PDL DRUG REVIEW

Proprietary Name: Fintepla®
Common Name: fenfluramine
PDL Category: Anticonvulsants

Comparable Products	Preferred Drug List Status
Diacomit	Non-Preferred
Epidiolex	Non-Preferred with Conditions

Summary

Pharmacology/Usage: The exact mechanism of action of fenfluramine, the active ingredient of Fintepla®, is not known. Fenfluramine and its metabolite, norfenfluramine, increase extracellular levels of serotonin through interaction with serotonin transporter proteins, and exhibit agonist activity at serotonin 5HT-2 receptors.

Fintepla® is a Schedule IV controlled substance.

Indication: For the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate Phuman or animal data on the developmental risks associated with the use in pregnant women. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs, such as Fintepla®, during pregnancy. Encourage women who are taking Fintepla® during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by visiting http://www.aedpregnancyregistry.org or by calling 1-888-233-2334. The safety and efficacy of use in the pediatric population less than 2 years of age have not been established.

Dosage Form: Oral Solution: 2.2mg/ml as a clear, colorless, cherry flavored liquid.

A calibrated measuring device (either a 3ml or a 6ml oral syringe) will be provided by the pharmacy and is recommended to measure and administer the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device and should not be used.

Discard any unused oral solution remaining after 3 months of first opening the bottle or the "Discard After" date on the bottle, whichever is sooner. Fintepla® is compatible with commercially available gastric and nasogastric feeding tubes.

Recommended Dosage: Prior to starting treatment, obtain an echocardiogram assessment to evaluate for valvular heart disease and pulmonary arterial hypertension. In addition, obtain an echocardiogram assessment every 6 months during treatment and 3 to 6 months after the final dose of Fintepla®.

The initial starting and maintenance dosage is 0.1mg/kg BID, which can be increased weekly based on efficacy and tolerability. Patients not on concomitant stiripentol who are tolerating Fintepla® 0.1mg/kg BID and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.35mg/kg BID (maximum daily dosage of 26mg). For patients taking concomitant stiripentol and clobazam who are tolerating Fintepla® at 0.1mg/kg BID and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 0.2mg/kg BID (maximum daily dosage of 17mg). Refer to the prescribing information for additional information regarding the recommended titration schedule.

As with most antiepileptics, Fintepla® should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. If withdrawal is needed because of a serious adverse reaction, rapid discontinuation can be considered.

Use in patients with moderate or severe renal impairment, as well as in patients with hepatic impairment, is not recommended.

Drug Interactions: Coadministration of Fintepla® with stiripentol plus clobazam, with or without valproate, increases fenfluramine levels and decreases its metabolite, norfenfluramine, because of the inhibition of the metabolism of fenfluramine. If Fintepla® is co-administered with stiripentol plus clobazam, the maximum daily dosage of Fintepla® is 0.2mg/kg BID (maximum daily dosage of 17mg).

Coadministration with rifampin or strong CYP1A2 and CYP2B6 inducers will decrease fenfluramine levels, which may lower the efficacy of Fintepla®. Consider an increase in Fintepla® dosage when co-administered with rifampin or a strong CYP1A2 and CYP2B6 inducer; however, do not exceed the maximum daily dosage.

If cyproheptadine or potent 5-HT1A, 5-HT1D, 5-HT2A, or 5-HT2C serotonin receptor antagonists are co-administered with Fintepla®, patients should be monitored appropriately.

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. Concomitant use of Fintepla® with MAO inhibitors is contraindicated. Use Fintepla® with caution in patients taking other medications that increase serotonin.

Box Warning: Fintepla® has a box warning regarding the risk of valvular heart disease and pulmonary arterial hypertension. The warning states that there is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with Fintepla®. The benefits versus risks of initiating or continuing Fintepla® must be considered, based on echocardiogram findings. The box warning adds that because of the risks of valvular heart disease and pulmonary arterial hypertension, Fintepla® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Fintepla® REMS.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Fintepla® 0.4mg/kg/day) minus reported % incidence for placebo (pooled placebo results from two studies). Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse event included decreased appetite (41%), somnolence/sedation/lethargy (12%), abnormal echocardiogram (3%), diarrhea (17%), constipation (7%), fatigue/malaise/asthenia (25%), ataxia/balance disorder/gait disturbance (6%), abnormal behavior (9%), blood pressure increased (0%), drooling/salivary hypersecretion (2%), rash (1%), chills (2%), insomnia (3%), pyrexia (7%), decreased activity (0%), upper respiratory tract infection (0%), vomiting (0%), weight decreased (6%), croup (0%), ear infection (4%), gastroenteritis (2%), increased heart rate (0%), irritability (7%), rhinitis (5%), tremor (9%), urinary incontinence (0%), decreased blood glucose (8%), bronchitis (8%), contusion (0%), eczema (5%), enuresis (0%), fall (0%), headache (0%), laryngitis (5%), status epilepticus (10%), urinary tract infection (5%), and viral infection (4%).

Due to the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and valvular heart disease as well as pulmonary arterial hypertension, cardiac monitoring is required prior to starting

treatment, during treatment, and after treatment with Fintepla® concludes. If valvular heart disease or pulmonary arterial hypertension is observed on echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing Fintepla® treatment.

Because of the risk of valvular heart disease and pulmonary arterial hypertension with Fintepla®, as discussed in the Box Warning section, Fintepla® is available only through a restricted distribution program. Notable requirements of the Fintepla® REMS Program include

- Prescribers must enroll in the program and counsel patients about the risks of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms, the need for baseline and periodic cardiac monitoring via echocardiogram, and cardiac monitoring after Fintepla® treatment
- Patients must enroll and comply with ongoing monitoring requirement
- Pharmacies must be certified by enrolling in the program and must only dispense to patients who are authorized to receive Fintepla®
- Wholesalers and distributors must only distribute to certified pharmacies
- Further information can be obtained at www.FinteplaREMS.com or by calling 1-877-964-3649.

Fintepla® can cause decreases in appetite and weight. Given the frequency of these adverse events, the growth of pediatric patients treated with Fintepla® should be carefully monitored. Weight should be monitored regularly during treatment with Fintepla® and dose modifications should be considered if a decrease in weight is observed.

Fintepla® can cause somnolence, sedation and lethargy. Other CNS depressants, including alcohol, could potentiate these effects of Fintepla®.

Fintepla® can cause an increase in blood pressure. Monitor blood pressure in patients treated with Fintepla®.

Antiepileptic drugs (AEDs) increase the risk of suicidal thoughts or behaviors in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior.

Fintepla® can cause an increase in blood pressure. Monitor blood pressure in patients treated with Fintepla®.

Fenfluramine can cause mydriasis and can precipitate angle closure glaucoma. Consider discontinuing treatment in patients with acute decreases in visual acuity or ocular pain.

Serotonin syndrome may occur with Fintepla®, especially with concomitant administration of Fintepla® with other serotonergic drugs. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome. If serotonin syndrome is suspected, stop Fintepla® immediately and start symptomatic treatment.

Contraindications: In persons who have shown hypersensitivity to fenfluramine or any of the excipients of the product; concomitant use of, or within 14 days of the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome

Manufacturer: Zogenix

Analysis: The safety and efficacy of Fintepla® for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older were assessed in two randomized, double-blind, placebo-controlled studies. Study 1 compared a 0.7mg/kg/day and a 0.2mg/kg/day dose of Fintepla® with placebo in patients who were not receiving stiripentol. Study 2 compared a 0.4mg/kg/day dose of Fintepla® with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both.

In both studies, patients had a clinical diagnosis of Dravet syndrome and were inadequately controlled on at least one antiepileptic drug (AED) or other antiseizure treatment, including vagal nerve stimulation or a ketogenic diet. Both trials had a 6-week baseline period, during which patients were required to have a minimum of 6 convulsive seizures while on stable AED treatment. The baseline period was followed by randomization into a 2-week (study 1)

or 3-week (study 2) titration period and a subsequent 12-week maintenance period, where the Fintepla® dose remained stable.

In study 1, 98% of patients were taking between 1 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients) were valproate (61%), clobazam (59%), and topiramate (25%). In study 2, 100% of patients were taking between 2 and 4 concomitant AEDs. The most frequently used concomitant AEDs (in at least 25% of patients) were stiripentol (100%), clobazam (94%), and valproate (89%).

The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined 14-week (study 1) or 15-week (study 2) titration and maintenance periods (i.e. treatment period). The median longest interval between convulsive seizures was also assessed. Results suggested that in both studies, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of Fintepla® as compared to placebo. A reduction in convulsive seizures was observed within 3 to 4 weeks of starting Fintepla®, and the effect remained generally consistent over the treatment periods. Results can be seen in the table below, which was adapted from the prescribing information.

	Placebo	Fintepla® 0.2mg/kg/day	Fintepla® 0.7mg/kg/day	Fintepla® 0.4mg/kg/day
Study 1				
Study 1	N=39	N=38	N=40	NA
Baseline Period Median	29.4	18.1	18.7	-
% difference relative to placebo	-	-31.7%	-70%	-
p-value compared to placebo	-	0.043	<0.001	-
Study 2				
Study 2	N=42	NA	NA	N=43
Baseline Period Median	11.5	-	-	15.0
% difference relative to placebo	-	-	-	-59.5%
p-value compared to placebo	-	-	-	<0.001

In study 1, 8% (N=3/40) in the Fintepla® 0.7mg/kg/day group and 8% (N=3/38) in the Fintepla® 0.2mg/kg/day group reported no convulsive seizures during the 14-week treatment period compared to 0 patients in the placebo group (NNT=13). In study 2, 2% (N=1/43) in the Fintepla® 0.4mg/kg/day group reported no convulsive seizures during the 15-week treatment period compared to 0 in the placebo group (NNT=50).

In addition, in both studies, Fintepla® was associated with a statistically significant longer interval between convulsive seizures compared to placebo. The median longest interval between convulsive seizures was 21 days with Fintepla® 0.7mg (treatment difference minus placebo of 13 days, p<0.001) and was 13 days with Fintepla® 0.2mg/kg/day minus placebo (treatment difference minus placebo of 5 days, p=0.043). The median longest interval between convulsive seizures was 17 days with Fintepla® 0.4mg/kg/day (treatment difference minus placebo of 5 days; p=0.01).

Place in Therapy: Fintepla® is an oral solution indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. It is a Schedule IV controlled substance and it is has a box warning regarding increased risk of valvular heart disease and pulmonary arterial hypertension. Cardiac monitoring is required before, during, and after treatment. Due to these risks, Fintepla® is available only through a restricted

program under a REMS called the Fintepla® REMS. In clinical trials compared with placebo, all doses of Fintepla® assessed statistically significantly reduced convulsive seizure frequency per 28 days. Comparator studies with active treatments were not found.

It is recommended that Fintepla® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Fintepla [package insert]. Emeryville, CA: Zogenix, Inc; 2020.