# New Drug Fact Blast

## Clinical Services

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| **Drug/Manufacturer:** | **Fintepla ® (fenfluramine) [Zogenix, Inc.]** |
| **Dosage Formulations:** | 2.2 mg/ml fenfluramine as a clear, colorless, cherry flavored oral solution |
| **FDA Approval Date:**<br>**FDB File Date:** | FDA: June 25, 2020<br>FDB: July 12, 2020 |
| **Indication:** | For the treatment of seizures associated with Dravet syndrome in patients aged ≥ 2 years |
| **Mechanism of Action:** | Fenfluramine and the metabolite, norfenfluramine, increase extracellular levels of serotonin through interaction with serotonin transporter proteins, and exhibit agonist activity at serotonin 5-HT2 receptors. How this exerts a therapeutic effect in the treatment of seizures associated with Dravet syndrome is unknown. |
| **Dose/ Administration:** | • Initial starting and maintenance dose is 0.1 mg/kg twice daily administered orally with or without food<br>• Recommended Titration Schedule: |

| | Without concomitant stiripentol* | | With concomitant stiripentol & clobazam | |
|---|---|---|---|---|
| | **Weight-based Dosage** | **Max Total Daily Dosage** | **Weight-based Dosage** | **Max Total Daily Dosage** |
| **Initial Dose** | 0.1 mg/kg BID | 26 mg | 0.1 mg/kg BID | 17 mg |
| **Day 7** | 0.2 mg/kg BID | | 0.15 mg/kg BID | |
| **Day 14** | 0.35 mg/kg BID | | 0.2 mg/kg BID | |

*for patients not on concomitant stiripentol in whom a more rapid titration is warranted, the dose may be increased every 4 days

- Any unused solution should be discarded 3 months after the first opening of the bottle
- Available only through the Fintepla REMS program and dispensed exclusively by the Zogenix Central pharmacy partner Anovo Rx
- Compatible with gastric and nasogastric feeding tubes

**Drug Clinical Highlights:**

- Fintepla is a reformulation of fenfluramine, an anorectic agent removed from the market in 1997 for increased risk of valvular heart disease when prescribed in higher doses (60 – 120 mg/day) and often combined with phentermine
- FDA granted Priority Review and Orphan Drug designation
- Effectiveness of Fintepla for the treatment of seizures associated with Dravet syndrome was established in 2 randomized, double-blind, placebo-controlled trials
  - Study 1: compared 0.7 mg/kg/day and 0.2 mg/kg/day of Fintepla to placebo
    - Participants aged 2 - 18 years on stable antiepileptic therapy with at least 4 convulsive seizures in a 4 week period
    - Exclusion criteria included treatment with stiripentol or cannabidiol
    - 6 week baseline period to establish monthly convulsive seizure frequency (MCSF)
    - 2 week titration period followed by a 12 week maintenance period (14 week treatment period)
    - Primary endpoint: change in mean MCSF between the baseline period and the treatment period in patients given fenfluramine 0.7 mg/kg/day compared to placebo
    - Key secondary endpoints:
      - change in mean MCSF between the baseline period and the treatment period in patients given fenfluramine 0.2 mg/kg/day compared to placebo
      - proportion of patients who achieved ≥ 50% reduction in mean MCSF from baseline
      - longest seizure-free interval in each treatment group

| Study 1 | Fenfluramine 0.7 mg/kg/day (n=40) | Fenfluramine 0.2 mg/kg/day (n=39) | Placebo (n=40) |
|---|---|---|---|
| **Change in MCSF from placebo** | -62.3% p<0.0001 | -32.4% p=0.0209 | - |
| **Patients with at least 50% reduction in MCSF** | 27 (68%) p<0.0001 | 15 (38%) p=0.0091 | 5 (12%) |
| **Longest seizure free interval, days** | Mean: 32.9 Median: 25.0 p=0.0001 | Mean: 26.0 Median: 15 p=0.0352 | Mean: 10.6 Median: 9.5 |
| **Median change in MCSF from baseline** | -74.9% p<0.0001 | -42.3% p=0.2035 | -19.2% |

- Study 2: compared 0.4 mg/kg/day of Fintepla to placebo
  - Participants aged 2 - 18 years on stable, stiripentol inclusive antiepileptic therapy (plus valproate or clobazam at minimum)
  - Exclusion criteria included treatment with cannabidiol
  - 6 week baseline period to establish MCSF
  - 3 week titration period followed by a 12 week maintenance period (15 week treatment period)
  - Primary endpoint: change in mean MCSF between the baseline period and the treatment period in patients given fenfluramine compared to placebo
  - Key secondary endpoints:
    - proportion of patients who achieved ≥ 50% reduction in mean MCSF from baseline
    - longest seizure-free interval in each treatment group

| Study 2 | Fenfluramine 0.4 mg/kg/day (n=43) | Placebo (n=44) |
|---|---|---|
| **Change in MCSF from placebo** | -54% p<0.001 | - |
| **Patients with at least 50% reduction in MCSF** | 23 (54%) p<0.001 | 2 (5%) |
| **Longest seizure free interval, days** | Mean: 29.7 Median: 22.0 p=0.004 | Mean: 13.4 Median: 13.0 |
| **Median change in MCSF from baseline** | -63.1% p<0.001 | -1.1% |

- Contraindicated with concomitant use or within 14 days of monoamine oxidase inhibitors (MAOIs) due to an increased risk of serotonin syndrome
- Warnings:
  - Valvular heart disease and pulmonary arterial hypertension:
    - Boxed Warning
    - Due to an association of disease with serotonergic drugs with 5-HT2B receptor agonist activity (such as fenfluramine)
    - Echocardiogram required before treatment, every 6 months during treatment, and 3 - 6 months after the final dose of treatment
    - Only available through the Fintepla REMS program
    - In clinical trials of up to 3 years duration, no patients developed valvular heart disease or pulmonary arterial hypertension
  - Decreased appetite and weight – the growth of pediatric patients on Fintepla should be carefully monitored and dose modified if a decrease in weight is observed
  - Somnolence, sedation, and lethargy
  - Suicidal behavior and ideation
  - Withdrawal of antiepileptics – Fintepla should be gradually withdrawn to minimize risk for increased seizure frequency and status epilepticus
  - Serotonin syndrome

- Increase in blood pressure
- Glaucoma – may cause mydriasis and precipitate angle closure glaucoma, discontinue in patients with acute decrease in visual acuity or ocular pain

- Adverse reactions (incidence ≥ 10% and greater than placebo):

| | Study 1 | | Study 2 | Combined placebo group |
|---|---|---|---|---|
| | 0.2 mg/kg/day N=39 | 0.7 mg/kg/day N=40 | 0.4 mg/kg/day* N=43 | N=84 |
| **Decreased appetite** | 23% | 38% | 49% | 8% |
| **Somnolence, sedation, lethargy** | 26% | 25% | 23% | 11% |
| **Abnormal echocardiogram**** | 18% | 23% | 9% | 6% |
| **Diarrhea** | 31% | 15% | 23% | 6% |
| **Constipation** | 3% | 10% | 7% | 0% |
| **Fatigue, malaise, asthenia** | 15% | 10% | 30% | 5% |
| **Ataxia, balance disorder, gait disturbance** | 10% | 10% | 7% | 1% |
| **Blood pressure increased** | 13% | 8% | 0% | 5% |
| **Drooling, salivary hypersecretion** | 13% | 8% | 2% | 0% |
| **Pyrexia** | 15% | 5% | 21% | 14% |
| **Upper respiratory tract infection** | 21% | 5% | 7% | 10% |
| **Vomiting** | 10% | 5% | 5% | 8% |
| **Weight decreased** | 13% | 5% | 7% | 1% |
| **Fall** | 10% | 0% | 0% | 4% |
| **Status epilepticus** | 3% | 0% | 12% | 2% |

*Patients on the 0.4 mg/kg/day dose were also taking concomitant stiripentol
**Consisted of trace and mild mitral regurgitation and trace aortic regurgitation (considered physiologic)

- Drug Interactions:
  - Dose adjustment is required for patients taking stiripentol
  - Rifampin or strong CYP1A2 and CYP2B6 inducers – consider dosage increase but do not exceed the maximum daily dose
  - Cyproheptadine and potent 5-HT1A, 5-HT1D, 5-HT2A, and 5-HT2C serotonin receptor antagonists may decrease efficacy – monitor appropriately
  - Concomitant administration with serotonergic drugs may increase risk of serotonin syndrome
- Not recommended in patients with moderate to severe renal impairment
- Not recommended in patients with hepatic impairment
- Schedule IV controlled substance

**Disease State Clinical Highlights:**

- Dravet syndrome (formerly known as severe myoclonic epilepsy of infancy) is a genetic epilepsy which appears during the first year of life in otherwise healthy infants as a prolonged seizure with fever. As the condition progresses, other types of seizures typically occur, as well as developmental delays and features of autism spectrum disorder.
- It is estimated that 1 in 20,000 to 1 in 40,000 people have Dravet syndrome and 3-8% of children who experience their first seizure by 12 months of age may have Dravet syndrome.
- Approximately 80% of children with Dravet syndrome have a pathogenic variant in the *SCN1A* gene.
- Approximately 45% of Dravet syndrome patients have more than 3 tonic-clonic seizures per month despite therapy with multiple antiepileptic drugs.
- Dravet syndrome patients have a 15-20% mortality rate due to SUDEP (Sudden Unexpected Death in Epilepsy), prolonged seizures, seizure-related accidents such as drowning, and infections.

**Price Per Unit (WAC):**

$42.60 per ml
$15,336.00 per 360 ml bottle (30 day supply at the max dose of 26 mg per day)

**Therapeutic Alternatives:**

- Three agents, each with different mechanisms of action, are now FDA approved for Dravet syndrome: Epidiolex® (cannabidiol), Diacomit® (stiripentol), and Fintepla (fenfluramine).
- Prior to the FDA approval of the above agents, the 2017 North American Consensus Panel recommendations for the management of Dravet syndrome found clobazam and valproic acid to be optimal first-line therapies
  - Topiramate and stiripentol (which must be used concomitantly with clobazam) are considered second line therapy
  - A ketogenic diet was also found to be moderately effective and considered second line therapy

| | Mechanism of Action | Dose | Cost of therapy per month (WAC) |
|---|---|---|---|
| **Cannabidiol** (Epidiolex) | Unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors but increases the excitability of inhibitory neurons and decreases the excitability of excitatory neurons without changing the activity of sodium channels. | 10 mg/kg/day | 20 kg pt = $786.00<br>40 kg pt = $1,572.00<br>60 kg pt = $2,358.00 |
| | | 20 mg/kg/day | 20 kg pt = $1,572.00<br>40 kg pt = $2,358.00<br>60 kg pt = $4,716.00 |
| **Stiripentol** (Diacomit) | There are several possible MOAs including various effects on the $GABA_A$ receptor and novel inhibition of lactate dehydrogenase. Indirectly, stiripentol also inhibits cytochrome P450 activity which increases blood concentrations of other antiepileptics including clobazam. | 50 mg/kg/day | 20 kg pt = $3,000.00<br>40 kg pt = $6,000.00<br>60 kg pt = $9,000.00 |
| **Fenfluramine** (Fintepla) | Unknown. Fenfluramine and its metabolite, norfenfluramine, increase extracellular concentrations of serotonin through interaction with serotonin transporter proteins and exhibit agonist activity at serotonin 5-HT2 receptors. | 0.7 mg/kg/day | 20 kg pt = $8,132.72<br>40 kg pt* = $15,336.00<br>60 kg pt*= $15,336.00 |

*Maximum daily dose of 26 mg/day is reached when patient weight reaches 37.2 kg

- Fintepla will directly compete with Epidiolex for the treatment of Dravet syndrome in patients who have not had an adequate response to other first and second line therapies. Although these agents have not been directly compared in clinical trials, a comparison of results from pivotal clinical trials is below:

| | % reduction in monthly convulsive seizures from baseline | % of patients with ≥ 50% reduction in monthly seizures | % of patients with ≥ 75% reduction in monthly seizures |
|---|---|---|---|
| **Fintepla (0.7 mg/kg/day)** | 74.9% | 70% | 57.5% |
| **Epidiolex (20 mg/kg/day)** | 39% | 43% | 23% |

**Prior Authorization Approval Criteria:**

**Must meet the following criteria:**

Initial Therapy:

- Participant aged 2 years or older **AND**
- Prescribed by or in consultation with a neurologist or other specialist in the treated disease state **AND**
- Documented diagnosis of Dravet syndrome in the past year **AND**
- Documented trial of valproate (defined as 30 days in the past year) **AND**

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|---|---|
| | • Documented trial of clobazam (defined as 30 days in the past year) **AND**<br>• Documented trial of Epidiolex (defined as 30 days in the past year) **AND**<br>• Documented trial of Diacomit (defined as 30 days in the past year) **AND**<br>• Dose does not exceed maximum daily limits:<br>  ○ With concomitant stiripentol: 17 mg per day<br>  ○ Without concomitant stiripentol: 26 mg per day<br>• Documentation of the following:<br>  ○ Baseline seizure frequency and duration **AND**<br>  ○ Baseline echocardiogram **AND**<br>  ○ Baseline measure of participant's weight **AND**<br>• Lack of MAOI therapy in the past 30 days<br>• Lack of moderate to severe renal impairment<br>• Lack of hepatic impairment<br>• Initial approval of prior authorization is 6 months<br><br><u>Continuation of Therapy:</u><br>• Documentation of the following required for prior authorization renewal:<br>  ○ Documentation of decrease in the frequency and duration of seizures **AND**<br>  ○ Documentation of echocardiogram at least every 6 months **AND**<br>  ○ Documentation of participant's current weight for demonstration of appropriate dosing within maximum daily limits and lack of inappropriate weight loss for age |
| **Implication to State Medicaid Program:** | • LOE: 6/26/2027<br>• Fintepla is in Phase III trials for other seizure disorders:<br>  ○ Epileptic encephalopathy<br>  ○ Sunflower Syndrome<br>  ○ Lennox-Gastaut syndrome (LGS)<br>  ▪ Phase III results released in February 2020 for LGS<br>  ▪ Primary endpoint: median percent change in monthly frequency of drop seizures<br>  ▪ Patients taking Fintepla 0.7 mg/kg/day achieved a median reduction of 26.5% vs 7.8% in the placebo group<br>  ▪ Epidiolex showed a 44% reduction in monthly drop seizures in its trial for LGS<br>• Fintepla is also currently being studied in combination with cannabidiol for Dravet Syndrome (Phase I) and Lennox-Gastaut syndrome (Phase II) |

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