Drug Monograph

Drug Name: **Fintepla® (fenfluramine) oral solution**
Drug Class: **Anticonvulsant, Dravet Syndrome**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Fintepla is available as a Schedule IV oral solution of 2.2mg/ml of fenfluramine.
Manufacturer:	Marketed by: Zogenix Inc., Emeryville, CA, 94608.
Summary of Findings:	The efficacy of Fintepla was demonstrated in 2 randomized, double-blind, placebo-controlled clinical trials in 206 patients. The primary efficacy endpoint was the change in mean monthly convulsive seizure frequency (MCSF) between baseline period and the treatment period in patients given fenfluramine compared to placebo. In both studies the primary endpoint was achieved ($p<0.001$). Secondary endpoints of at least a 50% reduction in MCSF and longest interval of seizure free days were also achieved ($p<0.001$ and $p=0.004$).

Status Recommendation:	☒ Clinical Edit ☐ Open Access	☐ PA Required ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ No PA Required	☐ Non-Preferred ☐ Preferred

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Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1-4]

Dravet syndrome (formerly known as severe myoclonic epilepsy of infancy) is a genetic epilepsy which appears during the first year of life in otherwise healthy infants as a prolonged seizure with fever. As the condition progresses, other types of seizures typically occur, as well as developmental delays and features of autism spectrum disorder. It is estimated that 1 in 20,000 to 1 in 40,000 people have Dravet syndrome and 3 to 8% of children who experience their first seizure by 12 months of age may have Dravet syndrome. Approximately 80% of children with Dravet syndrome have a pathogenic variant in the *SCN1A* gene. When Dravet syndrome is suspected, genetic testing to look for a pathogenic variant in the *SCN1A* gene should be done. If found, this can confirm the diagnosis. If not found, diagnosis may still be made purely based on symptoms as other less common pathogenic variants can cause Dravet syndrome. Approximately 45% of Dravet syndrome patients have more than 3 tonic-clonic seizures per month despite therapy with multiple antiepileptic drugs. Dravet syndrome patients have a 15 to 20% mortality rate due to SUDEP (Sudden Unexpected Death in Epilepsy), prolonged seizures, seizure-related accidents such as drowning, and infections.

Dosage Form [5]

Fintepla is available as a Schedule IV oral solution of 2.2mg/ml of fenfluramine.

Manufacturer [5]

Marketed by: Zogenix, Inc., Emeryville CA, 94608.

Indication(s) [5]

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

Clinical Efficacy [5-8] (mechanism of action/pharmacology, comparative efficacy)

The mechanisms by which fenfluramine exerts its therapeutic effects in the treatment of seizures associated with Dravet syndrome are unknown. Fenfluramine and the metabolite, norfenfluramine, increase extracellular levels of serotonin through interaction with serotonin transporter proteins, and exhibit agonist activity at serotonin 5HT-2 receptors.

Pharmacokinetics:

Absorption	T_{max}=4-5 hours; Bioavailability 68-74%
Metabolism	Hepatic (CYP1A2, CYP2B6, CYP2D6)
Excretion	Renal >90%, Feces <5%
Half-life	20 hours

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Clinical Trials Experience

STUDY 1 DESIGN	Randomized, double-blind, placebo controlled trial compared 0.7mg/kg/day and 0.2mg/kg/day of Fintepla to placebo (n=117)
INCLUSION CRITERIA	• Male or non-pregnant, non-lactating female, age 2 to 18 years, inclusive as of the day of the Screening Visit. • Clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs. • Must have a minimum # of convulsive seizures per 4-week period for past 12 weeks prior to screening • All medications or interventions for epilepsy must be stable for at least 4 weeks prior to screening and expected to remain stable throughout the study. • No cardiovascular or cardiopulmonary abnormality based on ECHO, ECG or physical examination • Parent/caregiver is willing and able to be compliant with diary completion, visit schedule and study drug accountability.
EXCLUSION CRITERIA	• Pulmonary arterial hypertension. • Current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke. • Current or past history of glaucoma. • Moderate or severe hepatic impairment. • Receiving concomitant therapy with: anorectic agents; monoamine-oxidase inhibitors; medications that act via serotonin including serotonin reuptake inhibitors; atomoxetine, or other centrally-acting noradrenergic agonist; or cyproheptadine. • Currently receiving or has received stiripentol in the past 21 days prior to Screening. • Currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days. • Positive result on tetrahydrocannabinol (THC) or cannabidiol (CBD) test at the Screening Visit. • A clinically significant medical condition,that would interfere with study participation, collection of study data, or pose a risk to the subject.
TREATMENT REGIMEN	• Six week baseline period to establish monthly convulsive seizure frequency (MCSF) • Two week titration period followed by a 12 week maintenance period (14 week treatment period) (n=40) or placebo (n=40)
RESULTS	The primary endpoint was the change in mean MCSF between baseline period and the treatment period in patients given fenfluramine 0.7mg/kg/day compared to placebo. Patients in the treatment group saw Median change in MCSF from baseline: treatment group= -74.9%, placebo= -19.2% ($p<0.0001$). Secondary endpoints were: • Change in mean MCSF between the baseline period and the treatment period in patients given fenfluramine 0.2mg/kg/day

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	compared to placebo (median= -42.3% in treatment group (n=39) versus -19.2% placebo (n=40) • 27 patients (68%) had at least 50% reduction in MCSF compared to 5 (12%) in placebo group (p<0.0001) • Longest seizure free interval in days: treatment group mean=32.9, median=25.0; placebo mean=10.6, median=9.5 (p=0.0001).
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN	Randomized, double-blind, placebo controlled trial compared 0.4mg/kg/day of Fintepla to placebo (n=85)
INCLUSION CRITERIA	• Subject must be male or non-pregnant, non-lactating female, age 2 to 18 years (inclusive) • Subject must have documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures are not completely controlled by current antiepileptic drugs. • Subject must be receiving a therapeutically relevant and stable dose of CLB, VP, and STP for at least 4 weeks prior to screening and are expected to remain stable throughout the study (Cohort 2 only). • Subject must be receiving a stable dose of CLB and VPA, administered twice daily, to be eligible for Dose Regimen 1 and 2 or subject must be receiving a stable dose of CLB, VPA, and STP, administered twice daily, to be eligible for Dose Regimen 3 (Cohort 1 only).
EXCLUSION CRITERIA	• Subject has a known hypersensitivity to fenfluramine or any of the excipients in the study medication. • Subject has pulmonary arterial hypertension. • Subject has a current or past history of cardiovascular or cerebrovascular disease, such as cardiac valvulopathy, myocardial infarction or stroke. • Subject has a current or recent history of anorexia nervosa, bulimia, or depression within the prior year that required medical treatment or psychological treatment for a duration greater than 1 month. • Subject has a current or past history of glaucoma. • Subject is receiving concomitant therapy with: centrally-acting anorectic agents; monoamine-oxidase inhibitors; any centrally-acting compound with clinically appreciable amount of serotonin agonist or antagonist properties, including serotonin re-uptake inhibition; triptans, atomoxetine, or other centrally-acting noradrenergic agonist; cyproheptadine, and/or CYP 2D6/3A4/2B6 inhibitors/substrates. • Subject is currently taking carbamazepine, oxcarbamazepine, eslicarbazepine, phenobarbital, or phenytoin, or has taken any of these within the past 30 days, as maintenance therapy. • Subject has a positive result on urine THC Panel or whole blood CBD at the Screening Visit.

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	• Subject has a clinically significant condition, or has had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to the Screening Visit, other than epilepsy, that would negatively impact study participation, collection of study data, or pose a risk to the subject.
TREATMENT REGIMEN	• Six week baseline period to establish monthly convulsive seizure frequency (MCSF) • Three week titration period followed by a 12 week maintenance period (15 week treatment period) (n=43) or placebo (n=44)
RESULTS	The primary endpoint was the change in mean MCSF between baseline period and the treatment period in patients given fenfluramine compared to placebo. Patients in the treatment group saw median change in MCSF from baseline: treatment group= -63.1%, placebo= -1.1% ($p<0.001$). Secondary endpoints were: • 23 patients (54%) had at least 50% reduction in MCSF compared to 2 (5%) in placebo group ($p<0.001$) • Longest seizure free interval in days: treatment group mean=29.7, median=22.0; placebo mean=13.4, median=13 ($p=0.004$).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [5]

- Hypersensitivity to fenfluramine or any of the excipients in Fintepla.
- Within 14 days of the administration of Monoamine Oxidase Inhibitors (MAOIs) due to an increased risk of serotonin syndrome.

Warnings and Precautions [5]

- **Boxed Warning: Valvular Heart Disease and Pulmonary Arterial Hypertension.** There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine and valvular heart disease and pulmonary hypertension. Echocardiogram assessments are required before, during, and after treatment with Fintepla. Fintepla is available only through a restricted program called the Fintepla REMS.
- Decreased appetite and decreased weight
- Somnolence, sedation, and lethargy
- Suicidal behavior and ideation
- Withdrawal of Fintepla should be gradual because of the risk of increased seizure frequency and status epilepticus
- Serotonin syndrome particularly with concomitant administration of other serotonergic drugs
- Increase in blood pressure, including hypertensive crisis
- Fintepla can cause mydriasis and can precipitate angle closure glaucoma

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Adverse Effects [5]

Most common, ≥ 5%	Fintepla 0.4mg/kg/day (n =43) %
Decreased appetite	49
Somnolence, sedation, lethargy	23
Diarrhea	23
Fatigue, malaise, asthenia	30
Constipation	7
Pyrexia	21
Ataxia, balance disorder, gait disturbance	7
Status epilepticus	12
Blood pressure increased	0 (reported at other dosages)
Drooling, salivary hypersecretion	2
Abnormal echocardiogram	9
Upper respiratory tract infection	7
Abnormal behavior	9
Fall	0 (reported at other dosages)
Vomiting	5
Ear infection	9
Decreased weight	7
Irritability	9
Tremor	9
Decreased blood glucose	9
Bronchitis	9

Drug Interactions [5]

- Coadministration of Fintepla with stiripentol plus clobazam, with or without valproate, increases fenfluramine plasma concentrations and decreases its metabolite, norfenfluramine, because of the inhibition of the metabolism of fenfluramine.
- Coadministration with rifampin or strong CYP1A2 and CYP2B6 inducers will decrease fenfluramine plasma concentrations, which may lower the efficacy of Fintepla.
- Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A and 5-HT2C serotonin receptor antagonists may decrease the efficacy of Fintepla.
- Concomitant administration of Fintepla and drugs (e.g., SSRIs, SNRIs, TCAs, MAOIs, 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. Concomitant use of Fintepla with MAOIs is contraindicated.

Dosage and Administration [5]

- FINTEPLA is to be administered orally and may be taken with or without food.
- The initial starting and maintenance dosage is 0.1 mg/kg twice daily, which can be increased weekly based on efficacy and tolerability. The table below provides the recommended titration schedule, if needed.
- Patients not on concomitant stiripentol who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35 mg/kg twice daily (maximum

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daily dosage of 26 mg).

- Patients taking concomitant stiripentol and clobazam who are tolerating FINTEPLA at 0.1 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2 mg/kg twice daily (maximum daily dosage of 17 mg).

Fintepla Recommended Titration Schedule*

	Without concomitant stiripentol		With concomitant stiripentol and clobazam	
	Weight-based Dosage	Maximum Total Daily Dosage	Weight-based Dosage	Maximum Total Daily Dosage
Initial Dosage	0.1mg/kg twice daily	26mg	0.1mg/kg twice daily	17mg
Day 7	0.2mg/kg twice daily	26mg	0.15mg/kg twice daily	17mg
Day 14	0.35mg/kg twice daily	26mg	0.2mg/kg twice daily	17mg

*For patients not on concomitant stiripentol in whom a more rapid titration is warranted, the dose may be increased every 4 days.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Fenfluramine	Fintepla®	Zogenix	0.1mg/kg twice daily titrated up to max maintenance dose of 0.35mg/kg twice daily (Max 26mg/day)	$1,278/30ml or $15,336/360ml bottle (30 days at max dose)

** Wholesale Acquisition Cost

Conclusion

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. The efficacy of Fintepla was demonstrated in 2 randomized, double-blind, placebo-controlled clinical trials in 206 patients. The primary efficacy endpoint was the change in mean monthly convulsive seizure frequency (MCSF) between baseline period and the treatment period in patients given fenfluramine compared to placebo. In both studies the primary endpoint was achieved ($p<0.001$). Secondary endpoints of at least a 50% reduction in MCSF and longest interval of seizure free days were also achieved ($p<0.001$ and $p=0.004$). The most common adverse reactions were decreased appetite; somnolence, sedation, lethargy; diarrhea; constipation; abnormal echocardiogram; fatigue, malaise, asthenia; ataxia, balance disorder, gait disturbance; blood pressure increased; drooling, salivary hypersecretion; pyrexia; upper respiratory tract infection; vomiting; decreased weight; fall; and status epilepticus.

Recommendation

The MO Healthnet Division recommends adding this drug to the Rare Disease - Fintepla clinical edit.

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