Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCNEU036.0824	**NEUROMUSCULAR DRUGS** **FINTEPLA®** (fenfluramine HCl oral solution)
Effective Date: 10/1/2024	**Review/Revised Date**: 07/21, 06/22, 07/22, 06/23, 06/24 (MTW)
Original Effective Date: 01/21	**P&T Committee Meeting Date**: 10/20, 08/21, 06/22, 08/22, 08/23, 08/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:
For New Starts:
1. Documentation that patient has one of the following:
    a. seizures associated with Dravet syndrome (DS)
    b. seizures associated with Lennox-Gastaut syndrome (LGS)
2. For Commercial: Documented trial, failure, intolerance, or contraindication to two of the following:
    a. For DS: clobazam, valproate/valproic acid, or topiramate
    b. For LGS: lamotrigine, valproate/valproic acid, topiramate, or rufinamide
3. For Medicaid: Documentation of uncontrolled seizures, intolerance, or contraindication to treatment with one of the following:
    a. For DS: clobazam, valproate/valproic acid, or topiramate
    b. For LGS: lamotrigine, valproate/valproic acid, topiramate, or rufinamide
4. Documentation that it will be used as adjunctive therapy with other antiepileptic drugs
5. Baseline echocardiogram has been performed within the past six months

For Patients Established on therapy:
1. Documentation of positive response to therapy such as a decrease in seizure frequency or intensity since beginning therapy

2. Documentation that patient is using as adjunctive therapy and has been adherent to all antiseizure medications
3. Echocardiogram has been performed within the past six months

EXCLUSION CRITERIA:
Concomitant use of, or within 14 days of administration of monoamine oxidase inhibitors because of an increased risk of serotonin syndrome

AGE RESTRICTIONS:
Must be two years of age or older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a neurologist.

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

QUANTITY LIMIT:
Fenfluramine (Fintepla®) 2.2 mg/mL solution: 12 mL per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Fintepla (fenfluramine HCl) is approved for use for a rare, severe form of childhood-onset epilepsy, called Dravet syndrome (DS). The mechanism by which Fintepla works is unknown but believed to increase extracellular levels of serotonin by interacting with serotonin transporter proteins and agonist activity at serotonin 5HT-2 receptors.

FDA APPROVED INDICATIONS:
Treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients two years of age and older

POSITION STATEMENT:
Dravet Syndrome (DS) and Lennox-Gastaut syndrome (LGS) are rare and severe forms of childhood-onset epilepsy. Both are associated with significant morbidity and high rates of early mortality. Diagnosis of DS typical clinical features include multiple seizure such as clonic or hemiclonic seizures, and seizures induced by heat or light. Genetic testing for an SCN1A mutation or an EEG can help confirm diagnosis. For diagnosis of LGS, a clinical triad consisting of having multiple seizures of different types, a distinctive EEG-brain wave pattern (slow [1.5 to 2.5 Hz] spike-and-wave pattern) and some degree of cognitive impairment and behavioral abnormalities are necessary.

Most patients with DS and LGS require multiple seizure medications and the majority are resistant to currently approved anti-epileptic drugs. The National Institute for Health and Care Excellence (NICE) Guidelines recommend sodium valproate monotherapy as first-line treatment in children with Dravet Syndrome. If first-line treatments are ineffective or not tolerated, triple therapy with stiripentol and clobazam as first-line add-on therapy should be considered. If triple therapy is unsuccessful for Dravet syndrome and the child is over two years old, the guidelines recommend cannabidiol in combination with clobazam as a second-line add-on treatment. NICE recommends reassessing therapy every six months. These recommendations are based on subgroup analysis of controlled studies. Fenfluramine is only recommended as an add-on to other antiseizure medications for people two years and older in Dravet syndrome only if: seizures have not been controlled after trying two or more antiseizure medicines and the frequency of convulsive seizures is checked every six months, and fenfluramine is stopped if it has not fallen by at least 30% compared with the six months before starting treatment.

For LGS, the National Institute for Health and Care Excellence (NICE) Guidelines recommends sodium valproate as first-line treatment. Lamotrigine is considered second-line monotherapy or add-on treatment. If second-line treatment is unsuccessful, the guidelines recommend the following as third-line add-on treatment options: cannabidiol in combination with clobazam if the child is over two years old, clobazam, rufinamide, or topiramate.

The safety and efficacy of fenfluramine in DS was demonstrated in two randomized, double-blind, placebo controlled trials composed of patients two to 18 years of age with a clinical diagnosis of DS. There is low to moderate quality evidence based on

the two trials that fenfluramine at doses of 0.7 mg/kg/day and 0.4 mg/kg/day (with the 0.4 mg/kg/day patients taking concurrent antiepileptic drug [AED] regimens) resulted in a statistically significant change in convulsive seizure frequency per 28 days of -62.3% and 54%, respectively, when compared to placebo.

The first trial included 119 individuals who were inadequately controlled on at least one AED or other anti-seizure treatment including vagal nerve stimulation or a ketogenic diet. Patients were randomized in a 1:1:1 fashion to fenfluramine 0.7 mg/kg/day (n=40), fenfluramine 0.2 mg/kg/day (n=39), or placebo (n=40). Fenfluramine was limited to a maximum of 26 mg per day. Upon enrollment, patients underwent a 2-week dose titration period followed by a 12-week maintenance treatment period. The primary endpoint was change from baseline in the frequency of convulsive seizures per 28 days in the 0.7 mg/kg/day group versus placebo. The estimated difference from placebo for the fenfluramine 0.7 mg/kg/day arm for change in convulsive seizure frequency per 28 days was -62.3% ($p<0.001$). Most common adverse events (occurring in at least 10% of patients and more frequently in the fenfluramine groups) were: decreased appetite, diarrhea, fatigue, lethargy, somnolence, and decreased weight. No signs of pulmonary arterial hypertension were observed in the trial.

The second trial included patients with DS with seizures that were poorly controlled with current AED regimens, which had to include stiripentol plus clobazam or valproic acid. Patients (N=87) were randomized to receive fenfluramine 0.4 mg/kg/day (n=43) or placebo (n=42). Fenfluramine was limited to a maximum dose of 17 mg per day. Upon enrollment, patients underwent a 3-week dose titration period followed by a 12-week maintenance treatment period. The primary endpoint was change in mean monthly convulsive seizure frequency between fenfluramine and placebo during the combined titration and maintenance periods relative to baseline. The primary endpoint, estimated difference from placebo in convulsive seizure frequency per 28 days for fenfluramine at 0.4 mg/kg/day was 54% ($p<0.001$). Most common adverse events in the fenfluramine group included decreased appetite, pyrexia, fatigue, and diarrhea with three patients discontinuing the treatment due to treatment-emergent adverse events. No cases of valvular heart disease or pulmonary arterial hypertension were observed.

The effectiveness of fenfluramine for the treatment of seizures associated with LGS in patients two years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients two to 35 years of age. Patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. Patients were randomized to 0.7 mg/kg/day and 0.2 mg/kg/day of Fintepla® and placebo. The primary efficacy endpoint was the median percent change from baseline in the frequency of drop

seizures per 28 days during the combined 14-week titration and maintenance periods. The median percent change form baseline in the frequency of drop seizures per 28 days was significantly greater for the 0.7 mg/kg/day dose group of Fintepla compared with placebo.

According to the package insert, echocardiogram assessment are required before, during, and after treatment with fenfluramine. Based on the findings, the benefits versus the risks of initiating or continuing therapy must be considered.

REFERENCE/RESOURCES:

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