1. NAME OF THE MEDICINAL PRODUCT

Fintepla

Patient and patient's parent safety information guide
The marketing of Fintepla is subject to a Risk management plan (RMP) including a "patient and patient's parent safety information guide". The "patient and patient's safety information guide", emphasizes important safety information that the patient or his parent should be aware of before and during the treatment. Please explain to the patient or his parent the need to review the guide before starting treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

Glucose (maize): 0.627 mg/mL
Sodium ethyl para-hydroxybenzoate (E 215): 0.23 mg/mL
Sodium methyl para-hydroxybenzoate (E 219): 2.3 mg/mL
Sulfur dioxide (E 220): 0.000009 mg/mL

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.
Fintepla is not indicated for the treatment of obesity

4.2 Posology and method of administration

Fintepla should be initiated by a neurologist with experience treating epilepsy and overseen by a clinician with experience treating epilepsy.

Posology

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

Table 1: Dosage recommendations for Dravet Syndrome

	without stiripentol	**with** stiripentol
Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)	
Day 7 - second week*	0.2 mg/kg twice daily (0.4 mg/kg/day)	Maintenance dose 0.2 mg/kg twice daily (0.4 mg/kg/day)
Day 14 - Further titration as applicable*	0.35 mg/kg twice daily (0.7 mg/kg/day)	Not applicable
Maximal recommended dose	26 mg (13 mg twice daily i.e. 6.0 mL twice daily)	17 mg (8.6 mg twice daily i.e. 4.0 mL twice daily)

* For patients who are tolerating fenfluramine and require a further reduction of seizures. For patients requiring more rapid titration, the dose may be increased every 4 days.

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

Table 2. Dosage recommendations for Lennox-Gastaut Syndrome

Starting dose – first week	0.1 mg/kg taken twice daily (0.2 mg/kg/day)
Day 7 - second week**	0.2 mg/kg twice daily (0.4 mg/kg/day)
Day 14 - maintenance dose**	0.35 mg/kg twice daily (0.7 mg/kg/day)
Maximal recommended dose	26 mg (13 mg twice daily i.e. 6.0 mL twice daily)

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

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

Discontinuation of treatment

When discontinuing treatment, the dose should be decreased gradually. As with all anti-epileptic medicines, abrupt discontinuation should be avoided when possible to minimize the risk of increased seizure frequency and status epilepticus.

Special populations

Patients with renal impairment
There are no clinical data available in subjects with renal impairment.

Patients with hepatic impairment
There are no clinical data available in subjects with hepatic impairment.

Administration to patients with moderate or severe liver impairment is not recommended.

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

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

Method of administration

Fintepla is to be administered orally.
Fintepla may be taken with or without food.
Fintepla is compatible with commercially available gastric and nasogastric feeding tubes (see section 6.6).
Fintepla contains a very limited amount of digestible carbohydrates and is compatible with a ketogenic diet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Aortic or mitral valvular heart disease.
Pulmonary arterial hypertension.
Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome.

4.4 Special warnings and precautions for use

Aortic or mitral valvular heart disease and pulmonary arterial hypertension

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

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

Echocardiogram monitoring should be conducted every 6 months for the first 2 years and annually thereafter. If an echocardiogram indicates pathological valvular changes, a follow-up echocardiogram should be considered at an earlier timeframe to evaluate whether the abnormality is persistent. If pathological abnormalities on the echocardiogram are observed, it is recommended to evaluate the benefit versus risk of continuing fenfluramine treatment with the prescriber, caregiver, and cardiologist.

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

With past use in higher doses to treat adult obesity, fenfluramine was reported to be associated with pulmonary arterial hypertension. Pulmonary arterial hypertension was not observed in the clinical programme, but because of the low incidence of this disease, the clinical trial experience with fenfluramine is inadequate to determine if fenfluramine increases the risk for pulmonary arterial hypertension in patients with Dravet syndrome and Lennox-Gastaut syndrome.

If echocardiogram findings are suggestive of pulmonary arterial hypertension, a repeat echocardiogram should be performed as soon as possible and within 3 months to confirm these findings. If the echocardiogram finding is confirmed suggestive of an increased probability of pulmonary arterial hypertension defined as “intermediate probability” by the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines, it should lead to a benefit-risk evaluation of continuation of Fintepla by the prescriber, carer, and cardiologist. If the echocardiogram finding, after confirmation, suggests of a high probability of pulmonary arterial hypertension, as defined by the 2015 ESC and ERS Guidelines, it is recommended fenfluramine treatment should be stopped.

Decreased appetite and weight loss

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

Fintepla Risk Management Plan

A risk management plan has been created to 1) prevent off-label use in weight management inobese patients and 2) confirm that prescribing physicians have been informed of the need for periodiccardiac monitoring in patients taking Fintepla.

Somnolence

Fenfluramine can cause somnolence.

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

Suicidal behaviour and ideation

Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials with anti-epileptic medicines that did not include fenfluramine has shown a small increased risk of suicidal behaviour and ideation. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for fenfluramine. Patients and caregivers of patients should be advised to seek medical advice should any signs of suicidal behaviour and ideation emerge.

Serotonin syndrome

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

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

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

Increased seizure frequency

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

Cyproheptadine

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

Glaucoma

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

Effect of CYP1A2 and CYP2B6 inducers Co-administration with strong CYP1A2 inducers or CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of fenfluramine (see section 4.5). If coadministration 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 AUC0-t of fenfluramine by a ratio of 2.1-fold and the Cmax by a ratio of 1.2-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.3-fold and the Cmax 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 AUC0-t of fenfluramine by a ratio of 1.8-fold and the Cmax by a ratio of 1.1-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.2-fold and the Cmax 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

Pharmacodyamic interactions

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

Pharmacokinetic interactions

Clinical studies

Effect of steady state stiripentol plus clobazam and/or valproate on fenfluramine
At steady state in the Phase 3 studies, the co-administration of 0.2 mg/kg twice daily (0.4 mg/kg/day), maximum 17 mg/day, fenfluramine with a standard anti-epileptic medicine regimen of stiripentol plus clobazam and/or valproate, resulted in a 130% increase in fenfluramine 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 0.354 mg/kg dose of Finteplafenfluramine with rifampicin at steady state (600 mg once daily) in healthy volunteers decreased the AUC0--t of fenfluramine by 58% and the Cmax by 40%, and decreased the AUC0-t of norfenfluramine by 50%, and increased the Cmax of norfenfluramine by 13%, as compared to fenfluramine Fintepla administered alone. An increase in fenfluramine Fintepla 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 AUC0-t of fenfluramine by a ratio of 2.1-fold and the Cmax by a ratio of 1.2-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.3-fold and the Cmax 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 AUC0-t of fenfluramine by a ratio of 1.8-fold and the Cmax by a ratio of 1.1-fold, and decreased the AUC0-t of norfenfluramine by a ratio of 1.2-fold and the Cmax 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 Fintepla may possibly affect female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile for Dravet Syndrome

The most commonly reported adverse reactions are decreased appetite (44.2%), diarrhoea (30.8%), pyrexia (25.6%), fatigue (25.6%), upper respiratory tract infection (20.5%), lethargy (17.5%), somnolence (15.4%), and bronchitis (11.6%).

Summary of the safety profile for Lennox-Gastaut Syndrome

The most commonly reported adverse reactions are decreased appetite (35.6%), fatigue (18.4%), somnolence (17.2%), vomiting (13.5%) and diarrhoea (12.6%).

Tabulated list of adverse reactions

Adverse reactions reported with fenfluramine in placebo-controlled clinical studies are listed in the table below by System Organ Class and frequency. Frequencies are defined as very common (≥1/10) or common (≥1/100 to <1/10).

Table 3: Adverse reactions for Dravet Syndrome

MedDRA System Organ Class	**Very common**	**Common**
Infections and infestations	Bronchitis Upper respiratory tract infection	Ear infection
Metabolism and nutrition disorders	Decreased appetite	
Psychiatric disorders		Abnormal behaviour Irritability
Nervous system disorders	Lethargy Somnolence Status epilepticus Tremor	
Gastrointestinal disorders	Constipation Diarrhoea Vomiting	
General disorders and administration site conditions	Pyrexia Fatigue	
Investigations	Blood glucose decreased Echocardiogram abnormal (trace regurgitation) Weight decreased	
Injury, poisoning, and procedural complications	Fall	

Table 4: Adverse reactions for Lennox-Gastaut Syndrome

MedDRA System Organ Class	**Very common**	**Common**
Infections and infestations	Upper respiratory tract infection	Bronchitis Influenza

		Otitis media Pneumonia
Metabolism and nutrition disorders	Decreased appetite	
Nervous system disorders	Somnolence	Seizure Status epilepticus Lethargy Tremor
Gastrointestinal disorders	Diarrhoea Vomiting	Constipation Salivary hypersecretion
General disorders and administrative site conditions	Fatigue	
Investigations		Blood prolactin increased Weight decreased
Injury, poisoning and procedural complications		Fall

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 34.4% of fenfluramine-treated patients had an adverse reaction of decreased appetite,compared to 8.3% of patients on placebo and approximately 18.9% of fenfluramine-treated patients had a decrease in weight ≥7% from their baseline weight, compared to 2.4% of patients on placebo. In the controlled clinical trials of children and adults with Lennox-Gastaut syndrome, 35.6% of fenfluramine-treated patients had an adverse reaction of decreased appetite, compared to 10.3% of patients on placebo, and approximately 8.0% of fenfluramine-treated patients had a decrease in weight of ≥7% from their baseline weight, compared to 0% of patients on placebo. The decreases in appetite and weight appeared to be dose related. Most subjects resumed weight gainover time while continuing fenfluramine treatment.

Status epilepticus and seizures

In the Dravet syndrome phase 3 clinical trials, the observed frequency of status epilepticus was 2.4% in the placebo group and 6.6% in the combined fenfluramine group. In the LGS phase 3 clinical trial, the observed frequency of status epilepticus was 1.1% in the placebo group and 3.4% 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, adverse reactions of seizures were reported more frequently in fenfluramine-treated patients compared to placebo with 4.1% in fenfluramine-treated patients compared to 2.3% of patients on placebo. In the LGS trial, seizures were reported with a similar frequency in the fenfluramine treated patients (6.8%) and patients on placebo (6.9%). However, seizures assessed as related to the study drug were more commonly reported in fenfluramine treated patients than placebo, 6.3% of fenfluramine-treated patients compared to 1.1% of patients on placebo.

The mean days to onset of seizure events in the LGS phase 3 trial after starting treatment was 26.3 days in the fenfluramine 0.2 mg/kg/day group, 31.3 days in the fenfluramine 0.8 mg/kg/day and 31.3 days in the placebo group.

Echocardiographic safety assessments of valvular regurgitation

Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo-controlled and open-label extension studies via echocardiography for 341 Dravet syndrome patients and 263 Lennox-Gastaut syndrome patients. No patient developed valvular heart disease or pulmonary arterial hypertension in the placebo-controlled studies or during the open-label extension studies with exposure of up to 3 years. In the Dravet syndrome double-blind studies, trace mitral valve regurgitation was reported in 17.9% of patients in the fenfluramine 0.2 mg/kg/day group (n=7/39), 23.3% in the fenfluramine 0.4 mg/kg/day group (n=10/43), 22.5% in the fenfluramine 0.7 mg/kg/day group (n=9/40), and in 9.5% in the placebo group (n=8/84). Mild mitral valve regurgitation was reported in 2.3% of patients in the fenfluramine 0.4 mg/kg/day group (n=1/43). Trace aortic valve regurgitation was reported in 7.9% of patients in the fenfluramine 0.7 mg/kg/day group (n=3/40). In the Lennox-Gastaut syndrome double-blind study, trace mitral valve regurgitation was reported in 14.8% of patients in the fenfluramine 0.2 mg/kg/day group (n=13/89), 17.6% in the fenfluramine 0.7 mg/kg/day group (n=15/87), (and 22.1% in the placebo group (n=19/87). Mild mitral valve regurgitation was reported in 1.1% of patients in the fenfluramine 0.7 mg/kg/day group (n=1/87). Trace aortic valve regurgitation was reported in 5.6% of patients in the fenfluramine 0.2 mg/kg/day group (n=5/89) and 2.3% in the placebo group (n=2/87). One 11-year-old patient in the fenfluramine 0.2 mg/kg/day group exhibited mild aortic valve regurgitation. No abnormalities in valve morphology were observed, and upon a diagnostic evaluation via transoesophageal echocardiogram, the finding was downgraded to absent. Trace and mild mitral regurgitation and trace aortic regurgitation are all non-pathologic findings as defined by the 2015 ESC and ERS Guidelines. Where trace mitral or aortic regurgitation were observed, the results were often transient.

Lethargy, somnolence, and fatigue

In the controlled trials in subjects with Dravet syndrome, lethargy, somnolence and fatigue/asthenia were very commonly reported in 13.9%, 10.7% and 15.6%, respectively in the fenfluramine treatment groups combined. In the controlled study with Lennox-Gastaut syndrome, lethargy was commonly reported in 4% of subjects. Fatigue/asthenia and somnolence were very commonly reported in 18.8% and 13.6% subjects, respectively. The majority of the adverse reactions of lethargy, somnolence, and fatigue/asthenia were reported in the first 2 weeks of treatment with fenfluramine and were mild or moderate in severity. Discontinuation due to lethargy, somnolence, and fatigue/asthenia was rare and, in most cases, these adverse events resolved or improved with ongoing treatment. In the controlled trials with Dravet syndrome, 0.8% and 1.6%nsubjects in the fenfluramine treatment groups combined discontinued due to lethargy and somnolence, respectively. In the LGS study, 1.7% subjects in the fenfluramine treatment group discontinued due to somnolence.

Gastrointestinal disorders

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

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

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

Infections and infestations disorders

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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 functionsshould 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 two randomised, multicentre, placebo-controlled studies.

Study 1 (N=119) was a 3-arm, multicentre, randomised, double-blind, parallel group, placebo-controlled study 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. 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 in Study 1 was 9.0 (4.7) years, with a range of 2 to 18 years. The majority of patients were ≥6 years of age (73.9%) and the minority <6 years (26.1%), male (53.8%), and white (82.4%). All enrolled patients were inadequately controlled on at least one anti-epileptic medicine, with or without vagal nerve stimulation and/or ketogenic diet. Patients were taking between one and five anti-epileptic medicines at study entry. The most frequently used concomitant anti-epileptic medicines (≥25% overall) were valproate (59.6%), clobazam (58.8%), and topiramate (25.2%). In Study 1, the median baseline convulsive seizure frequency per 28 days was 34.0, 17.5, and 21.2 in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively.

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

Table 5: Dravet syndrome: Study 1 and Study 2 (previously known as 1504): results of primary and selectedsecondary efficacy endpoints

		Study 1			**Study 2**	
		Placebo	**Fenfluramine 0.2 mg/kg/day**	**Fenfluramine 0.7 mg/kg/day**	**Placebo + stiripentol**	**Fenfluramine 0.4 mg/kg/day + stiripentol**
Convulsive Seizure Frequency	N Baseline. Median (min, max)	39 34.0 (3.3, 147.3)	39 17.5 (4.8, 623.5)	40 21.2 (4.9, 127.0)	44 10.7 (2.7, 162.7)	43 14.3 (2.7, 213.3)
Maintenance period	N At end of maintenance period. Median (min, max)	39 25.7 (3.6, 204.7)	39 17.1 (0.0, 194.3)	40 4.9 (0, 105.5)	44 11.4 (0.7, 169.3)	42 3.9 (0.0, 518.0)
	Reduction in mean monthly baseline-adjusted	-	36.7% p=0.016	67.3% p<0.001	-	54.9 % p<0.001

	Convulsive Seizure Frequency compared to					

		Study 1			Study 2	
		Placebo	**Fenfluramine 0.2 mg/kg/day**	**Fenfluramine 0.7 mg/kg/day**	**Placebo + stiripentol**	**Fenfluramine 0.4 mg/kg/day + stiripentol**
	Placebo					
% reduction in convulsive seizures **Maintenance period**	Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline Effect size[1] Relative Risk	4 (10.3%)	17 (43.6%) ES=33.3% RR: 4.25	29 (72.5%) ES=62.2% RR: 7.07	4 (9.1%)	23 (54.8%) ES=45.7 RR: 6.02
	Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline Effect size[1] Relative Risk	2 (5.1%)	10 (25.6%) ES=20.5% RR: 5.00	21 (52.5%) ES=47.4% RR: 10.24	2 (4.5%)	17 (40.5%) ES=36.0% RR: 8.90
	Number (%) of patients with ≥100% reduction in monthly convulsive seizures - change from baseline Effect size[1]	0 (0%)	6 (15.4%) ES=15.4%	6 (15.0%) ES=15.0%	0 (0%)	2 (4.8%) ES=4.8%
Longest seizure-free interval (median) **Titration + maintenance period**		9.5 days	15.0 days p=0.035	25.0 days p<0.001	13.0 days	22.0 days p=0.004

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

Adults

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

Open-label data

Dravet syndrome patients who participated in Study 1 and Study 2 could participate in an open-label extension study (Study 3). The primary objective of the open-label study was long-term effectiveness and safety of fenfluramine at doses of 0.2 to 0.7 mg/kg/day, whereby the dose of fenfluramine could

be titrated to optimize treatment. Data are reported for 330 patients who participated in the open-label study and received fenfluramine for up to 3 years (median treatment period: 631 days; range: 7-1086). A total of 23% of subjects discontinued study participation during the open-label extension treatment period, including 15% due to lack of efficacy and 1% due to adverse events.

Lennox-Gastaut syndrome

Children and adults with Lennox-Gastaut syndrome

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

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

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

The primary efficacy endpoint in Study 4 Part 1 was percent change from baseline in the frequency of drop seizures per 28 days during the combined 14-week titration and maintenance periods (i.e., treatment period) in the 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 0.7 mg/kg/day dose group of fenfluramine 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: results of selected endpoints in Study 4 Part 1 (Maintenance Period)

	Placebo (N = 87)	**Fenfluramine 0.7 mg/kg/day (N = 87)**
Primary Endpoint: Percentage Change from BL in DSF During M		
DSF Summary Statistics [a]		
Median at BL	53.00	82.00
Median during M	47.33	55.73
Median Percentage Change from BL During M	-7.28	-27.16
Nonparametric Model [b]		
p-value for comparison with placebo	—	0.0018

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

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

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]).

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

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

Pharmacokinetics

The pharmacokinetics of fenfluramine and norfenfluramine were studied in healthy subjects and in paediatric patients with Dravet 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 0.354 mg/kg or 0.78 mg/kg, respectively. The AUC_{inf} is 798 ng × h/mL and ~800 ng × h/mL following 0.35 mg/kg and 0.7 mg/kg, respectively. C_{max} and AUC_{inf} of fenfluramine appear dose proportional over the 0.35 to 0.7 mg/kg dose range in healthy volunteers. The C_{max} and AUC_{inf} of norfenfluramine are less than dose proportional over the 0.35 to 0.7 mg/kg dose range in healthy volunteers. The AUC_{inf} increase was 0.5-fold for the 0.7 mg/kg dose compared to the 0.35 mg/kg dose. The C_{max} increase was 0.7-fold for the 0.7 mg/kg dose compared to the 0.35 mg/kg dose.

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

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

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

Distribution

Fenfluramine is 50% bound to human plasma proteins in vitro and binding is independent of fenfluramine concentrations. The geometric mean (CV%) volume of distribution (V_z/F) of

fenfluramine is 11.9 (16.5%) L/kg following oral administration of fenfluramine in healthy subjects.

Biotransformation

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

Transporters

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

Elimination

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

Special populations

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

Renal impairment
Renal elimination is the predominant route of elimination of fenfluramine-related products, with more than 90% of the administered dose eliminated in the urine as parent or metabolites. There are no human clinical data on the effect of renal impairment on the PK of fenfluramine and norfenfluramine.

Hepatic impairment
No studies on the effect of hepatic impairment on the PK of fenfluramine in adults or children were found. With hepatic metabolism of fenfluramine, plasma drug concentrations may be affected in patients with significant hepatic impairment. Subjects with moderate or severe hepatic impairment were excluded from the phase 3 clinical trials.

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

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety

pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development..

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

Reproduction and development

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

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

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

In a pre- and post-natal study in rats, maternal toxicity was associated with an increase in stillbirths at the high dose. No adverse effects on the 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 Fintepla. In the first generation of offspring, there were no effects on overall reproductive function.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium citrate monohydrate
Citric acid monohydrate
Hydroxyethylcellulose
(Monosodium phosphate (E 339); Disodium phosphate (E 339)- pH stabilizers)
Sodium methyl para-hydroxybenzoate (E 219)
Sucralose (E 955)
Cherry flavouring powder:
- Dextrose (maize)
- Gum Arabic/ Acacia E414
- Ethyl benzoate
- Sulfur dioxide (E 220)
- Natural flavouring preparations

Natural flavouring substances
Flavouring substances
Maltodextrin (maize)

Sodium ethyl para-hydroxybenzoate (E 215)
Potassium citrate (E 332)
Citric acid monohydrate (E 330)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

Shelf life after first opening

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

6.4 Special precautions for storage

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

6.5 Nature and contents of container

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

Presentations:

Bottle containing 60 mL oral solution, a bottle adaptor, two 3 mL oral syringes with 0.1 mL graduations, and two 6 mL syringes with 0.2 mL graduations.
Bottle containing 120 mL oral solution, a bottle adaptor, two 3 mL oral syringes with 0.1 mL graduations, and two 6 mL syringes with 0.2 mL graduations.
Bottle containing 250 mL oral solution, a bottle adaptor, two 3 mL oral syringes with 0.1 mL graduations, and two 6 mL syringes with 0.2 mL graduations.
Bottle containing 360 mL oral solution, a bottle adaptor, two 3 mL oral syringes with 0.1 mL graduations, and two 6 mL syringes with 0.2 mL graduations.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Inserting the bottle adaptor:

When the bottle is first opened the bottle adaptor must be pushed into the bottle.
Wash and dry hands.
Remove the bottle adaptor packaging.
Place the bottle on a flat, firm surface.
Open the bottle.

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

Push the bottle adaptor into the bottle using the palm of the hand.
The bottle adaptor should be flush with the top of the bottle.
The bottle adaptor should not be removed after each use.
The bottle cap can be screwed onto the bottle with the bottle adaptor in place.

Cleaning the syringe:

Separate the plunger from the syringe to rinse each part.
Rinse the oral syringe with clean water and allow it to air dry after each use.
Rinse the inside of the syringe and the plunger.
The syringe and plunger can be cleaned in a dishwasher.
Clean water can be pulled into the syringe with the plunger and pushed out several times to clean the syringe.
The syringe and plunger must be completely dry before the next use.

Feeding tubes

Fintepla oral solution is compatible with most enteral feeding tubes.
To flush the feeding tube, fill the syringe used for dosing with water and flush the tube. Do this 3 times.

7. MANUFACTURER

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

8. License Holder

Medison Pharma Ltd. 10 Hashiloach St. , P.O.B. 7090, Petach Tikva

9. Registration Number

169-41-36976-99

Revised on September 2023 according to MOH guidelines

Fintepla-SPC-1023-V1