Facts about FINTEPLA®

What is FINTEPLA?

FINTEPLA is an approved treatment, in the U.S., for seizures associated with Dravet syndrome in patients 2 years of age and older.[1]

FINTEPLA is available only through a restricted distribution program called the FINTEPLA REMS because of the risk of valvular heart disease and pulmonary arterial hypertension.

Impact on Seizure Reduction

The U.S. Food and Drug Administration (FDA) approved FINTEPLA based on the results of two randomized, double-blinded, placebo-controlled Phase 3 clinical trials in Dravet syndrome (Study 1 and Study 2) in patients 2 to 18 years of age.

Across multiple clinical studies, FINTEPLA demonstrated significant and sustained reduction of convulsive seizures associated with Dravet syndrome.[2,3]

Study 1 (N=117) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of FINTEPLA with placebo in patients who were not receiving stiripentol. Study 2 (N=85) compared a 0.4 mg/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 AED or other antiseizure treatment including vagal nerve stimulation or a ketogenic diet.
- The mean age was 9 years (range 2 to 19 years) and approximately 46% of patients were female and 74% were White.
- Patients had a 6-week baseline period, during which a minimum of 6 convulsive seizures were required while on stable AED therapy.
- Convulsive seizures included tonic, clonic, generalized tonic-clonic, tonic-atonic, secondarily generalized tonic-clonic, hemiclonic, and focal with observable motor signs.
- 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 dose of FINTEPLA remained stable.
- 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.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: VALVULAR HEART DISEASE AND PULMONARY ARTERIAL HYPERTENSION

- **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 available only through a restricted program called the FINTEPLA REMS.**

CONTRAINDICATIONS

FINTEPLA is contraindicated in patients with Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA and with concomitant use of, or within 14 days of, the administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome.

Please see Important Safety Information throughout and full Prescribing Information, including Boxed WARNING.

In Study 1 and Study 2, the reduction in convulsive seizure frequency per 28 days was statistically significantly greater for all dose groups of FINTEPLA compared with placebo.

Study 1 (N=117)

Patients receiving FINTEPLA (0.7 mg/kg/day, N=40) experienced a 70% greater reduction in the median monthly convulsive seizure frequency (MCSF) compared with placebo (N=39, P<0.001). Patients receiving FINTEPLA (0.2 mg/kg/day, N=38) had a 31.7% greater reduction in MCSF compared with placebo (P=0.043).

In the FINTEPLA 0.7 mg/kg/day treatment group, the median longest interval between convulsive seizures was 21 days compared with 8 days for placebo (P<0.001).

Study 2 (n=85)

Patients receiving FINTEPLA (0.4 mg/kg/day, N=43) had a 59.5% greater reduction in the median MCSF compared with placebo (N=42, P<0.001).

In the FINTEPLA 0.4 mg/kg/day treatment group, the median longest interval between convulsive seizures was 17 days compared with 12 days for placebo (P=0.01).

All 0.4 mg/kg/day patients were also taking concomitant stiripentol, which increases the exposure of FINTEPLA.

A reduction in convulsive seizures was observed within 3 to 4 weeks of starting FINTEPLA, and the effect remained generally consistent over the 14- or 15-week treatment period.

FINTEPLA Mechanism of Action

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.

Acting as an agonist at specific serotonin receptors in the brain

Dravet Syndrome

Dravet syndrome is a rare, devastating, and life-long epileptic encephalopathy that begins in infancy and is marked by frequent treatment-resistant seizures, significant developmental and motor impairments, and an elevated risk of sudden death.[4,5]

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS & PRECAUTIONS

Valvular Heart Disease and Pulmonary Arterial Hypertension (see Boxed Warning)

Because of the 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, cardiac monitoring via echocardiogram is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes. Cardiac monitoring via echocardiogram can aid in early detection of this condition. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed valvular heart disease or pulmonary arterial hypertension.

FINTEPLA Dosing

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. 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 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).

See the full Prescribing Information for complete dosing instructions.

About the FINTEPLA REMS Program

The goal of the FINTEPLA Risk Evaluation and Mitigation Strategy (REMS) program is to mitigate the risk of valvular heart disease and pulmonary arterial hypertension associated with FINTEPLA, by ensuring that:

- Prescribers must be certified by enrolling in the FINTEPLA REMS program.
- Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment.
- Patients must enroll in the REMS program and comply with ongoing monitoring requirements.
- The pharmacy must be certified by enrolling in the REMS program and must only dispense to patients who are authorized to receive FINTEPLA.
- Wholesalers and distributers must only distribute to certified pharmacies.

Further information is available at www.FinteplaREMS.com or by telephone at **1-877-964-3649**.

IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS & PRECAUTIONS

Monitoring

Prior to starting treatment, patients must undergo an echocardiogram to evaluate for valvular heart disease and pulmonary arterial hypertension. Echocardiograms should be repeated every 6 months, and once at 3–6 months post-treatment with FINTEPLA.

If valvular heart disease or pulmonary arterial hypertension is observed on an echocardiogram, the prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA.

FINTEPLA REMS PROGRAM (SEE BOXED WARNING)

FINTEPLA is available only through a restricted distribution program called the FINTEPLA Risk Evaluation and Management Strategy (REMS) Program. Prescribers must be certified by enrolling in the FINTEPLA REMS. Prescribers must counsel patients receiving FINTEPLA about the risk of valvular heart disease and pulmonary arterial hypertension, how to recognize signs and symptoms of valvular heart disease and pulmonary arterial hypertension, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during FINTEPLA treatment, and cardiac monitoring after FINTEPLA treatment. Patients must enroll in the FINTEPLA REMS and comply with ongoing monitoring requirements. The pharmacy must be certified by enrolling in the FINTEPLA REMS and must only dispense to patients who are authorized to receive FINTEPLA. Wholesalers and distributors must only distribute to certified pharmacies. Further information is available at www.FinteplaREMS.com or by telephone at **1-877-964-3649**.

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IMPORTANT SAFETY INFORMATION (CONT.)

WARNINGS & PRECAUTIONS

Decreased Appetite and Decreased Weight

FINTEPLA can cause decreases in appetite and weight. Decreases in weight appear to be dose related. Most patients resumed the expected measured increases in weight by the end of the open-label extension study. Weight should be monitored regularly during treatment with FINTEPLA and dose modifications should be considered if a decrease in weight is observed.

Somnolence, Sedation, and Lethargy

FINTEPLA can cause somnolence, sedation, and lethargy. Other central nervous system (CNS) depressants, including alcohol, could potentiate these effects of FINTEPLA. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA to gauge whether it adversely affects their ability to drive or operate machinery.

Suicidal Behavior and Ideation

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.

Anyone considering prescribing FINTEPLA or any other AED must balance the risk of suicidal thoughts or behaviors with the risks of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviors. Should suicidal thoughts and behaviors emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Withdrawal of Antiepileptic Drugs

As with most AEDs, 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.

Serotonin Syndrome

Serotonin syndrome, a potentially life-threatening condition, may occur with FINTEPLA, particularly during concomitant administration of FINTEPLA with other serotonergic drugs, including, but not limited to, selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, dietary supplements (eg, St. John's Wort, tryptophan), drugs that impair metabolism of serotonin (including monoamine oxidase inhibitors [MAOIs], which are contraindicated with FINTEPLA), dextromethorphan, lithium, tramadol, and antipsychotics with serotonergic agonist activity. Patients should be monitored for the emergence of signs and symptoms of serotonin syndrome, which include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (eg, hyperreflexia, incoordination), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If serotonin syndrome is suspected, treatment with FINTEPLA should be stopped immediately, and symptomatic treatment should be started.

Increase in Blood Pressure

FINTEPLA can cause an increase in blood pressure. Significant elevation in blood pressure, including hypertensive crisis, has been reported rarely in adult patients treated with fenfluramine, including patients without a history of hypertension. Monitor blood pressure in patients treated with FINTEPLA. In clinical trials of up to 3 years in duration, no patient receiving FINTEPLA developed hypertensive crisis.

Glaucoma

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

IMPORTANT SAFETY INFORMATION (CONT.)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and greater than placebo) 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; status epilepticus.

DRUG INTERACTIONS

Strong CYP1A2 and CYP2B6 Inducers: Coadministration with rifampin or a strong CYP1A2 and CYP2B6 inducer will decrease fenfluramine plasma concentrations.

Consider an increase in FINTEPLA dosage when coadministered with rifampin or a strong CYP1A2 and CYP2B6 inducer.

USE IN SPECIFIC POPULATIONS

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

REFERENCES

1. Zogenix. 2020. FINTEPLA: Highlights of Prescribing Information. Emeryville, CA. Author.
2. Lagae L, Sullivan J, Knupp K, et al. Fenfluramine Hydrochloride for the Treatment of Seizures in Dravet Syndrome: A Randomised, Double-blind, Placebo-controlled Trial. Lancet. 2020 Dec 21;394(10216):2243-2254. https://www.ncbi.nlm.nih.gov/pubmed/31862249.
3. Nabbout R, Mistry A, Zuberi S, et al. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2019 Dec 2. https://www.ncbi.nlm.nih.gov/pubmed/31790543.
4. Dravet C. The Core Dravet Syndrome Phenotype. Epilepsia. 2011;52(suppl 2):3-9. https://www.ncbi.nlm.nih.gov/pubmed/21463272.
5. Dravet C. Dravet Syndrome History. Dev Med Child Neurol. 2011;53(suppl 2):1-6. https://www.ncbi.nlm.nih.gov/pubmed/21504424.

ZOGENIX

Please see Important Safety Information throughout and full Prescribing Information, including Boxed WARNING and Medication Guide.