fenfluramine (Fintepla®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO203

Description

Fenfluramine (Fintepla) is an orally administered amphetamine derivative serotonin 5HT-2 receptor agonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
fenfluramine (Fintepla)	Dravet Syndrome	2.2 mg/ml solution	360 ml/30 days Monthly quantity (in mL) to allow for a maximum of 26 mg (12 mL) per day
	Lennox-Gastaut Syndrome		

**The maximum daily dose differs with concomitant stiripentol and clobazam with a maximum daily dose of 17 mg (7.7mL) per day.*

Initial Evaluation

I. **Fenfluramine (Fintepla)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of baseline seizure frequency and severity**; AND**
   D. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
   E. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex); **AND**
   F. A diagnosis of one of the following:
      1. **Dravet syndrome; AND**:
         i. <u>All</u> of the following have been ineffective, not tolerated or are contraindicated (‡ Please note: These agents may be subject to prior authorization and may require an additional review):
            a. valproate
            b. clobazam
            c. cannabidiol (Epidiolex)‡

d. stiripentol (Diacomit)‡; **OR**

2. **Lennox-Gastaut Syndrome**; **AND**

i. Two of the following have been ineffective, not tolerated or all are contraindicated (‡ Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):

a. valproate
b. lamotrigine
c. rufinamide‡
d. clobazam
e. felbamate
f. topiramate**; AND**

ii. Treatment with cannabidiol (Epidiolex)‡ has been ineffective, not tolerated or contraindicated

II. Fenfluramine (Fintepla) is considered investigational when used for all other conditions, including but not limited to:

A. Epileptic encephalopathies associated with SCN1A mutations
B. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome
C. Use in combination with cannabidiol (Epidiolex)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex)**; AND**
IV. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
V. Provider attests member has exhibited improvement or stability of disease symptoms (e.g., reduction in seizure frequency).

Supporting Evidence

I. Fenfluramine (Fintepla) is FDA-approved for use in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) for patients aged two years and older. Fenfluramine was originally introduced as a weight-loss agent at higher doses and was pulled from the market due to reports of cardiovascular adverse events (i.e., valvular heart disease and pulmonary arterial hypertension). Given the serious adverse safety profile of fenfluramine (Fintepla), and lack of evaluation in patients under two years of age, use outside of the FDA-approved two years of age and older is not recommended.

II. Both Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are associated with treatment-resistant seizures of multiple types, neurodevelopmental delay, and profound cognitive impairment. Despite the use of numerous antiseizure medications (ASMs) in these conditions, ASMs tend to have limited efficacy. Due to these conditions being treatment refractory, high-touch care and monitoring required, fenfluramine (Fintepla) must be prescribed by, or in consultation with a neurologist.

III. Fenfluramine (Fintepla) may be used as monotherapy, concomitantly with stiripentol (Diacomit), or concomitantly as triple-therapy with stiripentol (Diacomit) and clobazam (in DS). However, concomitant use with cannabidiol (Epidiolex) has not been studied in DS nor LGS. The efficacy and safety of fenfluramine (Fintepla) used in combination with cannabidiol (Epidiolex) remains unknown.

IV. **Dravet syndrome:**

- Dravet syndrome is a rare pediatric genetic epilepsy syndrome characterized by refractory epilepsy and neurodevelopmental problems starting in infancy. Dravet syndrome is commonly misdiagnosed as other conditions such as cerebral palsy, Lennox-Gastaut syndrome, or vaccine encephalopathy.
- Fenfluramine (Fintepla) was studied in two randomized, double-blind, placebo-controlled Phase 3 trials in 206 patients aged two to 18 years with Dravet syndrome, where convulsive seizures were not completely controlled by current AED therapy.
- Trial one (Lagae L, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multicohort, multi-country trial that studied 119 patients ages two to 18 years, who had at least four convulsive seizures in a four-week period for the past 12 weeks prior to screening and were stable for at least four weeks prior to screening and throughout the trial on valproate, clobazam, topiramate, or levetiracetam. This trial excluded patients who were on concomitant stiripentol (Diacomit) therapy. Patients were randomized 1:1:1 to either fenfluramine (Fintepla) 0.7 mg/kg/day, fenfluramine (Fintepla) 0.2 mg/kg/day, or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 40.3 per 28 days and a mean baseline of 2.4 concomitant AEDs. The primary efficacy outcome was the reduction in mean monthly convulsive seizure frequency (MCSF) over the 14-week treatment period with fenfluramine (Fintepla)

0.7 mg/kg/day versus placebo. A key secondary endpoint was the reduction in MCSF over the 14-week treatment period with fenfluramine 0.2 mg/kg/day versus placebo. The primary end point result was a 62.3% (95% Cl -47.7 to -72.8) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine 0.7 mg/kg/day versus placebo (p<0.0001). The key secondary endpoint result was a 32.4% (95% Cl -6.2 to -51.3) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine (Fintepla) 0.2 mg/kg/day versus placebo (p=0.0209).

- Trial two (Nabbout R, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multi-country trial that studied 87 patients ages two to 18 years, who were receiving concomitant stiripentol (Diacomit), valproate, clobazam, levetiracetam, or topiramate, and who had a stable baseline with six or more convulsive seizures during the six-week baseline, with two or more seizures in the first three weeks and two or more seizures in the second three weeks. Less than 10% of the subjects were reported to have received one of the following concomitant AED's: acetazolamide, clonazepam, diazepam, ethosuximide, felbamate, gamma-aminobutyric acid, lorazepam, phenobarbital, pregabalin, or zonisamide. Patients were randomized 1:1 to either fenfluramine (Fintepla) 0.4 mg/kg/day or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 14 versus 10.7 in the fenfluramine (Fintepla) versus placebo arm. The primary efficacy outcome was the difference between fenfluramine (Fintepla) and placebo on the change in mean MCSF from baseline to the 15-week combined titration and maintenance (T+M) periods. A key secondary endpoint was the proportion achieving 50% or greater reduction from baseline levels in MCSF. The primary endpoint was 54% (95% CI, 35.6%-67.2%) achieved greater reduction in mean MCSF between the baseline and T + M periods with fenfluramine versus placebo (p<0.001). Results of the key secondary endpoint of reduction in mean MCSF in the fenfluramine group, 23 of 43 (54%) versus the placebo group, two of 44 (5%) (p <0.001).
- The NICE guidelines for Dravet syndrome, recommend valproate as first-line therapy, then clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) as second-line therapy. These guidelines have not been updated to include fenfluramine (Fintepla). In addition to these guidelines, the international consensus on diagnosis and treatment of Dravet syndrome recommend first-line treatment with valproate, second-line with stiripentol (Diacomit), clobazam, or fenfluramine (Fintepla), and third-line with cannabidiol (Epidiolex).
- Based on the established safety, efficacy, and cost effectiveness of valproate, clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) relative to fenfluramine

(Fintepla), trial of two generics, cannabidiol (Epidiolex), and stiripentol (Diacomit) is required before approval of fenfluramine (Fintepla).

V. **Lennox-Gastaut syndrome:**

- Lennox-Gastaut syndrome is associated with severe seizures in childhood that typically present before eight years of age. There are a variety of causes including cortical malformations, tumors, neurocutaneous syndromes (i.e., tuberous sclerosis complex), encephalopathies, meningitis, and head injuries.
- Fenfluramine (Fintepla) was studied in a Phase 3 randomized, double-blind, placebo-controlled trial in 263 patients aged two to 35 years with Lennox-Gastaut syndrome who were using stable antiseizure regimens. Patients were eligible to enroll if they had: onset of seizures at age 11 years or younger, multiple seizure types including tonic or atonic, stable 4-week seizure baseline with 2 or more drop seizures per week, abnormal cognitive development, and medication history showing electroencephalogram evidence of abnormal background activity with slow spike-and-wave pattern. The trial excluded patients with degenerative neurological disease, history of hemiclonic seizures in the first year of life, only drop seizure clusters, and previous or current cardiovascular abnormalities. Patients were randomized 1:1:1 into fenfluramine (Fintepla) 0.7 mg/kg/day, 0.2 mg/kg/day or placebo stratified by weight less than 37.5 kg or greater than 37.5. The population characteristics included: median age of 13 years (range 2-35 years), median drop seizure frequency per 28 days 85 in 0.7 mg/kg/day, 83 in 0.2 mg/kg/day, and 53 in placebo. A mean previous antiseizure medication use of 7-8 medications. Concomitant seizure medications >20% included valproate, clobazam, lamotrigine, rufinamide and levetiracetam. The primary efficacy outcome was the percentage change from baseline in drop seizure frequency for patients in the 0.7 mg/kg/day compared to placebo. The secondary efficacy endpoints were percentage change from baseline in frequency of drop seizures in the 0.2 mg/kg/day group, a 50% or greater response rate, and the proportion of patients who achieved improvement on the Clinical Global Impressions-Improvement (CGI-I) scale. The study met the primary efficacy endpoint, patients who received 0.7 mg/kg/day achieved a statistically significant median difference in drop seizure frequency of -19.9% (95% CI, -31 to -8.7, P=.001) compared to placebo. The study achieved statistically significant results in the secondary endpoint of 50% or greater reduction in drop seizure frequency, with 25% (P=.02) achieving greater than 50% reduction in the 0.7 mg/kg/day and 28% (P=.005) in the 0.2 mg/kg/day groups compared to 10% in placebo. Additionally, 26% (P=.001) of patients in 0.7 mg/kg/day group had a clinically meaningful improvement in CGI-I of much improved or very much improved compared to 20% in the 0.2 mg/kg/day group and 6% in placebo.
- The American Epilepsy Society guidelines for Lennox-Gastaut syndrome, recommend use of lamotrigine, topiramate, felbamate with clobazam, and rufinamide as add-on therapy, they do not make recommendations for sequential therapy. The NICE guidelines for LGS recommend use of valproate as well as

lamotrigine, cannabidiol (Epidiolex), clobazam, rufinamide, topiramate, and felbamate (though not licensed for use in the UK).

- Based on the established safety, efficacy, and cost effectiveness of valproate, lamotrigine, rufinamide**,** clobazam, felbamate, topiramate, and cannabidiol (Epidiolex) relative to fenfluramine (Fintepla), trial of two generic agents and cannabidiol (Epidiolex) is required before approval of fenfluramine (Fintepla).

VI. Fenfluramine (Fintepla) is a Schedule IV controlled substance that is only available through a restricted program called the Fintepla REMS. Fenfluramine (Fintepla) carries a black-box warning for valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). Echocardiogram assessments are required before, during, and after treatment with fenfluramine (Fintepla).

Investigational or Not Medically Necessary Uses

I. Fenfluramine (Fintepla) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome

Appendix

I. Table 1: fenfluramine (Fintepla) Recommended Titration Schedule

	Without concomitant stiripentol		**With concomitant stiripentol and clobazam**	
	Weight-based Dosage	**Maximum Total Daily Dosage**	**Weight-based Dosage**	**Maximum Total Daily Dosage**
Initial Dosage	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

References

1. Fintepla [Prescribing Information]. Zogenix, Inc: Emeryville, CA. March 2022.
2. Andrade DM, Nascimento FA, Nordli DR et al. (2020). Dravet syndrome: management and prognosis. UpToDate. Retrieved July 20, 2020, from: https://www-uptodate-com.liboff.ohsu.edu/contents/dravet-syndrome-management-and-prognosis
3. Sullivan J, Knupp K, Wirrell E et al. (2018). Dravet syndrome. National Organization for Rare Disorders. Retrieved July 22, 2020, from: https://rarediseases.org/rare-diseases/dravet-syndrome-spectrum/

4. (2014). Dravet syndrome. Orphanet. Retrieved July 22, 2020, from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33069&lng=EN
5. Shafer PO, Kiriakopoulos E, Wirrell E (2019). Dravet syndrome. Epilepsy Foundation. Retrieved July 22, 2020, from: https://www.epilepsy.com/learn/types-epilepsy-syndromes/dravet-syndrome
6. Wirrel EC, Laux L, Donner E et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. Pediatric Neurology 2017;68:18-34. Available from: https://www.pedneur.com/article/S0887-8994(16)31037-2/pdf
7. Lagae L, Sullivan J, Knupp K et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet 2020;394(10216):2243-2254. Available from: https://pubmed-ncbi-nlm-nih-gov.liboff.ohsu.edu/31862249/
8. Nabbout R, Mistry A, Zuberi S et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. JAMA Neurol 2019;77(3):300-308. Available from: https://pubmed-ncbi-nlm-nih-gov.liboff.ohsu.edu/31790543/
9. Wilfong A, Nordli DR et al. (2022). Epilepsy syndrome in children. UpToDate. Retrieved June 17,2022, from: https://www.uptodate.com/contents/epilepsy-syndromes-in-children
10. Lennox-gastaut syndrome. NORD (National Organization for Rare Disorders).
11. Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with lennox-gastaut syndrome: a randomized clinical trial. JAMA Neurol. Published online May 2, 2022.
12. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8(1):82-93.
13. Wirrell EC, Hood V, Knupp KG, et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. Published online May 12, 2022:epi.17274.
14. 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 deficiency disorder. Front Neurol. 2021;0.
15. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs: treatment-resistant epilepsy: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology and the american epilepsy society. Neurology. 2018;91(2):82-90.
16. National Instituite for Health and Care Excellence. Fenfluramine for treating seizures associated with dravet syndrome. Nice.org.uk. July 8, 2022. Accessed July 25, 2022. https://www.nice.org.uk/guidance/ta808

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
cannabidiol (Epidiolex)	Lennox-Gastaut syndrome Dravet syndrome Tuberous Sclerosis Complex
stiripentol (Diacomit)	Dravet syndrome
vigabatrin (Sabril, Vigadrone)	Refractory complex partial epileptic seizure, adjunct therapy West syndrome (infantile spasms)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication (Lennox-Gastaut syndrome), added weight-based dosing to QL for Dravet syndrome, updated initial and renewal evaluation criteria (Dravet syndrome), updated supporting evidence, added related policies table.	08/2022
Policy created	11/2020