▼This medicinal product is subject to additional monitoring **in Australia**. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

FINTEPLA® (FENFLURAMINE HYDROCHLORIDE) 2.2 MG/ML ORAL SOLUTION

WARNING: VALVULAR HEART DISEASE AND PULMONARY ARTERIAL HYPERTENSION

See Section 4.4 Special Warnings and Precautions for further detail.

- **There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in Fintepla), and valvular heart disease and pulmonary arterial hypertension.**
- **Echocardiogram assessments are required before, during and after treatment with Fintepla.**
- **Fintepla is only available through a controlled access program.**

1 NAME OF THE MEDICINE

Fenfluramine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fintepla oral solution contains 2.2 mg of fenfluramine (as hydrochloride) per mL.

Excipients with known effect: sucralose, hydroxybenzoates, benzoates, sulfites. For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Oral solution.

The solution is a clear, colourless, slightly viscous liquid.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fintepla is indicated as add-on therapy in the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

All patients are started at 0.1 mg/kg Fintepla taken twice daily (BD) and may be titrated every 7 days based on clinical response and tolerability, to an appropriate maintenance dose. The maximum daily maintenance dosage of Fintepla is based on whether patients are taking stiripentol concomitantly.

Dosage recommendations and titration schedule for paediatric (children aged 2 years and older) and adult populations are provided in Table 1.

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

	Without stiripentol*		**With stiripentol**	
	Weight based dose£	**Maximum daily dose**	**Weight based dose£**	**Maximum daily dose**
Starting dose+: Day 0	0.1 mg/kg BD	26 mg	0.1 mg/kg BD	17 mg
Day 7	0.2 mg/kg BD	13 mg BD (= 6.0 mL BD)	0.2 mg/kg BD	8.6 mg BD (= 4.0 mL BD)
Day 14**	0.35 mg/kg BD		Not applicable	

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

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

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

£To calculate the dose volume up to the maximal recommended dose: Weight (kg) x Weight-based dosage (mg/kg) ÷ 2.2 mg/ml = ml dose to be taken twice daily

Method of administration
Fintepla is to be administered orally and may be taken with or without food.

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

Graduated syringes are supplied with each bottle of Fintepla oral solution.

- 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.

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.

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.

Dose Adjustment
No dose adjustment is required based on age, gender, race or ethnicity, or in patients with mild to moderate renal impairment.

A dose reduction for Fintepla is recommended when it is co-administered with strong CYP1A2 or CYP2D6 inhibitors, in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2), in patients with mild hepatic impairment (Child-Pugh class A), moderate hepatic impairment (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C).

Mild, Moderate and Severe Hepatic Impairment

See Table 2 for dosage adjustments and recommendations for patients with hepatic impairment (see Section 4.4 Special Warnings and Precautions for Use). A maximum dosage of 0.2 mg/kg twice daily (maximum 17 mg/day) is recommended in patients with severe hepatic impairment (Child-Pugh Class C).

Table 2: Dosage modifications and recommendations for Patients with Hepatic Impairment

Hepatic Impairment Classification	**Without concomitant Stiripentol***	**With concomitant Stiripentol**
	Maximum total daily dosage	**Maximum total daily dosage**
Mild (Child-Pugh A)	20 mg	13 mg*
Moderate (Child-Pugh B)	20 mg	Use not recommended
Severe (Child-Pugh C)	17 mg	Use not recommended

* titrate as recommended in table 1

Severe Renal Impairment

For patients with severe renal impairment (estimated glomerular filtration rate (eGFR) 15 to 29 mL/min/1.73m^2), a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol is recommended (see Section 4.4 Special Warnings and Precautions for Use).

Concomitant Use of Strong CYP1A2 or CYP2D6 Inhibitors

For patients with concomitant use of Fintepla with a strong CYP1A2 or CYP2D6 inhibitor, a maximum total daily dosage of 20 mg without concomitant stiripentol and 17 mg with concomitant stiripentol is recommended (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 List of Excipients).

Aortic or mitral valvular heart disease (see Section 4.4 Special warnings and precautions for use).

Pulmonary arterial hypertension (see Section 4.4 Special warnings and precautions for use).

Concomitant use, or within 14 days of the administration, of monoamine oxidase inhibitors (MAOIs) because of an increased risk of serotonin (5-HT) syndrome (see Section 4.4 Special warnings and precautions for use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Valvular Heart Disease (VHD) and Pulmonary Arterial Hypertension (PAH)

Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in Fintepla), and VHD and PAH, as well as reported cases of valvular heart disease and pulmonary arterial hypertension that may have been caused by fenfluramine with past use at higher doses to treat adult obesity, cardiac monitoring using echocardiography is required. Patients with VHD or PAH were excluded from the controlled clinical studies of fenfluramine for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. In clinical trials of up to 3 years in duration, no patient receiving Fintepla developed VHD or PAH.

However, VHD and PAH have been reported from post-marketing surveillance of Fintepla used at the doses recommended for patients with Dravet syndrome and Lennox-Gastaut syndrome.

Monitoring

Prior to starting treatment

Prior to starting treatment, patients must undergo an echocardiogram to assess the patient for the risk of VHD and PAH to establish a baseline prior to initiating treatment and exclude any pre-existing valvular heart disease or pulmonary hypertension.

Ongoing monitoring

Echocardiograms should be conducted every 6 months for the first 2 years and then annually. A final echocardiogram should be done 6 months after the last dose of treatment with Fintepla.

Important echocardiogram findings to monitor for include:

- Valvular abnormality or new abnormality via echocardiogram.
- VHD as indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (e.g., valve thickening or restrictive valve motion).
- PAH as indicated by elevated right heart/pulmonary artery pressure (PASP > 35 mm Hg).

If echocardiogram findings are suggestive of VHD 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 echocardiogram findings are suggestive of PAH, a repeat echocardiogram should be performed as soon as possible and within 3 months to confirm these findings. If the echocardiogram finding is confirmed and suggestive of an increased probability of PAH 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 a high probability of PAH, it is recommended fenfluramine treatment should be stopped.

If treatment is stopped because of VHD or PAH, appropriate monitoring and follow-up should be provided in accordance with local guidelines for treatment.

Decreased appetite and weight loss

Fenfluramine can cause decreased appetite and weight loss. 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 or who are significantly underweight or likely to be adversely impacted by further weight loss.

Fintepla controlled access program

A controlled access program 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 (CNS) depressants, including alcohol, could potentiate the somnolence effect of fenfluramine.

Suicidal behaviour and ideation
Suicidal behaviour and ideation have been reported in patients treated with anti-epileptic drugs (AEDs) 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; with agents that impair metabolism of serotonin such as MAOIs; or with antipsychotics that may affect serotonergic neurotransmitter systems (including SSRIs, SNRIs, tricyclic antidepressants (TCAs), or triptans).

Symptoms of serotonin syndrome 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. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy with Fintepla and/or other serotonergic agents should be considered.

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, to optimise the benefit-risk balance.

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.

Use in hepatic impairment
Exposure to fenfluramine is increased in subjects with various degrees of hepatic impairment (Child-Pugh Class A, B, and C), necessitating a dosage adjustment in these patients (see Section 4.2 Dose and Method of Administration).

Use in renal impairment
Exposure to fenfluramine is increased in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73m^2), necessitating a dose adjustment in these patients (see Section 4.2 Dose and Method of Administration).

Use in the elderly
A study to evaluate the PK and safety of Fintepla in elderly subjects has not been conducted. Clinical studies of Fintepla for the treatment of Dravet syndrome or LGS did not include patients 65 years of age and over.

Paediatric use
The safety and efficacy of Fintepla in children below the age of 2 years have not been established. No data are available.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Serotonergic Drugs
Concomitant administration of Fintepla and drugs (e.g., SSRIs, SNRIs, TCAs, MAO inhibitors, trazodone, etc.), over-the-counter medications (e.g., dextromethorphan), or herbal supplements (e.g., St. John's Wort) that increase serotonin may increase the risk of serotonin syndrome (see Section 4.4 Special Warnings and Precautions). Concomitant use of Fintepla is contraindicated within 14 days of taking MAOIs. Use Fintepla with caution in patients taking other medications that increase serotonin.

Drug Interaction 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 BD (0.4 mg/kg/day), maximum 17 mg/day, fenfluramine with a standard AED 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.

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 PK of cannabidiol, as compared to cannabidiol alone. No dose adjustment is necessary when fenfluramine is co-administered with cannabidiol.

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 PK of stiripentol, nor the PK of clobazam or its N-desmethyl-metabolite norclobazam, nor the PK 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 the multidrug and toxin extrusion protein 1 (MATE1) transporter at clinically relevant concentrations. Co-administration of fenfluramine with MATE1 substrates may increase their plasma concentrations.

Effect of strong CYP1A2, CYP2B6 or CYP3A inducers

Coadministration of a single 0.35 mg/kg dose of Fintepla with rifampin (a CYP1A2, CYP2B6, and CYP3A inducer) at steady state (600 mg once daily) in healthy volunteers decreased the $AUC_{0\text{-}inf}$ of fenfluramine by 58% and the C_{max} by 40% and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 50%, and increased the C_{max} of norfenfluramine by 13%, as compared to Fintepla administered alone. An increase in Fintepla dosage should be considered when coadministered with a strong CYP1A2 or CYP2B6 inducer; however, do not exceed twice the maximum daily dosage of Fintepla (maximum of 52 mg/day).

Effect of strong CYP1A2 or CYP2D6 Inhibitors

Coadministration of a single 0.35 mg/kg dose of Fintepla with fluvoxamine (a strong CYP1A2 inhibitor) at steady state (50 mg once daily) in healthy volunteers increased the $AUC_{0\text{-}inf}$ of fenfluramine by 102% and the C_{max} by 22% and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 22% and the C_{max} by 44%, as compared to Fintepla administered alone.

Coadministration of a single 0.35 mg/kg dose of Fintepla with paroxetine (a strong CYP2D6 inhibitor) at steady state (30 mg once daily) in healthy volunteers increased the $AUC_{0\text{-}inf}$ of fenfluramine by 81% and the C_{max} by 13% and decreased the $AUC_{0\text{-}inf}$ of norfenfluramine by 13% and the C_{max} by 29%, as compared to Fintepla administered alone.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 male and female fertility. Oral administration of fenfluramine to male and female rats prior to and throughout mating and continuing in females to implantation resulted in a decrease in fertility and increases in abnormal sperm and

epithelial vacuolation of the epididymis at 17.3 mg/kg/day and altered oestrous cyclicity, decreased corpora lutea and implantations, and increased embryolethality at ≥6.9 mg/kg/day. These doses were associated with parental toxicity as seen by effects on body weight and lower food consumption. The no-effect doses for adverse effects on fertility and reproductive performance in rats (6.9 and 3 mg/kg/day in males and females, respectively) were associated with subclinical plasma fenfluramine exposures (AUC), and norfenfluramine exposures approximately 4 and 2 times, respectively, those in humans at the maximum recommended human dose (MRHD) of 26 mg/day fenfluramine hydrochloride.

Use in Pregnancy (Category D)
There is limited data in pregnant women who have taken fenfluramine and therefore it is difficult to draw conclusions on the use of fenfluramine in pregnant women.

Fenfluramine and norfenfluramine crossed placenta in pregnant rats and rabbits with fetal levels 2 to 5-fold higher than maternal plasma levels.

Oral administration of fenfluramine to pregnant rats and rabbits during organogenesis resulted in embryofetal death in both species, lower fetal body weights with correlating effects on ossification and marked increases in fetal malformations (cleft palate and malrotated hindlimb) were seen in rats. While these effects occurred with maternotoxicity, a direct effect of fenfluramine on embryofetal death and malformations cannot be dismissed. At the no effect dose for adverse effects on embryofetal development in rats (8.6 mg/kg/day), maternal plasma exposures (AUC) of fenfluramine and norfenfluramine were approximately 5 and 8 times, respectively, those in humans at the MRHD of 26 mg/day. A no adverse effect level was not established in rabbits with exposures (AUC) of fenfluramine and norfenfluramine subclinical at the lowest tested dose.

Oral administration of fenfluramine to female rats throughout gestation and lactation resulted in marked increases in stillborn pups and neonatal offspring deaths at 34.6 mg/kg/day. While maternal body weight gain was lower at this dose, a direct drug-related effect cannot be excluded. At the no effect dose for stillbirths and neonatal survival in rats (8.6 mg/kg/day), maternal plasma exposures (AUC) of fenfluramine and norfenfluramine were approximately 5 and 8 times, respectively, those in humans at the MRHD of 26 mg/day.

There are no or limited amount of data from the use of Fintepla in pregnant women. Studies in animals have shown reproductive toxicity. Fintepla is not recommended during pregnancy and in women of childbearing potential not using contraception.

Use in Lactation
It is not known whether Fintepla is excreted in human breast milk.

In a lactation study with dexfenfluramine, both dexfenfluramine and nordexfenfluramine were found in milk. Milk concentrations were up to 12-fold plasma concentrations.

In a pre- and postnatal study in rats in which fenfluramine was given orally daily throughout gestation and lactation, delayed growth and reflex development of breast-fed pups was seen at all doses during the preweaning period. At the lowest dose tested in rats (4.3 mg/kg/day), maternal plasma exposures of fenfluramine and norfenfluramine were approximately 2 and 3.5 times, respectively, those in humans at the MRHD.

A risk to the breastfed child cannot be excluded. Breastfeeding is contraindicated whilst on Fintepla.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Fintepla may cause somnolence and fatigue, which may influence the ability to drive and use machines. Patients should be advised not to drive or operate machinery until they have gained sufficient experience to gauge whether it adversely affects their abilities.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

Dravet Syndrome

The most commonly reported adverse reactions are decreased appetite, diarrhoea, upper respiratory tract infection, echocardiogram abnormal*, fatigue, pyrexia, blood glucose decreased and somnolence. Table 3 lists the TEAEs that were reported in Fintepla and at an incidence of at least 1% with a higher incidence than placebo in Study 1 and 2, and Study 3.

*Consisted of trace and mild mitral regurgitation, and trace aortic regurgitation.

Table 3: TEAEs by MedDRA SOC and PT in Study 1, Study 2 and Study 3 (occurring ≥ 1% patients in the active arms with a higher incidence than placebo)

MedDRA System Organ Class Preferred Term	Combined Fintepla active groups (N=216) n (%)	Placebo (N=132) n (%)
Blood and lymphatic system disorders		
Leukopenia	3 (1.4%)	0 (0%)
Thrombocytopenia	5 (2.3%)	0 (0%)
Gastrointestinal disorders		
Abdominal pain upper	3 (1.4%)	1 (0.8%)
Constipation	12 (5.6%)	1 (0.8%)
Diarrhoea	43 (19.9%)	10 (7.6%)
Nausea	3 (1.4%)	1 (0.8%)
Salivary hypersecretion	4 (1.9%)	0 (0%)
General disorders and administration site conditions		
Asthenia	9 (4.2%)	3 (2.3%)
Chills	3 (1.4%)	0 (0%)
Decreased activity	3 (1.4%)	1 (0.8%)
Fatigue	27 (12.5%)	4 (3.0%)
Gait disturbance	5 (2.3%)	1 (0.8%)
Pyrexia	34 (15.7%)	16 (12.1%)
Infections and infestations		
Bronchitis	6 (2.8%)	2 (1.5%)
Conjunctivitis	3 (1.4%)	0 (0%)
Croup infectious	5 (2.3%)	1 (0.8%)
Ear infection	10 (4.6%)	4 (3.0%)
Gastroenteritis	3 (1.4%)	1 (0.8%)
Respiratory tract infection	3 (1.4%)	0 (0%)
Rhinitis	9 (4.2%)	2 (1.5%)

Upper respiratory tract infection	19 (8.8%)	10 (7.6%)
Urinary tract infection	7 (3.2%)	0 (0%)
Viral infection	7 (3.2%)	1 (0.8%)
Viral upper respiratory tract infection	6 (2.8%)	2 (1.5%)
Injury, poisoning and procedural complications		
Ligament sprain	4 (1.9%)	1 (0.8%)
Investigations		
Blood glucose decreased	25 (11.6%)	8 (6.1%)
Blood prolactin increased	4 (1.9%)	0 (0%)
Blood thyroid stimulating hormone increased	5 (2.3%)	0 (0%)
Body temperature increased	4 (1.9%)	0 (0%)
Echocardiogram abnormal*	39 (18.1%)	10 (7.6%)
Gamma-glutamyltransferase increased	3 (1.4%)	0 (0%)
Platelet count decreased	6 (2.8%)	0 (0%)
Tri-iodothyronine decreased	3 (1.4%)	0 (0%)
Weight decreased	16 (7.4%)	1 (0.8%)
Metabolism and nutrition disorders		
Decreased appetite	72 (33.3%)	10 (7.6%)
Hypoglycaemia	6 (2.8%)	3 (2.3%)
Hypophagia	3 (1.4%)	0 (0%)
Nervous system disorders		
Ataxia	9 (4.2%)	2 (1.5%)
Balance disorder	5 (2.3%)	1 (0.8%)
Disturbance in attention	3 (1.4%)	0 (0%)
Drooling	9 (4.2%)	0 (0%)
Hypotonia	4 (1.9%)	0 (0%)
Lethargy	21 (9.7%)	6 (4.5%)
Myoclonus	3 (1.4%)	1 (0.8%)
Seizure cluster	3 (1.4%)	1 (0.8%)
Somnolence	28 (13.0%)	11 (8.3%)
Status epilepticus	11 (5.1%)	2 (1.5%)
Tremor	14 (6.5%)	2 (1.5%)
Psychiatric disorders		
Abnormal behaviour	10 (4.6%)	2 (1.5%)
Aggression	5 (2.3%)	0 (0%)
Agitation	4 (1.9%)	1 (0.8%)
Insomnia	5 (2.3%)	2 (1.5%)
Mood swings	3 (1.4%)	0 (0%)
Sleep disorder	4 (1.9%)	0 (0%)
Renal and urinary disorders		
Urinary incontinence	4 (1.9%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	3 (1.4%)	1 (0.8%)
Rhinorrhoea	8 (3.7%)	3 (2.3%)

Skin and subcutaneous tissue disorders		
Eczema	3 (1.4%)	0 (0%)

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

Lennox-Gastaut Syndrome

The most commonly reported adverse reactions are decreased appetite, fatigue, upper respiratory tract infection, somnolence, diarrhoea and vomiting. Table 4 lists the TEAEs that were reported in Fintepla at an incidence of at least 1% with a higher incidence than placebo during the titration and maintenance phases of Study 4.

Table 4: TEAEs in Study 4 Part 1 Cohort A during Titration and Maintenance Periods (occurring ≥ 1% patients in the active arms and with a higher incidence than placebo)

MedDRA System Organ Class Preferred Term	**Combined ZX008 Groups (N=176) n (%)**	**Placebo (N=87) n (%)**
Gastrointestinal disorders		
Constipation	13 (7.4%)	5 (5.7%)
Dental caries	2 (1.1%)	0 (0%)
Diarrhoea	21 (11.9%)	4 (4.6%)
Dysphagia	3 (1.7%)	0 (0%)
Stomatitis	2 (1.1%)	0 (0%)
Vomiting	19 (10.8%)	5 (5.7%)
General disorders and administrative site conditions		
Asthenia	9 (5.1%)	3 (3.4%)
Fatigue	24 (13.6%)	9 (10.3%)
Infections and infestations		
Bronchitis	4 (2.3%)	0 (0%)
Conjunctivitis	3 (1.7%)	0 (0%)
Hordeolum	2 (1.1%)	0 (0%)
Influenza	4 (2.3%)	1 (1.1%)
Otitis media	2 (1.1%)	0 (0%)
Pharyngitis streptococcal	3 (1.7%)	0 (0%)
Pharyngotonsillitis	2 (1.1%)	0 (0%)
Pneumonia	4 (2.3%)	1 (1.1%)
Rhinitis	2 (1.1%)	0 (0%)
Sinusitis	2 (1.1%)	0 (0%)
Upper respiratory tract infection	13 (7.4%)	3 (3.4%)
Urinary tract infection	5 (2.8%)	0 (0%)
Viral upper respiratory tract infection	3 (1.7%)	0 (0%)
Injury, poisoning, and procedural complications		
Contusion	6 (3.4%)	1 (1.1%)
Fall	6 (3.4%)	1 (1.1%)

Laceration	4 (2.3%)	1 (1.1%)
Skin abrasion	2 (1.1%)	0 (0%)
Investigations		
Blood prolactin increased + hyperprolactinemia	6 (3.4%)	1 (1.1%)
Platelet count decreased	2 (1.1%)	0 (0%)
Weight decreased	9 (5.1%)	2 (2.3%)
Metabolism and nutrition disorders		
Decreased appetite	49 (27.8%)	10 (11.5%)
Dehydration	2 (1.1%)	0 (0%)
Nervous system disorders		
Drooling + salivary hypersecretion	5 (2.8%)	1 (1.1%)
Headache	4 (2.3%)	1 (1.1%)
Lethargy	7 (4.0%)	2 (2.3%)
Seizure*	12 (6.8%)	6 (6.9%)
Somnolence	24 (13.6%)	9 (10.3%)
Status epilepticus*	2 (1.1%)	1 (1.1%)
Tremor	4 (2.3%)	1 (1.1%)
Psychiatric disorders		
Affect lability	2 (1.1%)	0 (0%)
Renal and urinary disorders		
Urinary retention	2 (1.1%)	0 (0%)
Reproductive system and breast disorders		
Menstruation irregular	2 (1.1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders		
Hiccups	3 (1.7%)	0 (0%)
Productive cough	2 (1.1%)	0 (0%)
Rhinorrhoea	3 (1.7%)	0 (0%)
Skin and subcutaneous tissue disorders		
Eczema	2 (1.11%)	0 (0%)
Vascular disorders		
Haematoma	5 (2.8%)	0 (0%)

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 DS (Study 1 and Study 2) 34.7% of Fintepla-treated patients had an adverse reaction of decreased appetite, compared with 7.6% of patients on placebo. Additional analyses were conducted on body weight changes of ≥ 7% from baseline at one or more visits. In the DS double-blind studies (Study 1, Study 2 and Study 3), more subjects randomized to any Fintepla treatment group compared to placebo had weight decrease of ≥ 7% from baseline (18.9% vs 2.4%) at the end of the double-blind treatment period. In the placebo-controlled study for LGS, approximately 27.8% of

patients treated with Fintepla reported decreased appetite compared with 11.5% of patients on placebo. During the placebo-controlled studies, weight loss from baseline of ≥ 7% was recorded in 6.3% of subjects in any Fintepla treatment group, and 0% in the placebo group at the end of double-blind period. The decreases in appetite and weight appeared to be dose related. Most subjects resumed weight gain over time while continuing Fintepla treatment.

Echocardiographic safety assessments of VHD and PAH

VHD and PAH were evaluated in the placebo-controlled and open-label extension (OLE) studies via echocardiogram for up to 3 years in duration for 341 DS patients and 263 LGS patients. Screening for VHD assessed for mild or greater aortic regurgitation (AR) or moderate or greater mitral regurgitation, and assessed for additional characteristics of VHD (e.g., valve thickening or restrictive valve motion). In these clinical studies, 2 patients with LGS exhibited mild AR but neither patient had any cardiac signs or symptoms or evidence of valvular structural changes. Neither patient had VHD. The rates of mild AR are consistent with those seen in the screening period prior to treatment (3 patients in LGS and 1 patient in DS clinical trials).

Lethargy, somnolence and fatigue

In the controlled trials in patients with DS, lethargy was commonly reported in 9.7% and somnolence and fatigue/asthenia were very commonly reported in 13.0% and 18.1%, respectively in the Fintepla treatment groups combined. In the controlled study with LGS, 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 were reported in the first 2 weeks of treatment with Fintepla and were mild or moderate in severity. Discontinuation due to lethargy, somnolence, and fatigue was rare and, in most cases, these adverse events resolved or improved with ongoing treatment. In the controlled trials with DS, 0.8% and 1.6% of subjects in the combined Fintepla treatment groups discontinued due to lethargy and somnolence, respectively. In the LGS study, 1.7% subjects in the Fintepla treatment group discontinued due to somnolence.

Seizures

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

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. In the LGS controlled trial through the open-label trial, diarrhoea and constipation were observed more frequently in the higher dose groups.

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.

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.

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.

Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in post-marketing experience. It is not always possible to reliably estimate the frequency of their incidence in the population to be treated.

Nervous system disorders

Serotonin syndrome

Psychiatric disorders

Aggression

Abnormal behaviour

Irritability

Insomnia

Cardiac disorders

VHD

Respiratory, thoracic and mediastinal disorders

PAH

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 as a positive modulator of the sigma-1 receptor. The precise mode of action of fenfluramine in DS and LGS is not known.

Pharmacodynamics
Pharmacodynamic interactions with other CNS depressants increase the risk of aggravated CNS depression (see Section 4.4 Special Warnings and Precautions - Somnolence).

Cardiac Electrophysiology

The effect of multiple oral administrations of therapeutic (26 mg/day, ie, 13 mg BD) and supratherapeutic (103.7 mg/day, i.e., 51.8 mg BD) doses of Fintepla on the heart rate-corrected QT interval using Fridericia's correction formula (QTcF) was studied in a placebo- and positive-controlled study in healthy adult male and female volunteers. The supratherapeutic Fintepla dose of 103.7 mg/day provided a 4-fold higher dose than the maximum recommended daily dose for clinical use. Steady-state systemic exposures (C_{max} and AUC) of fenfluramine and norfenfluramine were slightly greater than dose proportional over the dose range of 13 to 51.8 mg BD. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

Fintepla did not prolong the QT interval following multiple doses up to 4 times the maximum recommended dose.

Clinical trials

Dravet syndrome
The effectiveness of Fintepla in children and young adults with DS was evaluated in 3 randomised, multicentre, placebo-controlled studies (ZX008-1501, ZX008-1502 and ZX008-1504).

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 subsequently enrolled patients (Study 3) from 2 identical double-blind, placebo-controlled studies, ZX008-1501 and ZX008-1502, to assess the efficacy, safety, and pharmacokinetics of Fintepla when used as adjunctive therapy in paediatric and young adult subjects with Dravet syndrome. Study ZX008-1501 and Study ZX008-1502 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. Eligible patients were randomised 1:1:1 to 1 of 2 doses of fenfluramine (0.7 mg/kg/day or 0.2 mg/kg/day, maximum 26 mg/day) or placebo. The mean (standard deviation [SD]) 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), male (53.8% in

Study 1 and 51.4% in Study 3), and white (82.4% in Study 1 and 74.6% in Study 3). All enrolled patients were inadequately controlled on at least 1 AED, with or without vagal nerve stimulation and/or ketogenic diet. Patients were taking between 1 and 5 AEDs at study entry.

The most frequently used concomitant AEDs (≥25% overall) were valproate (59.6% in Study 1 and 57.7% in Study 3), clobazam (58.8% in Study 1 and 56.3% in Study 3), topiramate (25.2% in Study 1 and 26.8% in Study 3) and levetiracetam (28.2% in Study 3). Stiripentol was excluded as a concomitant AED from Study 1 and 3.

The results of primary and selected secondary endpoints from Study 1 and Study 3 are provided in Table 5.

At the end of the T+M period, the median CSF (per 28 days) in Study 1 was 26.0, 14.3, and 5.4 in the placebo, 0.2 mg/kg/day, and 0.7 mg/kg/day groups, respectively and in Study 3 was 12.0, 6.6, and 3.1 in treatment groups, respectively. This resulted in a mean reduction in monthly CS compared with placebo, of 32.4% and 49.9% in the 0.2 mg/kg/day dose groups ($p=0.016$ and $p<0.001$ respectively) for Study 1 and Study 3 respectively and 62.3% and 64.8% in the 0.7 mg/kg/day dose groups (both $p<0.001$) for Study 1 and Study 3 respectively.

Patients achieving ≥ 50% reduction in monthly CS from baseline were considered responders. Patients in the placebo groups of both studies achieved responder status (7.5% and 6.3% in Study 1 and Study 3 respectively). However, statistically significantly higher levels of response were observed in the Fintepla treated groups. In both studies over 40% of patients were responders after 0.2 mg/kg/day (41.0% Study 1 and 45.7% Study 3) and more than 70% of patients achieved at least a 50% reduction after 0.7 mg/kg/day. At least 20.5% of patients achieved ≥ 75% reduction (both dose groups in each study) and more than 7.5% achieved ≥ 100% reduction (both dose groups in Study 1 and the higher dose group in Study 3).

The longest (median) seizure free interval in Study 1 was 9.0, 14.0, and 20.5 days in the placebo, 0.2 mg/kg/day, and 0.7 mg/kg/day groups, respectively and in Study 3 was 10, 18.5 and 30 days in the treatment groups, respectively.

Table 5: Dravet syndrome: Study 1 and Study 3 results of primary and selected secondary efficacy endpoints (Titration + 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 (CSF) during Titration + 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, 2701.0)
CSF at end of T + M **N,** **Median** **(min, max)**	40 26.0 (3.2, 180.6)	39 14.3 (0.0, 202.1)	40 5.4 (0, 169.9)	48 12.0 (0.9, 137.8)	46 6.6 (0.5, 1990.0)	48 3.1 (0.0, 3498.6)
Reduction in mean monthly baseline-adjusted Convulsive Seizure Frequency compared to Placebo	-	32.4% p=0.019	62.3% p<0.001	-	49.9% p< 0.0001	64.8% p< 0.0001
% Reduction in convulsive seizures during Titration + Maintenance period						
Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline	5 (12.5%)	15 (38.5%) p=0.009	27 (67.5%) p<0.001	3 (6.3%)	21 (45.7%) p=0.0001	35 (72.9%) p<0.0001
Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline	1 (2.5%)	9 (23.1%) p=0.023	20 (50.0%) p<0.001	2 (4.2%)	13 (28.3%) p=0.0047	23 (47.9%) p<0.0001
Number (%) of patients with ≥100% reduction in monthly convulsive seizures - change from baseline	0 (0%)	3 (7.7%) p value **	3 (7.5%) p value **	0 (0%)	0 (0.0%) p value: NA	6 (12.5%) p value: NA
Longest seizure-free interval during Titration + Maintenance period						
Longest seizure-free interval (median)	9.0 days	14.0 days p=0.011	20.5 days p<0.001	10.0 days	18.5 days p=0.0002	30 days p<0.0001

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

** Validity of the model fit is questionable and the maximum likelihood estimate for the odds ratio may not exist. No model statistics are reported.

Study 2 (previously known as Study ZX008-1504) (N=87) was a 2-arm, multicentre, randomised, double-blind, parallel group, placebo-controlled study consisting of a 6-week baseline period, 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 Fintepla 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 (SD) 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 1 AED, 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.

The results of primary and selected secondary endpoints from Study 2 are provided in Table 6.

At the end of the maintenance period, the median CSF (per 28 days) was 11.4 in the placebo group and 5.2 in the Fintepla group, a 54.0% reduction (p<0.001).

Responders (achieving ≥ 50% reduction in monthly CS from baseline) were reported in both treatment groups, 4.5% in the placebo group and 53.5% in the Fintepla group. In the Fintepla group 34.9% of patients reported ≥75% reduction in monthly CS from baseline and 2.3% reported ≥75% reduction in monthly CS from baseline in the placebo group.

The longest (median) seizure free interval in Study 2 was 13 days in the placebo and 22.0 days in the 0.4 mg/kg/day group.

Table 6: Dravet syndrome: Study 2 (ZX008-1504) results of primary and selected secondary efficacy endpoints (Titration + Maintenance)

	Study 2	
	Placebo **[+ stiripentol]**	**Fenfluramine 0.4 mg/kg/day** **[+ stiripentol]**
Convulsive Seizure Frequency (CSF) during Titration + Maintenance period		
N Baseline. **Median (min, max)**	44 10.7 (2.7, 162.7)	43 14.0 (2.7, 213.3)
N At end of Titration + Maintenance period. **Median (min, max)**	44 11.4 (2.2, 170.1)	43 5.2 (0.0, 458.6)
Reduction in mean monthly baseline-adjusted Convulsive Seizure Frequency compared to Placebo	-	54.0 % p<0.001
% reduction in convulsive seizures during Titration + Maintenance period		
Number (%) of patients with ≥50% reduction in monthly convulsive seizures - change from baseline	2 (4.5%)	23 (53.5%) p<0.001
Number (%) of patients with ≥75% reduction in monthly convulsive seizures - change from baseline	1 (2.3%)	15 (34.9%) p=0.003
Longest seizure-free interval during Titration + Maintenance period		
Longest seizure-free interval (median)	13.0 days	22.0 days p=0.004

Adults

The DS population in Study 1, Study 2 and Study 3 was predominantly paediatric patients, with only 11 adult subjects (3.2%) who were 18-19 years old, and therefore limited efficacy and safety data were obtained in the adult DS population.

Open-label data

DS patients who participated in Study 1, Study 2 and Study 3 could participate in an open-label extension (OLE) study (Study ZX008-1503). The primary objective of the OLE study was long-term effectiveness and safety of Fintepla, whereby the dose could be titrated to optimise treatment. Data are reported for 330 patients who participated in the OLE study and received Fintepla for up to 3 years (median treatment period: 631 days; range: 7-1086). A total of 23% of subjects discontinued study participation during the OLE treatment period, including 15% due to lack of efficacy and 1% due to adverse events.

Lennox-Gastaut syndrome
Children and adults

Study 4 Part 1 (ZX008-1601 Part 1) was a randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of 2 fixed doses of Fintepla. The primary analysis cohort (Cohort A) and included subjects from North America, Europe, and Australia.

Study 4 compared a 0.7 mg/kg/day (N=87) and a 0.2 mg/kg/day (N=89) dose (up to a maximum daily dose of 26 mg/kg) of Fintepla with placebo. Patients with a diagnosis of LGS and were inadequately controlled on at least 1 AED, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of Fintepla remained stable.

The most frequently used concomitant AEDs (in at least 25% of patients) were clobazam (45.2%), lamotrigine (33.5%), and valproate (55.9%).

The primary efficacy endpoint in Study 4 was the percentage change from baseline in the frequency of drop seizures per 28 days (DSF) during the combined 14-week titration and maintenance periods (i.e., treatment period) in the fenfluramine 0.7 mg/kg/day group compared with the placebo group. Key secondary endpoints included the proportion of patients who achieve a ≥50% reduction from baseline in DSF for the fenfluramine 0.7 mg/kg/day group compared with the placebo group. Results are presented in Table 7.

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

	Placebo **(N = 87)**	**Fenfluramine 0.7 mg/kg/day (N = 87)**
Primary Endpoint: Percentage Change from Baseline in DSF during Titration + Maintenance		
DSF Summary Statistics [a]		
Median at Baseline	53.00	83.00
Median during Maintenance	46.85	54.57
Median Percentage Change from Baseline During Maintenance	-7.59	-26.49
Nonparametric Model [b]		
p-value for comparison with placebo		0.0013
HL Estimate for Median Difference (A-P)		
Estimate (Std Err)		19.88 (5.684)
95% CI		-31.02, -8.74
Key Secondary Endpoint: Percentage of Patients with ≥ 50% Reduction from Baseline in DSF (50% Responder Rate) during Titration + Maintenance		
≥ 50% reduction in DSF, n (%)	9 (10.3%)	22 (25.3%)
p-value for comparison with placebo [c]		0.0150

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

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.

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]).

Open-label data

LGS patients who completed Study 4 Part 1 could participate in Part 2, a 52-week, flexible-dose OLE study. The primary objective of the OLE 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.

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%]).

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of fenfluramine and norfenfluramine were studied in healthy adult subjects, in paediatric patients with DS, and in paediatric and adult patients with LGS.

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.

The plasma half-lives of fenfluramine and norfenfluramine indicate that approximately 94% of steady state would be reached in approximately 4 days for fenfluramine and 5 days for norfenfluramine (4 half-lives).

Distribution

Fenfluramine is 50% bound to human plasma proteins *in vitro* and binding is independent of fenfluramine concentrations up to 100 ng/mL. The geometric mean (CV%) volume of distribution (Vz/F) of fenfluramine is 11.9 L/kg (16.5%) following oral administration of fenfluramine in healthy subjects.

Metabolism

Over 75% of fenfluramine is metabolised to norfenfluramine prior to elimination, primarily by CYP1A2, CYP2B6, and CYP2D6. Other CYP enzymes CYP2C9, CYP2C19, and CYP3A4/5 are involved to a minor extent. Norfenfluramine is then deaminated and oxidised to form additional metabolites. The extent to which these additional metabolites are present in plasma and urine is unknown. The involvement of enzymes other than CYPs (e.g. UDP-glucuronosyltransferases) in the metabolism of norfenfluramine is unknown.

Excretion

Most of an orally administered dose of fenfluramine (>90%) is excreted in the urine mainly as metabolites; 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

The effects of renal impairment on the PK of a single oral dose of Fintepla 0.35 mg/kg has been evaluated in 8 subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73m^2) and 8 healthy subjects as controls. The geometric mean value of total exposure ($AUC_{0\text{-}inf}$) of fenfluramine was increased by 88% in the severe renal impairment group compared with healthy matched controls, with a smaller increase (20%) in C_{max} in subjects with severe renal impairment. Increase in norfenfluramine AUC in subjects with severe renal impairment was small (approximately 13%), with a decrease in C_{max} (21%). Fintepla has not been studied in patients with end-stage renal disease. It is not known if fenfluramine or its active metabolite, norfenfluramine, are dialyzable.

Hepatic impairment

The PK and safety of a single oral dose of Fintepla 0.35 mg/kg has been evaluated in adult subjects with various degrees of hepatic impairment (7-8 per group) and matching healthy subjects as controls. The geometric mean $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of fenfluramine were 95%, 98%, and 19% higher, respectively, in the mild hepatic impairment group; 113%, 113%, and 16% higher, respectively, in the moderate hepatic impairment group; and 185%, 177%, and 29% higher, respectively, in the severe hepatic impairment group, compared with the healthy controls. Fintepla is titrated gradually based on tolerability and response (Section 4.2).

Racial and ethnic groups

The evaluation in subjects with DS and LGS was limited by the small sample size of non-white subjects such that no conclusion on the effect of race on the PK of Fintepla can be made. The PK profile of fenfluramine and norfenfluramine following a single oral dose of Fintepla 0.35 mg/kg alone and in combination with multiple doses of stiripentol and clobazam has been studied in healthy adult Japanese and Caucasian subjects. Fenfluramine and norfenfluramine exposures were similar between Caucasian and Japanese subjects with and without the combination of stiripentol and clobazam.

Gender

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

Body weight

Drug clearance and PK exposure of fenfluramine and norfenfluramine are consistent across a broad range of BMI (12.3 to 35 kg/m^2).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fenfluramine was not genotoxic when tested in the *in vitro* bacterial reverse mutation test (Ames) and an *in vivo* micronucleus and comet assay in rats.

Carcinogenicity
Once daily oral administration of fenfluramine to Tg.rasH2 mice (up to 51.8 mg/kg/day) for 26 weeks and to male and female rats (up to 6.9 mg/kg/day) for up to 89 and 97 weeks, respectively, resulted in no evidence of drug-induced tumours in either species. In rats, plasma exposures (AUC) of fenfluramine and norfenfluramine (the major metabolite) at the highest dose tested were approximately 5 and 11 times, respectively, those in humans at the MRHD of 26 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients are:

- Sodium ethyl hydroxybenzoate: 0.23 mg/mL
- Sodium methyl hydroxybenzoate: 2.3 mg/mL
- Sucralose
- Hyetellose
- Monosodium phosphate
- Disodium phosphates
- Cherry flavour SN932130 (Proprietary Ingredient ID: 147573)
- Potassium citrate
- Citric acid monohydrate
- Water for injections

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

4 years.

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not refrigerate or freeze. Store the bottle and syringe together.

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 4 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, 2x 3 mL oral syringes with 0.1 mL graduations, and 2x 6 mL syringes with 0.2 mL graduations.
- Bottle containing 120 mL oral solution, a bottle adaptor, 2x 3 mL oral syringes with 0.1 mL graduations, and 2x 6 mL syringes with 0.2 mL graduations.
- Bottle containing 250 mL oral solution, a bottle adaptor, 2x 3 mL oral syringes with 0.1 mL graduations, and 2x 6 mL syringes with 0.2 mL graduations.

- Bottle containing 360 mL oral solution, a bottle adaptor, 2x 3 mL oral syringes with 0.1 mL graduations, and 2x 6 mL syringes with 0.2 mL graduations.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

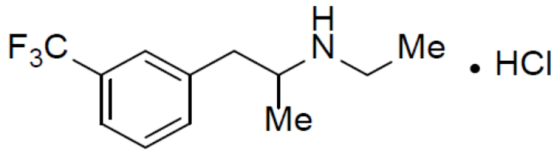
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name

Fenfluramine hydrochloride

Chemical structure



CAS Number
404-82-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

28 November 2024

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Initial Submission