Echocardiogram Assessment for FINTEPLA

Fintepla® (fenfluramine) CIV 2.2 mg/mL oral solution

The patient's healthcare provider wants to prescribe or continue FINTEPLA® (fenfluramine) oral solution, CIV, because the patient is experiencing seizures associated with Dravet syndrome or Lennox-Gastaut syndrome (LGS).

Dravet syndrome and LGS are rare, severe, potentially catastrophic, developmental epileptic encephalopathies, characterized by drug-refractory seizures and multiple morbidities that evolve over the patient's lifetime. Mortality due to sudden unexpected death in epilepsy (SUDEP) and status epilepticus is a major concern. Dravet syndrome and LGS are difficult-to-treat and life-threatening conditions that have far-reaching effects beyond seizures. These may include issues with severe cognitive impairment and learning difficulties, behavioral and conduct problems, and inattention/hyperactivity symptoms.[1-3]

Q: Why has this patient been referred for an echocardiogram?

A: Because of the risk of valvular heart disease and pulmonary arterial hypertension, cardiac monitoring is required prior to starting treatment, during treatment, and after treatment with FINTEPLA concludes.

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.**

Cardiac monitoring can identify evidence of valvular heart disease and pulmonary arterial hypertension prior to a patient becoming symptomatic, aiding in early detection of these conditions.

Q: How many cases of valvular heart disease or pulmonary arterial hypertension have been seen in patients treated with FINTEPLA?

A: No cases of valvular heart disease or pulmonary arterial hypertension have been seen in over 1500 patients treated with FINTEPLA in clinical trials and in the US registry, some for up to 5 years[4,*]

*Includes patients from Dravet syndrome and LGS clinical trials and all patients on the commercial drug in the US as of February 2022.

Important information for the echocardiogram

Please include the following in your report, as these are requirements of the REMS Program:

☑ Degree of Valve Regurgitation as Measured by Echocardiogram

Valve	Absent/Trace	Mild	Moderate	Severe
Aortic				
Mitral				

☑ Pulmonary arterial hypertension as indicated by elevated right heart/pulmonary artery pressure (pulmonary arterial systolic pressure >35 mm Hg)

☑ Any other valvular abnormality such as valve thickening or restrictive valve motion

Considerations for echocardiography technicians when evaluating PEDIATRIC patients for potential valvular heart disease

To ensure consistency of pediatric echocardiogram evaluations over time, the following echocardiogram settings were used during the FINTEPLA clinical development program:

- A minimum of 3-5 consecutive cardiac cycles was required, and excessive transducer movement was avoided while capturing optimized images in each cycle[4]
- Transducer frequency was optimized to obtain the best image quality while also choosing appropriate presets for the color Doppler.[4,5] Multiple imaging transducers, ranging from low frequency (2-2.5 MHz) to high frequency (7.5 MHz or higher), were available[6]
- Nyquist settings were 60-80 cm/sec[4]
- Blood pressure was recorded before and after echocardiogram[4,7]

Please see additional Important Safety Information on back and full Prescribing Information, including Boxed Warning.

References: 1. Chin RF, Mingorance A, Ruban-Fell B, et al. Treatment guidelines for rare, early-onset, treatment-resistant epileptic conditions: a literature review on Dravet syndrome, Lennox-Gastaut syndrome and CDKL5 defi ciency disorder. *Front Neurol.* 2021;12:734612. doi:10.3389/ fneur.2021.734612; **2.** Mastrangelo M. Lennox-Gastaut syndrome: a state of the art review. *Neuropediatrics.* 2017;48(3):143-151. doi:10.1055/s-0037-1601324; **3.** Knupp KG, Scarbro S, Wilkening G, Juarez-Colunga E, Kempe A, Dempsey A. Parental perception of comorbidities in children with Dravet syndrome. *Pediatr Neurol.* 2017;76:60-65. doi:10.1016/j.pediatrneurol.2017.06.008; **4.** Data on file. Zogenix Inc; **5.** Tissot C, Muehlethaler V, Sekarski N. Basics of functional echocardiography in children and neonates. *Front Pediatr.* 2017;5:235. doi:10.3389/fped.2017.00235; **6.** Lai WW, Geva T, Shirali GS, et al; Task Force of Pediatric Council of American Society of Echocardiography; Pediatric Council of American Society of Echocardiography. Guidelines and standards for performance of a pediatric echocardiogram: a report from the Task Force of the Pediatric Council of the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2006;19(12):1413-1430. doi:10.1016/j.echo.2006.09.001; **7.** Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr.* 2019;32(1):1-64. doi:10.1016/j.echo.2018.06.004

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INDICATIONS AND USAGE

FINTEPLA is indicated for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) 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-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, 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: Because of the association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine (the active ingredient in FINTEPLA), and valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), 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 these conditions. In clinical trials for DS and LGS of up to 3 years in duration, no patient receiving FINTEPLA developed VHD or PAH.

Monitoring: Prior to starting treatment, patients must undergo an echocardiogram to evaluate for VHD and PAH. Echocardiograms should be repeated every 6 months, and once at 3-6 months post treatment with FINTEPLA.

The prescriber must consider the benefits versus the risks of initiating or continuing treatment with FINTEPLA if any of the following signs are observed via echocardiogram: valvular abnormality or new abnormality; VHD indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (eg, valve thickening or restrictive valve motion); PAH indicated by elevated right heart/pulmonary artery pressure (PASP >35 mm Hg).

FINTEPLA REMS Program: 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, the need for baseline (pretreatment) and periodic cardiac monitoring via echocardiogram during treatment, and cardiac monitoring after 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. Weight should be monitored regularly, and dose modifications should be considered if weight decreases.

Somnolence, Sedation, and Lethargy: FINTEPLA can cause somnolence, sedation, and lethargy. Other central nervous system (CNS) depressants,

Warnings and Precautions (cont.)

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), including FINTEPLA, increase the risk of suicidal thoughts or behaviors in patients. Patients treated with an AED 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 must balance the risk of suicidal thoughts or behaviors with the risks of untreated illness. Epilepsy is associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviors.

Withdrawal of Antiepileptic Drugs: FINTEPLA should 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. Rare cases of significant elevation in blood pressure, including hypertensive crisis, have been reported in adult patients treated with fenfluramine, including patients without a history of hypertension. In clinical trials for DS and LGS of up to 3 years in duration, no pediatric or adult patient receiving FINTEPLA developed hypertensive crisis. Monitor blood pressure in patients treated with FINTEPLA.

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 observed in DS studies 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.

The most common adverse reactions observed in the LGS study were diarrhea; decreased appetite; fatigue; somnolence; vomiting.

To report SUSPECTED ADVERSE REACTIONS, contact Zogenix Inc. at 1-866-964-3649 (1-866-Zogenix) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information, including Boxed Warning, for additional Important Safety Information on FINTEPLA.

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