PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY POLICY – 5.01.649

Pharmacologic Treatment of Seizures

Effective Date:	Mar. 1, 2025	RELATED MEDICAL POLICIES:	
Last Revised:	Feb. 11, 2025	5.01.521	Pharmacologic Treatment of Neuropathy, Fibromyalgia, and Seizure Disorders
Replaces:	N/A	5.01.561	Repository Corticotropin Injection

Select a hyperlink below to be directed to that section.

Clicking this icon returns you to the hyperlinks menu above.

Introduction

Seizures are waves of abnormal electrical activity in the brain that can make you move or behave strangely or cause you to pass out. Most seizures last only a few seconds or minutes. Epilepsy is a condition that causes people to have repeated seizures but not everyone who has had a seizure has epilepsy. Problems such as low blood sugar, an infection, or brain injury can cause seizures. There are also many types of seizures such as generalized seizures that affect large areas of the brain and focal seizures that originate in a specific part of the brain. Treatment depends on the type of seizure, age, and other factors and may include drugs, diet, surgery, and devices. This policy describes when drugs used to treat seizures may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Aptiom (eslicarbazepine)	**Aptiom (eslicarbazepine) may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 4 years and older **AND** • Has tried and failed two generic anti-seizure medications **AND** • The dose is at least 1,600 mg per day
Banzel (rufinamide)	**Banzel (rufinamide) may be considered medically necessary for the treatment of seizures associated with Lennox-Gastaut syndrome when all the following criteria are met:** • The individual is aged 1 year and older **AND** • For Banzel (rufinamide) oral suspension, the individual has tried generic rufinamide oral suspension and had an inadequate response or intolerance to generic rufinamide oral suspension
Briviact (brivaracetam)	**Briviact (brivaracetam) may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 1 month and older **AND** • Has tried and failed two generic anti-seizure medications **AND** • The dose is at least 200 mg per day
Diacomit (stiripentol)	**Diacomit (stiripentol) may be considered medically necessary for the treatment of seizures associated with Dravet syndrome when all the following criteria are met:** • The individual is aged 6 months and older **AND** • Taking clobazam
Epidiolex (cannabidiol)	**Epidiolex (cannabidiol) may be considered medically necessary for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex when all the following criteria are met:** • The individual is aged 1 year and older **AND**

Drug	Medical Necessity
	• Has tried and failed at least one generic anti-seizure medication **AND** • The dose is at least 20 mg/kg/day for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome **OR** • The dose is at least 25 mg/kg/day for seizures associated with tuberous sclerosis complex
Fintepla (fenfluramine)	**Fintepla (fenfluramine) may be considered medically necessary for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome when all the following criteria are met:** • The individual is aged 2 years and older **AND** • Has tried four anti-seizure medications **AND** • The maximum total daily dose is at least 26 mg without concomitant Diacomit (stiripentol) **OR** • The maximum total daily dose is at least 17 mg with concomitant clobazam plus Diacomit (stiripentol)
Fycompa (perampanel)	**Fycompa (perampanel) may be considered medically necessary for:** • The treatment of one of the following: ○ Partial-onset seizures in individuals aged 4 years and older **OR** ○ Generalized tonic-clonic seizures in individuals aged 12 years and older **AND** • The individual has tried and failed two generic anti-seizure medications **AND** • The dose is at least 12 mg per day
Libervant (diazepam)	**Libervant (diazepam) may be considered medically necessary for the acute treatment of intermittent episodes of frequent seizure activity when all the following are met:** • The individual is aged 2 to 5 years

Drug	Medical Necessity
	AND • The quantity is limited to 10 films per 30 days

Motpoly XR (lacosamide extended-release)	**Motpoly XR (lacosamide extended-release) may be considered medically necessary for the following:**
	• The treatment of one of the following:
	  ○ Partial-onset seizures in individuals weighing at least 50 kg
	OR
	  ○ Primary generalized tonic-clonic seizures in individuals weighing at least 50 kg
	AND
	• The individual has tried generic lacosamide first and had an inadequate response or intolerance to generic lacosamide
	AND
	• Has tried and failed at least one additional generic anti-seizure medication
	AND
	• The dose is at least 400 mg per day

Generic oxcarbazepine extended-release	**Generic oxcarbazepine extended-release may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 6 years and older **AND** • Has tried generic oxcarbazepine and had an inadequate response or intolerance to generic oxcarbazepine **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 2,400 mg per day
Oxtellar XR (oxcarbazepine extended-release)	**Oxtellar XR (oxcarbazepine extended-release) may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 6 years and older **AND** • Has tried generic oxcarbazepine and had an inadequate response or intolerance to generic oxcarbazepine **AND**

Drug	Medical Necessity
	• Has tried generic oxcarbazepine extended release and had an inadequate response or intolerance to generic oxcarbazepine extended release **AND** • The dose is at least 2,400 mg per day
• **Qudexy XR (topiramate extended-release capsules)** • **Brand topiramate extended-release capsules**	**Qudexy XR (topiramate extended-release capsules) and brand topiramate extended-release capsules may be considered medically necessary for the treatment of partial-onset, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome when all the following criteria are met:** • The individual is aged 2 years and older **AND** • Has tried generic topiramate first and had an inadequate response or intolerance to generic topiramate **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 400 mg per day **Qudexy XR (topiramate extended-release capsules) and brand topiramate extended-release capsules may be considered medically necessary for the preventive treatment of migraines when all the following criteria are met:** • The individual is aged 12 years or older **AND** • Has tried generic topiramate first and had an inadequate response or intolerance to generic topiramate **AND** • The dose is at least 100 mg per day
Generic rufinamide	**Generic rufinamide may be considered medically necessary for the treatment of seizures associated with Lennox-Gastaut syndrome when:** • The individual is aged 1 year and older
Sabril (vigabatrin)	**Sabril (vigabatrin) may be considered medically necessary for:** • The treatment of one of the following:

Drug	Medical Necessity
	○ Refractory complex partial seizures as adjunctive therapy in individuals aged 2 years and older who have responded inadequately to greater than or equal to 3 alternative treatments **OR** ○ Monotherapy for pediatric individuals with infantile spasms 1 month to 2 years of age **AND** • The individual has tried generic vigabatrin, Vigpoder (vigabatrin), or Vigadrone (vigabatrin) first and had an inadequate response or intolerance to generic vigabatrin, Vigpoder, or Vigadrone (documentation required)
Spritam (levetiracetam tablets for oral suspension)	**Spritam (levetiracetam tablets for oral suspension) may be considered medically necessary for:** • The treatment of one of the following: ○ Partial onset seizures in individuals aged 4 years and older **OR** ○ Myoclonic seizures in individuals aged 12 years and older **OR** ○ Primary generalized tonic-clonic seizures in individuals aged 6 years and older **AND** • The individual has tried generic levetiracetam tablet or levetiracetam solution first and had an inadequate response or intolerance to generic levetiracetam tablet or levetiracetam solution **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 3,000 mg per day
Sympazan (clobazam oral film)	**Sympazan (clobazam oral film) may be considered medically necessary for the treatment of seizures associated with Lennox-Gastaut syndrome when all the following criteria are met:** • The individual is aged 2 years and older **AND**

Drug	Medical Necessity
	• Has tried generic clobazam tablet or clobazam suspension first and had an inadequate response or intolerance to generic clobazam tablet or clobazam suspension **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 40 mg per day
Trokendi XR (topiramate extended-release capsules)	**Trokendi XR (topiramate extended-release capsules) may be considered medically necessary for the treatment of partial-onset, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome when all the following criteria are met:** • The individual is aged 6 years and older **AND** • Has tried generic topiramate first and had an inadequate response or intolerance to generic topiramate **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 400 mg per day **Trokendi XR (topiramate extended-release capsules) may be considered medically necessary for the preventive treatment of migraines when the following criteria are met:** • The individual is aged 12 years or older **AND** • Has tried generic topiramate first and had an inadequate response or intolerance to generic topiramate **AND** • The dose is at least 100 mg per day
• **Vigabatrin, generic** • **Generic Vigadrone (vigabatrin), generic** • **Generic Vigpoder (vigabatrin)**	**Generic vigabatrin, Vigadrone (vigabatrin), and Vigpoder (vigabatrin) may be considered medically necessary for the following:** • Refractory complex partial seizures as adjunctive therapy in individuals aged 2 years and older who have responded

Drug	Medical Necessity
	inadequately to greater than or equal to 3 alternative treatments **OR** • Monotherapy for pediatric individuals with infantile spasms 1 month to 2 years of age
Vigafyde (vigabatrin)	**Vigafyde (vigabatrin) may be considered medically necessary for the treatment of infantile spasms when all the following criteria are met:** • The individual is aged 1 month to 2 years **AND** • Has tried generic vigabatrin, Vigpoder (vigabatrin), or Vigadrone (vigabatrin) first and had an inadequate response or intolerance to generic vigabatrin, Vigpoder, or Vigadrone (documentation required) **AND** • Vigafyde (vigabatrin) will be used as monotherapy **Initial authorization may be approved for up to 1 year. Re-authorization may be approved for up to 1 year and requires documentation of continued clinical response.**
Vimpat (lacosamide)	**Vimpat (lacosamide) may be considered medically necessary for:** • The treatment of one of the following: ○ Partial-onset seizures in individuals aged 1 month and older **OR** ○ Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in individuals aged 4 years and older **AND** • The individual has tried generic lacosamide first and had an inadequate response or intolerance to generic lacosamide **AND** • Has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 400 mg per day

Drug	Medical Necessity
Xcopri (cenobamate)	**Xcopri (cenobamate) may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 18 years and older **AND** • Has tried and failed two generic anticonvulsants
Zonisade (zonisamide oral suspension)	**Zonisade (zonisamide oral suspension) may be considered medically necessary for the treatment of partial-onset seizures when all the following criteria are met:** • The individual is aged 16 years and older **AND** • Has tried generic zonisamide capsules first and had an inadequate response or intolerance to generic zonisamide capsules **OR** • Documentation is provided that the oral suspension is clinically necessary (e.g., trouble swallowing, etc.) **AND** • The individual has tried and failed at least one additional generic anti-seizure medication **AND** • The dose is at least 600 mg per day
Ztalmy (ganaxolone)	**Ztalmy (ganaxolone) may be considered medically necessary for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) when all the following criteria are met:** • The individual is aged 2 years and older **AND** • Has tried and failed two generic anticonvulsants **AND** • The dose is at least 1,800 mg per day (taken as 600 mg three times daily) **AND** • Prescribed by or in consultation with a neurologist

Drug	Medical Necessity
	Initial authorization may be approved for up to 1 year. Re-authorization may be approved for up to 3 years and requires documentation of continued clinical response.

Drug	Investigational
As listed	Use of the drugs for conditions not listed in this policy are considered investigational. The drugs listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.

Length of Approval	
Approval	**Criteria**
Initial authorization	Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months. All other reviews for all drugs listed in policy, unless noted otherwise for specific drugs under the medical necessity criteria, may be approved up to 3 years.
Re-authorization criteria	Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy. All other reviews for re-authorization of all drugs listed in policy, unless noted otherwise for specific drugs under the medical necessity criteria, may be approved up to 3 years as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.

Documentation Requirements

The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:

- Office visit notes that contain the diagnosis, relevant history, physical evaluation and medication history

Coding

N/A

Related Information

Consideration of Age

Ages stated in this policy for which the drugs are considered medically necessary are based on the FDA labeling for the drug.

Benefit Application

The drugs in this policy are managed through the pharmacy benefit.

Evidence Review

Background

Epilepsy is defined as two or more unprovoked seizures >24 hours apart, a single seizure if the risk of recurrence is >60% in 10 years, or a diagnosis of an epilepsy syndrome. The International League Against Epilepsy (ILAE) classification of epilepsy is based on the seizure type (onset), epilepsy type, and syndrome (if present). Seizure type includes focal (partial), generalized, and unknown seizures. Epilepsy type includes focal, generalized, combined focal/generalized, and

unknown. Focal seizures can be further subdivided based on 1) awareness or impairment during the seizure and 2) motor vs non-motor dominant symptoms.

The incidence of epilepsy is 50 per 100,000 persons per year and the prevalence is 4-12 per 1,000 persons. The self-reported prevalence of epilepsy in the United States (US) is 1.2-2.2%. Partial seizures constitute 66% of seizures in adults. Approximately one-third of patients with newly diagnosed epilepsy remain uncontrolled despite therapy with anti-epileptic drugs. This figure has remained unchanged over the past 30 years.

Causes of epilepsy are varied including genetic, structural, metabolic, and infectious factors among others. A seizure involves abnormal excessive or synchronous neuronal activity in the brain and is associated with an imbalance in excitatory and inhibitory activity. Partial seizures begin with activation in a specific area of the cortex, although secondary generalization may occur. In contrast, generalized seizures include diffuse cortical activation at seizure onset.

Summary of Evidence

Fintepla (fenfluramine)

Dravet syndrome has an incidence of 1 per 22,000. Seizures typically begin at approximately 6 months of age. Development and electroencephalograms (EEGs) are often normal until 1-2 years of age. As development slows at ages ≥1-2 years, pyramidal signs and ataxia often develop, and poor cognitive and behavioral outcomes occur. Seizures initially begin with prolonged fever and may include tonic clonic and unilateral clonic seizures. Prolonged seizures requiring emergency room or hospital care often occur with Dravet syndrome, more commonly in younger patients. Premature mortality occurs in 21% of patients. Common causes of death are sudden unexplained death in epilepsy (SUDEP) (49%) and status epilepticus (32%). The mean age of death is 8.7 years. Approximately 80%-85% of patients with Dravet syndrome have a heterozygous loss-of-function mutation of the sodium channel α-1 subunit gene (SCN1A) which codes for the α-1 subunit of the neuronal, voltage-gated sodium channel. It is hypothesized that physical and cognitive development in patients with Dravet syndrome are impacted by the effects of the SCN1A mutation in addition to the seizures themselves.

Fenfluramine causes rapid release of serotonin and inhibition of serotonin reuptake. Animal studies have found increases in central nervous system serotonin inhibit seizures. Fenfluramine is a racemic mixture; the d-isomer promotes serotonin-mediated neurotransmission and is more selective for the central serotonergic system. The l-enantiomer suppresses dopaminergic

transmission. Fenfluramine may also modulate the sigma 1 receptor, a protein which has neuromodulator effects on serotonergic and glutamatergic synapses.

Fenfluramine was studied in two good-quality, Phase 3 studies in 206 children and young adults with Dravet syndrome. Both trials were multicenter, double-blind, placebo-controlled trials that randomized children 2-18 years of age with Dravet syndrome to adjunctive fenfluramine or placebo. Both trials excluded patients with a history of PAH, cardiovascular disease, or cerebrovascular disease.

Lagae published a trial which randomized patients to adjunctive fenfluramine 0.7 mg/kg/day, fenfluramine 0.2 mg/kg/day, or placebo for 14 weeks. Concomitant stiripentol and cannabidiol use was not permitted. The primary endpoint of mean change in monthly seizure frequency from baseline was significantly decreased with fenfluramine 0.7 mg/kg/day compared to placebo (62.3% decrease vs placebo, $p<0.0001$). The secondary outcome of mean change in seizure frequency from baseline with 0.2 mg/kg/day fenfluramine was also significantly decreased compared to placebo (32.4% decrease vs placebo, $p=0.021$). Significantly more patients in the fenfluramine groups met criteria for ≥50% responder rate (68% and 38% for fenfluramine 0.7 and 0.2 mg/kg/day) compared to placebo (12%, $p<0.0001$, $p=0.0091$, respectively). Parent-rated clinical global impression of change (CGIC) of very much or much improved occurred in 55%, 41%, and 10% of patients receiving fenfluramine 0.7 mg/kg/day ($p<0.0001$), fenfluramine 0.2 mg/kg/day ($p=0.0036$), and placebo, respectively. Assessments of quality of life (QoL) found no change between groups with the Childhood Epilepsy assessment while the Pediatric QoL Inventory found both doses of fenfluramine increased QoL compared to placebo ($p=0.02$ and $p=0.003$ for fenfluramine 0.7 mg/kg/day and 0.2 mg/kg/day). The Behavior rating inventory of executive function, second edition (BRIEF2), an assessment of cognitive function, found the 0.7 mg/kg/day dose of fenfluramine improved cognitive function ($p=0.024$) while the lower dose did not reach significance ($p=0.067$).

Nabbout published a second Phase 3 trial which randomized patients to fenfluramine 0.4 mg/kg/day or placebo for 15 weeks. The trial permitted concomitant use of stiripentol. Fenfluramine significantly decreased the primary endpoint of mean change in monthly seizure frequency from baseline compared to placebo (54% decrease vs placebo, $p<0.001$). A total of 54% of patients were ≥50% responders with fenfluramine compared to 5% with placebo ($p<0.001$). The median longest seizure-free interval was significantly longer with fenfluramine compared to placebo (22 vs 13 days, $p=0.004$). Investigator-rated CGIC significantly favored fenfluramine compared to placebo (44% vs 16%, $p=0.008$). Parent CGIC and QoL assessments did not different between study groups.

A research group from Belgium has published two small, long-term trials with fenfluramine in patients with Dravet syndrome. A 1.5 year prospective, open-label trial in nine patients (age

range 6 months to 50 years) found the initial 75% decrease in median seizure frequency with fenfluramine (0.25-1 mg/kg/day) was maintained throughout the trial. A 5-year, retrospective, uncontrolled trial in 10 patients with Dravet syndrome (7-40 years of age) found a seizure frequency decreased to <1/month in 90% of patients on fenfluramine (0.2-0.8 mg/kg/day).

Fenfluramine was also studied in a 14-week, Phase 3 trial in patients with Lennox-Gastaut syndrome. The double-blind, placebo-controlled study randomized 263 patients ages 2-35 years with uncontrolled Lennox-Gastaut syndrome to adjunctive fenfluramine 0.7 mg/kg/day, fenfluramine 0.2 mg/kg/day, or placebo. The primary endpoint of median change in monthly drop seizure frequency was significantly improved with fenfluramine 0.7 mg/kg/day compared to placebo (26.5% decrease vs placebo, p=0.0034). However, a significant difference was not seen in the mean drop of seizure frequency with fenfluramine 0.2 mg/kg/day compared to placebo, a secondary outcome (13.2% decrease vs placebo, p=0.09). Significantly more patients on fenfluramine 0.7 mg/kg/day met criteria for ≥50% reduction in monthly drop seizures compared to those receiving placebo (25.3% vs 10.3%, p=0.0165) as well as with clinical global impression of change-improvement much or very much improved (26.3% vs 6.3%, respectively, p=0.0007). Results with the 0.2 mg/kg/day dose of fenfluramine for these outcomes were not reported.

Fenfluramine was previously approved for weight loss and was removed from the market in 1997 due to numerous reports of valvulopathy. Possible proposed mechanisms of cardiovascular adverse events with fenfluramine are vasoconstrictive actions of serotonin and alterations in the depolarization of pulmonary vascular smooth-muscle membrane. Additionally, the fenfluramine metabolite norfenfluramine activates the $5HT_{2b}$ receptors, is associated with valvulopathy, and plays a role in cardiac development.

In 1997, Connolly reported 24 cases of valvular disease in patients taking the combination of fenfluramine (20-120 mg) and phentermine as appetite suppressants. All patients were without cardiovascular disease (CVD) at treatment onset. A total of 20 presented with new cardiovascular (CV) symptoms at a mean of 12.3 months after treatment initiation. Eight patients had evidence of pulmonary hypertension. Hopkins analyzed all published studies with echocardiogram data following fenfluramine or dexfenfluramine use (alone or with phentermine) and found the risk of atrial regurgitation (AR) was dependent on the duration of exposure. The predictive cumulative incidence of AR after 1 year of exposure was 9.6%. The weighted estimate of incidence of AR for all studies was 6.29% compared to an expected incidence of 0.42% based on pooled control groups. The summary relative risk (RR) for AR was 19.6, 95% confidence interval (CI) 16.3-23.5, p<0.00001. The weighted estimate of incidence of mitral regurgitation (MR) was 1.09%; the expected incidence was 0.16% based on pooled control groups. The summary RR for MR was 5.9, 95% CI 4.0-8.6, p<0.00001. The number needed to harm was 16.4 for AR and 99 for MR.

Currently, all controlled trials with fenfluramine in Dravet syndrome assessed patients for valvulopathy and PAH and exclude patients with cardiovascular disease. The trials also limited the dose of fenfluramine to a maximum of 17-30 mg. In contrast, the dose of fenfluramine as an anorexiant ranged from 20-120 mg/day. In the past, fenfluramine was also often given with phentermine, a monoamine oxidase inhibitor (MAOI). This practice is significant as concomitant therapy with an MAOI inhibits two mechanisms of serotonin inactivation (uptake into platelets and oxidative deamination via monoamine oxidase), increasing the likelihood of adverse events with combination therapy.

Current data available with fenfluramine administered for Dravet syndrome is insufficient to evaluate risk of valvulopathy or PAH. No evidence of valvulopathy or PAH was seen in either of the Phase 3 trials with fenfluramine; however, both trials were of short duration (14-15 weeks). The long-term trial extension of the Phase 3 fenfluramine trials assessed 232 patients with a mean exposure to fenfluramine of 256 days (approximately 9 months) and found no evidence of valvulopathy or PAH.

Other common adverse events seen with fenfluramine in the Phase 3 trials include decreased appetite (20%-44%), pyrexia (5%-26%), diarrhea (18%-31%), fatigue (10%-26%), and weight decrease ≥7% (21%).

Xcopri (cenobamate)

Cenobamate is a tetrazole derivative which modulates GABA and voltage-gated sodium ion channels. Cenobamate is associated with positive allosteric modulation of the GABA A receptor and enhancement of GABA-mediated inhibitory currents. Cenobamate decreases excitation through the inhibition of persistent sodium currents (INAP). Voltage-gated sodium channels are involved in the generation and conduction of action potentials. Sodium influx into the cell causes a depolarizing inward current followed by inactivation. Inactivation persists until the cell repolarizes. However, INAP, which continues following inactivation of the transient current, increases excitability and facilitates repetitive firing.

Cenobamate was studied in two similarly designed, randomized, double-blind, placebo-controlled, Phase 2 trials (C013 and C017) in adults with uncontrolled partial-onset seizures (simple partial with a motor component, complex partial, or secondary generalized tonic-clinic [SGTC]).

In study C013, 222 patients 18-65 years of age were randomized to cenobamate 200 mg or placebo for 12 weeks including a 6-week titration period and a 6-week maintenance period. The

primary outcome measure was the median percent change in seizure frequency compared to baseline for weeks 1-4. Cenobamate reduced the seizure frequency 40.6% compared to a 14.3% reduction with placebo (difference 26%). No statistical analysis was available. The study reported the reduction in seizure frequency was maintained beyond 4 weeks, but no data was presented. Additionally, the time to first seizure was longer with cenobamate compared to placebo (13.9 days vs 8.8 days; statistical analysis not reported).

In study C017, 437 patients 18-70 years of age were randomized to cenobamate (100 mg, 200 mg, or 400 mg/day) or placebo for 18 weeks (6-week titration and 12-week maintenance). The primary outcome measure of median percent reduction from baseline in seizure frequency for weeks 1-4 was decreased with all doses of cenobamate compared to placebo (45%-50% cenobamate vs 17% placebo; statistical analysis not provided). Cenobamate significantly reduced the secondary outcome of median decrease in seizure frequency compared to placebo for the overall trial duration (35.5%, 55%, 55% cenobamate 100 mg, 200 mg, and 400 mg, respectively, vs 24% placebo; $p=0.007$, $p<0.001$ and $p<0.001$, respectively). Median decrease in seizure frequency ranged from 48% to 91% across seizure types and doses of cenobamate compared to 7% seizure increase to 33% decrease seen with placebo. The mean time to first seizure was 14.7 days with cenobamate and 6.4 days with placebo (statistical analysis not reported).

Serious adverse events (SAEs) occurred in 8.5% of patients in the Phase 3 safety study. The most common SAEs were seizures. Additionally, four deaths occurred in this study (sudden death, hemorrhage following a fall, car accident, and respiratory failure in a patient with Angelman syndrome). The authors did not discuss whether the deaths were considered treatment related. No information on deaths or SAEs is available for Phase 2 studies (C013 and C017). Common adverse events with cenobamate (at least 10% for cenobamate and more frequently than placebo) include somnolence, dizziness, fatigue, diplopia, and headache.

Ztalmy (ganaxolone)

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a complex of clinical symptoms resulting from the presence of non-functional CDKL5 protein. The clinical picture is characterized by epileptic seizures (that start within the first three months of life and most often do not respond to pharmacological treatment), epileptic encephalopathy secondary to seizures, and retardation of psychomotor development, which are often observed already in the first months of life. CDD appears to be a rare condition with an incidence of 1 in 40,000 to 60,000 newborns. About 90 percent of those diagnosed with CDD are girls. Since CDKL5 is located on the X chromosome, the prevalence of CDD among women is four times higher than in men.

However, the course is usually more severe among male patients. Due to the limited therapeutic possibilities, patients with CDD may experience permanent symptoms of epileptic encephalopathy and significant developmental impairment. It is reasonable to provide genetic counseling to couples whose child is affected with CDD or offer an extension of prenatal diagnosis, including a mutation of the CDKL5 gene in subsequent pregnancies.

Ganaxolone is a neuroactive steroid gamma-aminobutyric acid (GABA A) receptor positive modulator. A single, randomized, double-blind, placebo-controlled study was conducted in patients between 2 and 19 years of age (Marigold trial/Study 1, NCT03572933) to establish the efficacy of ganaxolone for the treatment of CDD-associated seizures. It was followed by long-term open-label treatment. A total of 102 participants from age 2 to 21 years old underwent a baseline period before being randomized to receive, in addition to their existing anti-seizure treatment, either ganaxolone or placebo for 17 weeks. Following the treatment period, all patients that meet certain eligibility requirements had the opportunity to receive ganaxolone in the open label phase of the study. The study's primary efficacy endpoint was the percent reduction in seizures. Secondary outcome measures included non-seizure-related endpoints to capture certain behavioral and sleep disturbances that had been seen in previous clinical studies with ganaxolone.

Prior to the study, patients had tried a median of 7 prior antiepileptic drugs (AEDs). In the baseline period, patients experienced a median 28-day major motor seizure frequency of 50.0 and 57.3 in the placebo and ganaxolone groups, respectively. Patients on ganaxolone experienced a median 32.2% reduction in major motor seizure frequency compared to a 4.0% reduction in the placebo group during the treatment period relative to baseline (p=0.002, Wilcoxon Rank-Sum Test). Ganaxolone demonstrated improving trends but did not achieve statistical significance in the key secondary endpoints.

Data from the open label extension (OLE) phase of the Phase III Marigold study in CDD provides supportive evidence for maintenance of effect on reducing major motor seizures associated with CDD at approximately eight months and up to 12 months in patients who continue ganaxolone treatment. The median major motor seizure frequency reduction from baseline in the OLE was 30.1% in patients continuing ganaxolone (n=38) and 33.3% in patients transitioning from placebo (n=34) at eight months and 46.5% (n=22) and 53.8% (n=26), respectively, at 12 months.

Per the abstract, of 101 patients entering the double-blind phase, 88 (87.1%) continued into the OLE (43 were initially randomized to ganaxolone (GNX-GNX) and 45 to placebo (PBO-GNX)). At the time of entry into the double-blind study, median age of patients was 5 years; 79.5% were female. The most common concomitant antiseizure medications were valproic acid (36.4%), clobazam (29.5%), levetiracetam (26.1%), and vigabatrin (22.7%). Median treatment time (range) in the OLE was 262 days (16,706). At the time of analysis, 31 (35.2%) patients dropped out of the

OLE, with lack of efficacy (13.6%) and adverse events (10.2%) being the most common reasons for discontinuation. Improvements on CGI-I assessments (minimally improved or better) were similar between GNX-GNX and PBO-GNX groups ranging 66.6% to 82.1% for the caregiver and 68.9% to 76.9% for the clinician observations at approximately 8 months.

The most common adverse events observed with ganaxolone were somnolence, pyrexia, salivary hypersecretion, and seasonal allergy.

References

1. Thijs RD, Surges R, O'Brien TJ, Sander JW. Epilepsy in adults. Lancet. 2019;393:689-701.
2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-521.
3. Adams SM, Knowles PD. Evaluation of a first seizure. Am Fam Physicians. 2007;75:1342-1347.
4. Huff JS, Murr N. Seizure. In: StatPearls [internet]. Treasure Island, FL: StatPearls Publishing; 2019 Jan-.
5. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs. JAMA Neurol. 2018;75(3):279-286.
6. Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. Epilepsy Behav. 2016;64:69-74.
7. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. The genetic landscape of the epileptic encephalopathies of infancy and childhood. Lancet Neurol. 2016;15:304-316.
8. Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrine R, Lagae L. Dravet syndrome: treatment options and management of prolonged seizures. Epilepsia. 2019;60(S3):S39-S48.
9. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus panel. Ped Neurol. 2017;68:18-34.
10. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. New Engl J Med. 1997;337(9):581-588.
11. Polster T. Individualized treatment approaches: fenfluramine, a novel antiepileptic medication for the treatment of seizures in Dravet syndrome. Epilepsy Behav. 2019:91:99-102.
12. Wurtman RJ, Wurtman J. Fenfluramine: back from the dead. Clin Ther. 2018;40(8):1420-1422.
13. Martin P, de Witte PA, Maurice T, Gammaitoni A, Farfel G, Galer B. Fenfluramine acts a s a positive modulator of signma-1 receptors. Epilepsy Behav. 2020;105:106989.
14. Federal Register. Determination that Pondimin (fenfluramine hydrochloride) tablets, 20 milligrams and 60 milligrams, and Ponderex (fenfluramine hydrochloride) capsules, 20 milligrams were withdrawn from sale for reasons of safety or efficacy. Available from: **https://www.federalregister.gov/documents/2015/09/29/2015-24619/determination-that-pondimin-fenfluramine-hydrochloride-tablets-20-milligrams-and-60-milligrams-and**. Accessed on January 21, 2025.
15. Lagae L, Sullivan J, Knupp K, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomized, double-blind, placebo-controlled trial. Lancet. 2019;394:2243-2254.

16. 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. doi: 10.1001/jamaneurol.2019.4113. [Epub ahead of print].

17. Bishop KI, Isquith PI, Bioia G, et al. Profound reduction in seizure frequency (≥75%) leads to improved everyday executive function: analysis from a Phase 3 study of ZX008 (fenfluramine HCl) in children/young adults with Dravet syndrome [abstract]. Presented at the AES 2019 Annual Meeting; December 6-10, 2019; Baltimore, MD.

18. Schoonjans A, Paelinck BP, Marchau F, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. Eur J Neurol. 2017;24:309-314.

19. Ceulemans B, Schoonjans AS, Marchau F, Paelinck BP, Lagae L. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. Epilepsia. 2016;57(7):e129-e134.

20. Nakamura M, Cho JH, Shin H, Jang IS. Effects of cenobamate (YKP3089), a newly developed anti-epileptic drug, on voltage-gated sodium channels in rat hippocampal CA3 neurons. Eur J Pharmacol. 2019;855:175-182.

21. Sharma R, Song WS, Nakamura M, et al. Effects of cenobamate on GABA-A receptor modulation [abstract]. Neurology. 2019;92(15 Supplemennt).

22. Kastelejn-Nolst Trenite DG, DiVentura BD, Pollard JR, Krauss GL, Mizne S, French JA. Suppression of the photoparoxysmal response in photosensitive epilepsy with cenobamate (YKP3089). Neurology. 2019;93(6):e559-3567.

23. Greene S, Orlinski L, Streicher C, Vernillet L. The pharmacokinetics of cenobamate in special populations [abstract]. Neurology. 2019;92 (15 Supplement).

24. Kraus G, Kamin M. Efficacy and tolerability of adjunctive cenobamate therapy in different types of partial-onset seizures [abstract]. Neurology. 2018;90(15 Supplement).

25. Kamin M, Ferrari L. Time to onset of efficacy in seizure reduction with cenobamate (YKP3089) in patients with uncontrolled partial seizures from 2 randomized clinical trials [abstract]. Neurology. 2019;90 (15 Supplement).

26. Sperling M, Klein P, Kamin M. Safety of cenobamate (YKP3089) as adjunctive treatment for uncontrolled partial seizures in a large, multicenter, open-label study [abstract]. Neurology. 2019;92(15 Supplement).

27. Jakimiec M, Paprocka J, Śmigiel R. CDKL5 Deficiency Disorder-A Complex Epileptic Encephalopathy. Brain Sci. 2020;10(2):107. Published 2020 Feb 17.

28. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J Neurodev Disord. 2021;13(1):40. Published 2021 Sep 16. doi:10.1186/s11689-021-09384-z

29. Aptiom (eslicarbazepine) [package insert]. Sumitomo Pharma America, Inc., Marlborough, MA. Revised March 2019.

30. Banzel (rufinamide) [package insert]. Eisai Inc., Nutley, NJ. Revised December 2022.

31. Briviact (brivaracetam) [package insert]. UCB, Inc., Smyrna, GA. Revised May 2023.

32. Diacomit (stiripentol) [package insert]. Biocodex, Inc. Bedminster, NJ. Revised June 2024.

33. Epidiolex (cannabidiol) [package insert]. Jazz Pharmaceuticals, Inc., Palo Alto, CA. Revised March 2024.

34. Fintepla (fenfluramine) [package insert]. UCB, Inc., Smyrna, GA. Revised December 2023.

35. Fycompa (perampanel) [package insert]. Catalyst Pharmaceuticals, Inc., Coral Gables, FL. Revised June 2023.

36. Libervant (diazepam) [package insert]. Aquestive Therapeutics, Warren, N. Revised April 2024.

37. Motpoly XR (lacosamide extended-release) [package insert]. Aucta Pharmaceuticals, Inc., Piscataway, NJ. Revised June 2024.

38. Oxtellar XR (oxcarbazepine extended-release) [package insert]. Supernus Pharmaceuticals, Inc., Rockville, MD. Revised August 2024.

39. Qudexy XR (topiramate extended-release capsules) [package insert]. Upsher-Smith Laboratories LLC, Maple Grove, MN. Revised June 2024.

40. Sabril (vigabatrin) [package insert]. Patheon, Cincinnati, OH. Revised October 2021.
41. Spritam (levetiracetam tablets for oral suspension) [package insert]. Aprecia Pharmaceuticals, LLC, Blue Ash, OH. Revised June 2024.
42. Sympazan (clobazam oral film) [package insert]. Aquestive Therapeutics, Warren, NJ. Revised March 2024.
43. Trokendi XR (topiramate extended-release capsules) [package insert]. Catalent Pharma Solutions, Winchester, KY. Revised January 2024.
44. Vigadrone (vigabatrin) [package insert]. Upsher-Smith Laboratories LLC, Maple Grove, MN. Revised January 2024.
45. Vigpoder (vigabatrin) [package insert]. Pyros Pharmaceuticals, Inc., Parsippany, NJ. Revised July 2023.
46. Vigafyde (vigabatrin) [package insert]. Pyros Pharmaceuticals, Inc., Parsippany, NJ. Revised November 2024.
47. Vimpat (lacosamide) [package insert]. UCB, Inc., Smyrna, GA. Revised October 2023.
48. Xcopri (cenobamate) [package insert]. SK Life Science, Inc., Paramus, NJ. Revised April 2024.
49. Zonisade (zonisamide oral suspension) [package insert]. Azurity Pharmaceuticals, Inc., Wilmington, MA. Revised March 2023.
50. Ztalmy (ganaxolone) [package insert]. Marinus Pharmaceuticals, Inc., Radnor, PA. Revised April 2024.

History

Date	Comments
03/01/25	New policy, approved February 11, 2025. Add to Prescription Drug section. Moved the seizures drugs Aptiom (eslicarbazepine), Banzel (rufinamide), generic rufinamide, Briviact (brivaracetam), Diacomit (stiripentol), Epidiolex (cannabidiol), Fintepla (fenfluramine), Fycompa (perampanel), Libervant (diazepam), Motpoly XR (lacosamide extended-release), generic oxcarbazepine extended-release, Oxtellar XR (oxcarbazepine extended-release), Peganone (ethotoin), Qudexy XR (topiramate extended-release capsules), brand topiramate extended-release capsules, Sabril (vigabatrin), Spritam (levetiracetam tablets for oral suspension), Sympazan (clobazam oral film), Trokendi XR (topiramate extended-release capsules), generic vigabatrin, Vigadrone (vigabatrin), Vigpoder (vigabatrin), Vigafyde (vigabatrin), Vimpat (lacosamide), Xcopri (cenobamate), Zonisade (zonisamide oral suspension), Zonisamide (zonisamide oral suspension), and Ztalmy (ganaxolone) from Policy 5.01.605 to Policy 5.01.649 Pharmacologic Treatment of Seizures. Updated Vimpat (lacosamide) for the treatment of partial-onset seizures from 4 years and older to 1 month and older. Removed the product name Zonisamide (zonisamide oral suspension) as product is not available and only Zonisade (zonisamide oral suspension) is commercially available. Removed Peganone (ethotoin) as the product has been discontinued.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and

local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.