

Echocardiogram Assessment for FINTEPLA® (fenfluramine) oral solution, CIV

This patient has been referred to you as part of a Risk Evaluation and Mitigation Strategy (REMS) program for FINTEPLA, a treatment for seizures associated with Dravet syndrome. Because of the association between serotonergic drugs with 5-HT_{2B} receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes.¹

An echocardiogram can identify evidence of valvular heart disease or pulmonary arterial hypertension prior to a patient becoming symptomatic.¹

See full Important Safety Information, including Boxed Warning, on the back of this page.

WHAT IS DRAVET SYNDROME?

Dravet syndrome is a rare, devastating, and life-long form of epilepsy that begins in infancy and is associated with frequent treatment-resistant seizures, long-term disability, and a high risk of premature mortality.^{2,3} Most patients follow a course of developmental delay with cognitive, motor, and behavioral deficits that persist into adulthood.^{2,4,5}

CARDIOVASCULAR (CV) SAFETY MONITORING PROGRAM FOR FINTEPLA

If valvular heart disease and/or pulmonary arterial hypertension is observed on an echocardiogram, the benefits versus the risks of initiating or continuing treatment with FINTEPLA will be considered by the patient's physician.¹

In clinical trials of FINTEPLA for the treatment of Dravet syndrome, no cases of valvular heart disease or pulmonary hypertension were reported. Across clinical trials of FINTEPLA for the treatment of Dravet syndrome, 0.4-1.6% of patients taking FINTEPLA were found to have trace aortic or mitral regurgitation compared with 0-6% of patients taking placebo. Trace aortic or mitral regurgitation is considered a physiologic or normal finding in the absence of valvular abnormalities.¹

CONSIDERATIONS FOR ECHOCARDIOGRAPHY TECHNICIANS WHEN EVALUATING PEDIATRIC PATIENTS FOR POTENTIAL VALVULAR HEART DISEASE.

In order to ensure consistency of echocardiogram evaluations over time, the following echocardiogram settings were used during the FINTEPLA clinical development program:

- Imaging was done in 2 planes; apical 4 chamber for the aortic, mitral, and tricuspid valves, parasternal long axis for all 4 valves, and parasternal short axis for the pulmonary valve^{6,7}
 - In each view, the imaging plane was moved through the plane of coaptation to capture the vena contracta and jet length if regurgitation is present⁸
- A minimum of 3-5 consecutive cardiac cycles was required and excessive transducer movement was avoided while capturing optimized images in each cycle⁹
- Transducer frequency was optimized to obtain the best image quality while also choosing appropriate presets for the color Doppler.^{6,9} Multiple imaging transducers, ranging from low frequency (2-2.5 MHz) to high frequency (7.5 MHz or higher), were available¹⁰
- Depth settings were optimized for each individual patient. Sector width was reduced to annulus width and sector depth to length of regurgitant jet chamber^{7,9}
- Nyquist settings were 60-80 cm/sec⁹
- Blood pressure was recorded before and after echocardiogram^{7,9}

For more information about Dravet syndrome or FINTEPLA, or to see full Prescribing Information, including Boxed Warning, please visit FinteplaHCP.com.

See full Important Safety Information, including Boxed Warning, on the back of this page.

References: 1. FINTEPLA [prescribing information]. Emeryville, CA: Zogenix, Inc; 2020. 2. Aras LM et al. *Epilepsy Behav.* 2015;44:104-109. 3. Cooper MS et al. *Epilepsy Res.* 2016;128:43-47. 4. Chiron C et al. *Epilepsia.* 2018;59(9):1705-1717. 5. O'Reilly H et al. *Epilepsia.* 2018;59(12):2240-2248. 6. Tissot C et al. *Front Pediatr.* 2017;5:235. 7. Mitchell C et al. *J Am Soc Echocardiogr.* 2018;32(1):1-64. 8. Zoghbi WA et al. *J Am Soc Echocardiogr.* 2017;30(4):303-371. 9. Data on File, Zogenix, Inc. 10. Lai WW et al. *J Am Soc Echocardiogr.* 2006;19(12):1413-1430.

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

BOXED WARNING: VALVULAR HEART DISEASE and PULMONARY ARTERIAL HYPERTENSION

- **There is an association between serotonergic drugs with 5-HT_{2B} 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.

WARNINGS AND PRECAUTIONS

Valvular Heart Disease and Pulmonary Arterial Hypertension (see Boxed Warning): Because of the association between serotonergic drugs with 5-HT_{2B} 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.

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 Mitigation 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.

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.

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.

Please see full Prescribing Information, including Boxed Warning, for additional important information on FINTEPLA.