FINTEPLA® (fenfluramine), oral solution, CIV

Indication: For the treatment of seizures associated with Dravet syndrome (DS) in patients 2 years of age and older. DS is a rare and severe form of epileptic and developmental encephalopathy that is highly refractory to existing anticonvulsant therapy.

Formulation: Oral (base) solution, 2.2 mg/ml, to be administered via a pharmacy provided calibrated oral syringe.

Dosing Information: 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 every 4-7 days 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).

Boxed Warning: 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.

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. FINTEPLA has also been shown to have a positive modulatory effect on the sigma-1 receptor which has been linked to anti-seizure effects and shown to improve cognitive function of spatial and contextual learning in preclinical models.

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 (RCTs)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. 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. At baseline, patients were documented as having 1 – 1.5 convulsive seizures per day; and in Study 1, 44% were on ≥ 3 antiseizure medications versus 98% in Study 2.

- In Study 1 and Study 2, the reduction in monthly convulsive seizure frequency (MCSF) was statistically significantly greater for all dose groups of FINTEPLA compared to placebo
    - Study 1: Difference Relative to Placebo: -31.7% (0.2 mg/kg/d) and -70.0% (0.7 mg/kg/d)
    - Study 2: Difference Relative to Placebo: -59.5% (0.4 mg/kg/d)
- A profound seizure reduction (≥75%) was observed in 58% of patients in study 1 and 40% in study 2
    - NNT 50% Reduction in MCSF = 1.8-2.0
    - NNT 75% Reduction in MCSF = 2.1-3.1
- In Study 1 and Study 2, FINTEPLA was associated with a statistically significant longer interval between convulsive seizures compared to placebo

Eligible patients in the RCTs continued into an Open Label Extension Study (OLE). An interim analysis of 330 FINTEPLA patients, (445 days, range: 7 – 899; 60% exposed to FINTEPLA for ≥ 12 months) showed:

- Magnitude of effect in RCTs maintained over entire OLE with a median change in seizure frequency of 63%
- Additionally, 64% of patients experienced a ≥ 50% reduction in MCSF and 41% experienced a ≥ 75% reduction in MCSF.
- Reduction in MCSF was associated with improvement in overall executive function
    - Patients who had profound reduction in MCSF (≥75%) were significantly more likely to show clinically meaningful improvements in overall executive function than patients who had minimal reduction in MCSF (<25%)

Safety: The most common adverse reactions that occurred in patients treated with FINTEPLA (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. Valvular heart disease and pulmonary arterial hypertension were evaluated in the placebo controlled and open-label extension studies via echocardiography for up to 3 years in duration. No patient developed echocardiographic findings consistent with either valvular heart disease or pulmonary arterial hypertension in the placebo-controlled studies or during the open-label extension study of up to 3 years in duration.