RXADVANCE
2 Park Central Drive
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NEW DRUG APPROVAL

Brand Name	FINTEPLA®
Generic Name	fenfluramine
Drug Manufacturer	Zogenix, Inc

New Drug Approval

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

FDA Approval Date: June 25, 2020

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Dravet syndrome is a rare childhood-onset epilepsy marked by frequent debilitating seizures, lifelong developmental and motor impairments, and an increased risk of sudden death. Despite existing therapies, there remains a great unmet need in Dravet syndrome to reduce convulsive seizures that can lead to medical emergencies, hospitalizations, and SUDEP (sudden unexpected death in epilepsy). The severity and unpredictability of the disease, coupled with around-the-clock concern for the diagnosed child's well-being, can present significant emotional and logistical challenges for all members of the family.

More than 80% of patients with Dravet syndrome have a mutation in the SCN1A gene, but not all SCN1A mutations lead to Dravet syndrome. DS is considered an epileptic encephalopathy, or disorder of the brain due to seizures.

Dravet syndrome affects an estimated 1:15,700 individuals in the U.S., or 0.0064% of the population. Approximately 80-90% of those, or 1:20,900 individuals, have both an SCN1A mutation and a clinical diagnosis of DS. This represents an estimated 0.17% of all epilepsies.

Efficacy

The effectiveness of FINTEPLA® for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older was established in two randomized, double-blind, placebo controlled trials in patients 2 to 18 years of age.

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 (NCT02682927 and NCT02826863).

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 (NCT02926898).

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. 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 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 14- or 15-week treatment period.

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In Study 1, 3 of 40 (8%) patients in the FINTEPLA® 0.7 mg/kg/day group and 3 of 38 (8%) patients in the FINTEPLA® 0.2 mg/kg/day group reported no convulsive seizures during the 14-week treatment period, compared to 0 patients in the placebo group.

In Study 2, 1 of 43 (2%) patients in the FINTEPLA® 0.4 mg/kg/day group reported no convulsive seizures during the 15-week treatment period, compared to 0 patients in the placebo group.

In Study 1 and Study 2, FINTEPLA® was associated with a statistically significant longer interval between convulsive seizures compared to placebo.

Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

- Decreased Appetite and Decreased Weight: Advise patients that FINTEPLA® can cause decreased appetite and decreased weight.
- Somnolence, Sedation, and Lethargy: Monitor for somnolence and sedation. Advise patients not to drive or operate machinery until they have gained sufficient experience on FINTEPLA®
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts.
- Withdrawal of Antiepileptic Drugs: FINTEPLA® should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus.
- Serotonin Syndrome: Advise patients that serotonin syndrome is a potentially life-threatening condition and may occur with FINTEPLA, particularly with concomitant administration of FINTEPLA with other serotonergic drugs
- Increase in Blood Pressure: Monitor blood pressure during treatment.
- Glaucoma: Discontinue therapy in patients with acute decrease in visual acuity or ocular pain.

CONTRAINDICATIONS

- Hypersensitivity to fenfluramine or any of the excipients in FINTEPLA ®
- Within 14 days of the administration of monoamine oxidase inhibitors due to an increased risk of serotonin syndrome

Clinical Pharmacology

MECHANISMS 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.

Dose & Administration

ADULTS

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Dosage recommendations for patient not receiving concomitant stiripentol: Oral: Initial: 0.1 mg/kg twice daily; may increase based on response and tolerability after 7 days to 0.2 mg/kg twice daily; may further increase based on response and tolerability after 7 days to 0.35 mg/kg twice daily. Maximum dose: 26 mg/day.

PEDIATRICS

- 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: The maximum daily maintenance dosage of FINTEPLA is 0.35 mg/kg twice daily (maximum daily dosage of 26 mg).
- Patients taking concomitant stiripentol plus clobazam: The maximum daily maintenance dosage of FINTEPLA for patients taking these medications is 0.2 mg/kg twice daily (maximum daily dosage of 17 mg).

GERIATRICS

Clinical studies of FINTEPLA for the treatment of Dravet syndrome did not include patients

65 years of age and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

RENAL IMPAIRMENT

Administration of FINTEPLA® to patients with moderate or severe renal impairment is not recommended.

HEPATIC IMPAIRMENT

Administration of FINTEPLA® to patients with hepatic impairment is not recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral solution: 2.2 mg/mL fenfluramine