 (Epilepsy, Seizure cluster, Change in seizure)
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 1.0% in the placebo group and 1.5% 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 (6.9%) than in patients on placebo (10.6%). However, seizures assessed as related to the study drug were more commonly reported in fenfluramine treated patients than placebo, 3.7% 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 (9.1%) and patients on placebo (9.2%). However, seizures assessed as related to the study drug were more commonly reported in fenfluramine treated patients than placebo, 6.1% of fenfluramine-treated patients compared to 1.0% of patients on placebo.

The mean days to onset of seizure events in the LGS phase 3 trial after starting treatment was 44.4 days in the combined fenfluramine groups and 36.6 days in the placebo group.

Echocardiographic safety assessments
Valvular heart disease and pulmonary arterial hypertension were evaluated via echocardiography in the clinical studies for Dravet syndrome and Lennox-Gastaut syndrome. No patient developed valvular heart disease or pulmonary arterial hypertension in the completed clinical studies for both indications. The percentage of trace and mild mitral regurgitation and trace aortic regurgitation from pooled double blinded DS and LGS clinical studies are shown below. These are defined as non-pathologic findings by the ESC/EACTS guidelines. Where trace mitral or aortic regurgitation were observed, the results were often transient.

- Trace of mitral regurgitation:
  - Combined fenfluramine group: 18.6% (77/414)
  - Placebo: 13.9% (32/230)
- Mild mitral regurgitation:
  - Combined fenfluramine group: 0.7% (3/414)
  - Placebo: 0% (0/230)
- Trace aortic regurgitation:
  - Combined fenfluramine group: 2.4% (10/414)
  - Placebo: 0.9% (2/230)

Nevertheless, pulmonary arterial hypertension and valvular heart disease associated with fenfluramine for Dravet syndrome and Lennox-Gastaut syndrome have been reported. Resolution of pulmonary arterial hypertension has been reported following discontinuation in at least one case (see section 4.4).

Lethargy, somnolence, and fatigue (grouping of fatigue/asthenia/malaise/decreased activity)
In the controlled trials in subjects with Dravet syndrome, lethargy was commonly reported in 9.7%, and somnolence and fatigue were very commonly reported in 13.9% and 19%, respectively in the fenfluramine treatment groups combined. In the controlled study with Lennox-Gastaut syndrome, lethargy was commonly reported in 4.5% of subjects in the fenfluramine treatment group. Fatigue and somnolence were very commonly reported in 16.2% and 16.2% of 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 reactions resolved or improved with ongoing treatment. In the controlled trials with Dravet syndrome, 0.5% and 1.4% of subjects in the fenfluramine treatment groups combined discontinued due to lethargy and somnolence, respectively. In the LGS study 4, 1.5% of 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 (13.1%) and vomiting (10.6%) were observed more frequently in the combined fenfluramine groups than in the placebo group (4.1% and 6.1%, respectively) during the 14-week titration and maintenance periods. In Study 4 the mean time to onset of diarrhoea in the combined fenfluramine groups was 25.4 days versus 46.0 days in the placebo group while the mean time to onset of vomiting in the combined fenfluramine groups was 36.7 days versus 38.2 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.

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-HT1D, 5-HT2A, and 5-HT2C 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 (≥25% overall) being valproate, clobazam, topiramate and levetiracetam.

Table 4. Dravet syndrome: Study 1 and Study 3 results of primary and selected secondary efficacy endpoints during maintenance period

	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 during Maintenance period						
CSF at Baseline, N, Median (per 28 days) (min, max)	40 31.4 (3.3, 147.3)	39 17.5 (4.8, 623.5)	40 21.2 (4.9, 127.0)	48 12.7 (4.0, 229.3)	46 18.0 (4.0, 1464.0)	48* 13.0 (2.7, 2700.7)
CSF at end of maintenance period. N, Median (min, max)	39 25.7 (3.6, 204.7)	39 17.1 (0.0, 194.3)	40 4.9 (0, 105.5)	48 10.6 (1.0, 139.0)	46 7.6 (0.0, 2006.8)	48 3.2 (0.0, 3651.7)
Reduction in mean monthly baseline-adjusted CSF 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 during Maintenance period						
Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline	4 (10.3%)	17 (43.6%) ES[1]=33.3% RR[2]: 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
Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline	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	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 during Titration + Maintenance period						
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

[1] Effect size (ES) (Risk difference) calculated as proportion of Active-Placebo; [2] RR: Relative Risk

*49 patients were enrolled and only 48 were administered with the treatment

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 14.0 in the placebo and fenfluramine 0.4 mg/kg/day groups, respectively.

Table 5. Dravet syndrome: Study 2 (previously known as Study ZX008-1504) results of primary and selected secondary efficacy endpoints during maintenance period

	Study 2	
	Placebo + stiripentol	**Fenfluramine 0.4 mg/kg/day + stiripentol**
Convulsive Seizure Frequency during Maintenance period		
N Baseline. **Median (min, max)**	44 10.7 (2.7, 162.7)	43 14.3 (2.7, 213.3)
N At end of maintenance period. **Median (min, max)**	44 11.4 (0.7, 169.3)	42 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 during Maintenance period		
Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline	4 (9.1%)	23 (54.8%) ES[1]=45.7 RR[2]: 6.02
Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline	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	0 (0%)	2 (4.8%) ES=4.8%
Longest seizure-free interval during Titration + maintenance period		
Longest seizure-free interval (median)	13.0 days	22.0 days p=0.004

[1] Effect size (ES) (Risk difference) calculated as proportion of Active-Placebo; [2] RR: Relative Risk

Adults
The Dravet syndrome population in Study 1, Study 2 and Study 3 was predominantly paediatric patients, with only 11 adult patients who were 18-19 years old (3.2%), 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, Study 2 and Study 3 could participate in an open-label extension study (Study 5). The primary objective of the open-label extension (OLE) study was long-term 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 374 patients who participated in the open-label study and received fenfluramine for up to 3 years (median treatment period: 824 days; range: 7-1280). A median percentage change from Baseline in convulsive seizure frequency (CSF) during the overall OLE Treatment Period of -66.81% (p <0.001) was observed. Of 375 study participants, 12.8% discontinued the study due to lack of efficacy, 2.9% due to adverse events, 5.3% due to physician or family request.

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). Part 1 includes 2 independently analyzed cohorts, Cohort A and Cohort B. Cohort A is the primary analysis cohort and includes subjects from North America, Europe, and Australia, and Cohort B includes subjects from Japan.

Study 4 Part 1 Cohort A
Study 4 Part 1 Cohort A 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) of fenfluramine with placebo (N=87). 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 ≥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 6. Lennox-Gastaut syndrome: Study 4 Part 1 Cohort A of primary and selected secondary efficacy endpoints during maintenance period

	Study 4 Part 1 Cohort A	
	Placebo (N = 87)	**Fenfluramine 0.7 mg/kg/day (N = 87)**
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
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
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
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

a BL, T+M, and percentage change from BL in M values for seizure frequency per 28 days are presented in original scale.

b 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

c 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.

d Minimally, much, or very much improved

e 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]).

Study 4 Part 1 Cohort B

This study compared a 0.7 mg/kg/day (N=11) and a 0.2 mg/kg/day (N=11) dose (up to a maximum dose per day of 26 mg) of fenfluramine with placebo (N=11).
The primary study endpoint was assessed from Part 1 Cohort A data only, due to the small size of Cohort B.

The results from Cohort B support the clinical benefit of fenfluramine reported for Cohort A for the adjunctive treatment of drop seizures associated with LGS in Japanese subjects.

Table 7: Lennox-Gastaut syndrome: Study 4 Part 1 Cohort B of primary and selected secondary efficacy endpoints during maintenance period

	Study 4 Part 1 Cohort B	
	Placebo (N = 11)	**Fenfluramine 0.7 mg/kg/day (N = 11)**
Primary Endpoint: Percentage Change from BL in DSF During M		
DSF Summary Statistics [a]		
Median at BL	53.00	58.00
Median during M	51.90	31.86
Median Percentage Change from BL During M	-18.18	-45.07
HL Estimate for Median Difference (A-P)		
Estimate (Std Err)		-25.54 (17.000)
95% CI		(-57.57, 9.07)
Key Secondary Endpoint: Percentage of Patients with ≥ 50% Reduction from BL in DSF (50% Responder Rate) During M		
≥ 50% reduction in DSF, n (%)	1 (9.1%)	4 (36.4%)

ANCOVA = analysis of covariance; A-P = active group–placebo group; BL = Baseline Period; CI = confidence interval; DSF = drop seizure frequency per 28 days; HL = Hodges-Lehmann; Std Err = standard error; M = Maintenance Period

a BL, M, and percentage change from BL in M values for seizure frequency per 28 days are presented in original scale.

Open-label data

Lennox-Gastaut patients who completed Study 4 Part 1 (ZX008-1601) 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. 279 patients were enrolled in the open label extension study received fenfluramine 0.2 mg/kg/day for 1 month, then the dose was titrated to optimize treatment. The safety data from open-label phase of Study 4 are consistent with known safety profile of fenfluramine.

Among the 177 LGS subjects treated with fenfluramine for ≥12 months, 24.3% received a fenfluramine mean daily dose of >0 to <0.4 mg/kg/day, 45.2% had received a fenfluramine mean daily dose of 0.4 to <0.6 mg/kg/day and 30.5% received a fenfluramine mean daily dose ≥0.6 mg/kg/day.

The most common reason for discontinuation during the open label extension study was lack of efficacy (58 [20.8%]), adverse event (15 [5.4%]), and withdrawal by subject (17 [6.1%]).

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 fenfluramine 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/1.73 m^2) 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 ≤ 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 fenfluramine.

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 fenfluramine.

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 fenfluramine.

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 F_0 and F_1 generations were confirmed at five-fold higher plasma exposures (AUC) than in humans at the maximum recommended therapeutic dose of fenfluramine. 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 fenfluramine.

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. Do not use detergent to clean the syringe and plunger.
Rinse the oral syringe with cold water and allow it to air dry after each use.
Rinse the inside of the syringe and the plunger.
Do not clean the syringe and plunger in a dishwasher.
Cold 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
Date of latest renewal: 17 November 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

Or

UCB Pharma SA
Chemin du Foriest
1420 Braine-l'Alleud
Belgium

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.

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 identified risks of valvular heart disease and 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.
- Cases of VHD and PAH have been identified from post-marketing experience with doses used to treat Dravet syndrome and Lennox-Gastaut syndrome.
- 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 identified 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**
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 identified risks of VHD and 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.	Final report: Q1 2034

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER 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 2.5 mg fenfluramine 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 2.5 mg fenfluramine 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

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

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

Fintepla contains the active substance fenfluramine.

Fintepla is used as adjunctive therapy 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 used for the treatment of depression called monoamine oxidase inhibitors in the last 2 weeks.

Do not take Fintepla if any of the above applies 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.
- you or your child have experienced an increase in frequency of seizures.
- you or your child have experienced more sleepiness.

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 3-6 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 or decrease your appetite.

'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.
- clobazam, valproate and cannabidiol, which are medicines used to treat epilepsy.

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 or tired 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.

Your doctor, pharmacist or nurse will calculate the dose volume up to the maximal recommended dose, using the formula:

Weight (kg) x Weight-based dosage (mg/kg) ÷ 2.2 mg/ml = ml dose to be taken **twice daily**
Always round the calculated dose up or down to the nearest graduation mark, following standard rounding conventions. For example, for a patient that needs a dose of 2.15 ml, the applied volume needs to be rounded up to 2.2 ml as the 3 ml syringe can only deliver 2.1 ml or 2.2 ml. Likewise a volume of 1.13 ml would need to be rounded down to a delivered volume of 1.1 ml. For a patient that needs a dose of 3.15 ml, the applied volume needs to be rounded up to 3.2 ml as the 6 ml syringe can only deliver 3.0 ml or 3.2 ml. Likewise a volume of 4.25 ml would need to be rounded down to a delivered volume of 4.2 ml.

The table below must only be used as a check on the calculated dose volume. Table 1 does **not replace** the requirement to calculate the specific dose volume.

Table 1: Range of dose volumes in ml for calculation check

	Dosing without concomitant STP*			**Dosing with concomitant STP****	
Weight category	**Starting dose**	**Day 7-13**	**Day 14 and further**	**Starting dose**	**Day 7 and further**
	0.1 mg/kg twice daily	0.2 mg/kg twice daily	0.35 mg/kg twice daily	0.1 mg/kg twice daily	0.2 mg/kg twice daily

3-5 kg	0.1-0.2 ml	0.3-0.5 ml	0.5-0.8 ml	0.1-0.2 ml	0.3-0.5 ml
5-7 kg	0.2-0.3 ml	0.5-0.6 ml	0.8-1.1 ml	0.2-0.3 ml	0.5-0.6 ml
7-10 kg	0.3-0.5 ml	0.6-0.9 ml	1.1-1.6 ml	0.3-0.5 ml	0.6-0.9 ml
10-15 kg	0.5-0.7 ml	0.9-1.4 ml	1.6-2.4 ml	0.5-0.7 ml	0.9-1.4 ml
15-20 kg	0.7-0.9 ml	1.4-1.8 ml	2.4-3.2 ml	0.7-0.9 ml	1.4-1.8 ml
20-30 kg	0.9-1.4 ml	1.8-2.7 ml	3.2-4.8 ml	0.9-1.4 ml	1.8-2.7 ml
30-38 kg	1.4-1.7 ml	2.7-3.4 ml	4.8-6 ml (maximum dose)	1.4-1.7 ml	2.7-3.4 ml
38-43 kg	1.7-2 ml	3.4-4 ml	6 ml (maximum dose)	1.7-2 ml	3.4-4 ml (maximum dose)
43-55 kg	2-2.5 ml	4-5 ml	6 ml (maximum dose)	2-2.5 ml	4 ml (maximum dose)
55-65 kg	2.5-3 ml	5-6 ml (maximum dose)	6 ml (maximum dose)	2.5-3 ml	4 ml (maximum dose)
65-86 kg	3-4 ml	6 ml (maximum dose)	6 ml (maximum dose)	3-4 ml (maximum dose)	4 ml (maximum dose)
86-130 kg	4-6 ml (maximum dose)	6 ml (maximum dose)	6 ml (maximum dose)	4 ml (maximum dose)	4 ml (maximum dose)

*Without concomitant STP: The maximum dose 13 mg twice daily corresponds to 6 ml twice daily.
**With concomitant STP: The maximum dose of 8.6 mg twice daily corresponds to 4 ml twice daily.

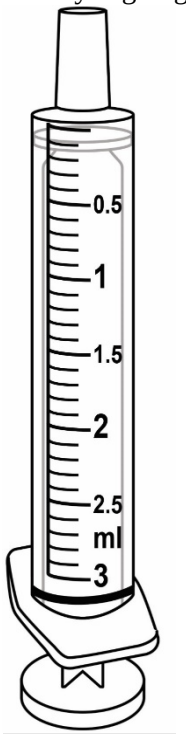
How much to take

- 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.

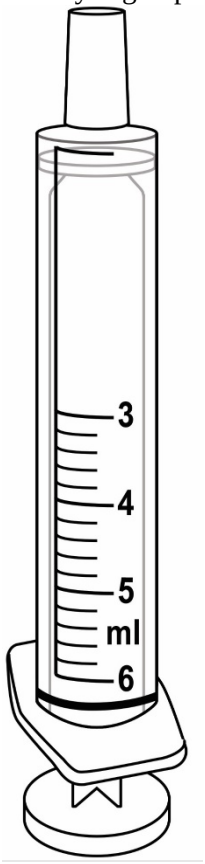
Taking this medicine

- 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 ml.
- Use the purple 6 ml syringe for doses between 3.2 ml and 6 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.

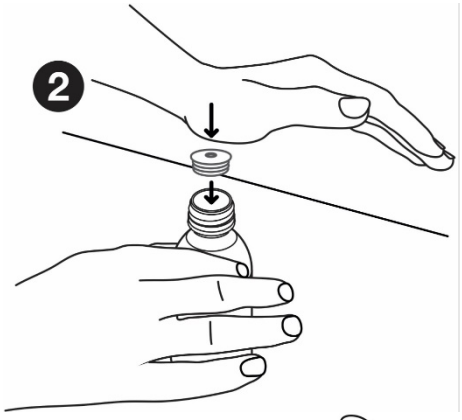
3 ml syringe - green



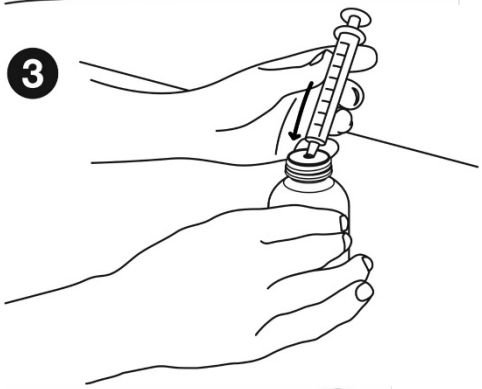
6 ml syringe - purple



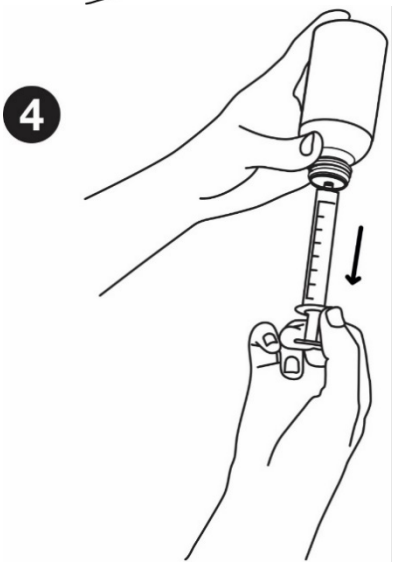
Write on the carton the date you first opened the bottle.
You must attach the bottle adaptor the first time you open the bottle. The following instructions tell you how to attach the adaptor.
Inserting the bottle adaptor:
When the bottle is first opened the bottle adaptor must be pushed into the bottle.
Wash and dry your hands.
Remove the bottle adaptor from its packaging.
Place the bottle on a flat, firm surface.
Open the bottle.



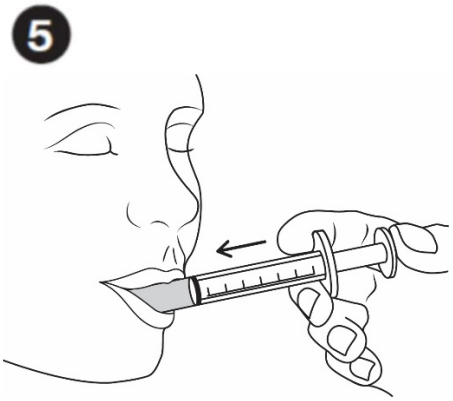
Hold the bottle firmly.
Line up the bottle adapter with the open top of the bottle.
Push the bottle adaptor into the bottle with your palm until the adaptor is flush with the top of the bottle.
Leave in the bottle adaptor after using the medicine.
Screw the bottle cap onto the bottle with the bottle adaptor left in.



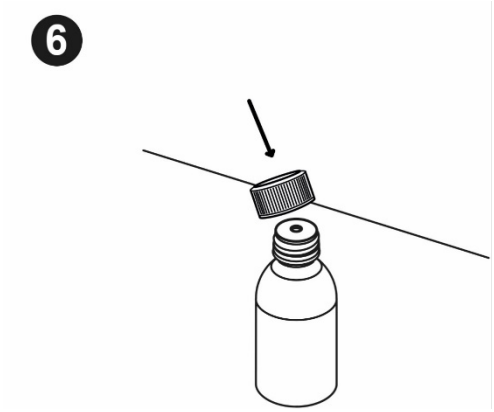
Taking the medicine:
Before you measure out the dose, make sure the plunger is pushed all the way into the oral syringe.
Hold the bottle of medicine firmly on a hard, flat surface.
Push the tip of the oral syringe into the bottle adaptor until it cannot be pushed further.



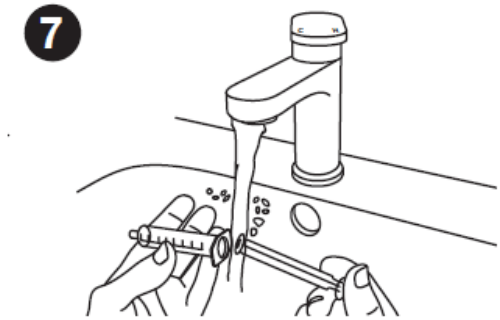
Hold the oral syringe and bottle together and turn upside down.
Slowly pull the plunger to draw up the right dose.
Hold the oral syringe and bottle together and then turn over.
Holding the bottle firmly, gently pull the oral syringe out of the bottle adaptor.



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.



Place the cap back on the bottle and turn until it stops.
Always leave the adaptor in place in the bottle.



Cleaning the syringe:
Rinse the oral syringe with cold water and allow it to air dry after each use.
Rinse the inside of the syringe and the plunger.
Cold 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. Do not use detergent to clean the syringe and plunger.
Do not 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.
Three to 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.

Very common: may affect more than 1 in 10 people
- decreased appetite
- sleepiness
- diarrhoea
- tiredness

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
- increased production of saliva
- vomiting
- rash
- lower blood sugar
- increased blood prolactin

Not known (frequency cannot be estimated from the available data):
- irritability
- serotonin syndrome
- high blood pressure in the arteries of the lungs (pulmonary arterial hypertension)
- heart valve disease

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.

- 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 2.5 mg 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
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

Or

UCB Pharma SA
Chemin du Foriest
1420 Braine-l'Alleud
Belgium

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

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

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

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

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

Eesti
OÜ Medfiles
Tel: +372 730 5415

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

Lietuva
UAB Medfiles
Tel: +370 5 246 16 40

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

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

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

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

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

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

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

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

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

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

Latvija
Medfiles SIA
Tel: . +371 67 370 250

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

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://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:

New definite cases of valvular heart disease (VHD) and pulmonary arterial hypertension (PAH) were identified in the post-marketing setting, which are possibly related to fenfluramine used to treat DS and LGS. VHD and PAH represent important 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, the known association between VHD/PAH and higher doses of fenfluramine used as an appetite suppressant and a first definite case of valvular heart disease in a child treated with lower doses of fenfluramine (6.6 mg/day) for DS identified in the last PSUR, the PRAC considers that the identification of further definite cases of VHD as well as PAH, which are possibly related to fenfluramine, warrants an update of the product information to provide clinicians with the most up-to-date evidence on this important risk.

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.