Pharmacy Policy Bulletin

Title:	Seizure Disorder Agents
Policy #:	Rx.01.209

Application of pharmacy policy is determined by benefits and contracts. Benefits may vary based on product line, group, or contract. Some medications may be subject to precertification, age, quantity, or formulary restrictions (ie limits on non-preferred drugs). Individual member benefits must be verified.

This pharmacy policy document describes the status of pharmaceutical information and/or technology at the time the document was developed. Since that time, new information relating to drug efficacy, interactions, contraindications, dosage, administration routes, safety, or FDA approval may have changed. This Pharmacy Policy will be regularly updated as scientific and medical literature becomes available. This information may include new FDA-approved indications, withdrawals, or other FDA alerts. This type of information is relevant not only when considering whether this policy should be updated, but also when applying it to current requests for coverage.

Members are advised to use participating pharmacies in order to receive the highest level of benefits.

Intent:

The intent of this policy is to communicate the medical necessity criteria for **Epidiolex ® (cannabidiol), Diacomit® (stiripentol), Onfi®, Sympazan® (clobazam), Banzel® (rufinamide), Fintepla® (fenfluramine), and Vigabatrin (Sabril®)** as provided under the member's prescription drug benefit.

Description:

Lennox-Gastaut syndrome: A form of severe epilepsy that begins in childhood. It is characterized by multiple types of seizures and intellectual disability. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5 years.

Dravet syndrome (DS): A severe form of epilepsy which appears during the first year of life characterized by frequent, prolonged seizures often triggered by high body temperature (hyperthermia), developmental delay, speech impairment, loss of full control of bodily movements, low muscle tone, sleep disturbances, and other health problems.

Epidiolex ® (cannabidiol (CBD)); the exact mechanism by which CBD produces its anticonvulsant effects is unknown. CBD may exert a cumulative anticonvulsant effect, modulating a number of endogenous systems including, but not limited to, neuronal inhibition (synaptic and extrasynaptic GABA channels), modulation of intracellular calcium (TRPV, VDAC, GPR55), and possible anti-inflammatory effects (adenosine).

Diacomit® (stiripentol); the mechanism of action by which stiripentol exerts its anticonvulsant effect in humans is unknown. Possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid $(GABA)_A$ receptor and indirect effects involving inhibition of cytochrome P450 activity with resulting increase in blood levels of clobazam and its active metabolite.

Onfi® (clobazam); The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABAA receptor.

Banzel® (rufinamide); The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. The results of in vitro studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide (≥ 1 μM) significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive firing of sodium-dependent action potentials (EC50 of 3.8 μM).

Fintepla® (fenfluramine): 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.

Sabril® (vigabatrin): The precise mechanism of vigabatrin's anti-seizure effect is unknown, but it is believed to be the result of its action as an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased levels of GABA in the central nervous system.

Epidiolex ® is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older.

Diacomit® is indicated for the treatment of seizures associated with Dravet syndrome in patients 6 months of age and older and weighing 7 kg or more taking clobazam. There are no clinical data to support the use of Diacomit® as monotherapy in Dravet syndrome

Onfi® and Sympazan® are indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients2 years of age or older.

Banzel® indicated for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in pediatric patients 1 year of age and older, and in adults.

Fintepla® (fenfluramine) is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age and older.

Sabril® is indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss and as adjunctive therapy for adults and pediatric patients 2 years of age and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss

Policy:

Dravet Syndrome

INITIAL CRITERIA: Cannabidiol (Epidiolex) is approved when ALL of the following are met:

1. Member is 1 years of age or older; and
2. Baseline CBC, serum transaminases and total bilirubin obtained prior to initiating therapy; and
3. Diagnosis of Dravet syndrome; and
4. Inadequate response or inability to tolerate ONE of the following:
    a. Clobazam*; or
    b. Valproic acid; or
    c. Levetiracetam; o
    d. Topiramate; and
5. Documentation of concurrent use with additional anti-epileptic(s); and
6. Prescribed by or in consultation with a neurologist

INITIAL CRITERIA: Stiripentol (Diacomit®) is approved when ALL of the following are met:

1. Diagnosis of seizures associated with Dravet syndrome; and
2. Member is 6 months of age or older and weighing 7kg or more; and
3. Used in combination with clobazam*; and
4. Prescribed by or in consultation with a neurologist

INITIAL CRITERIA: Clobazam (Onfi®, Sympazan®) tablets, films, or oral suspension is approved when ALL of the following are met:

1. Member is 2 years of age and older; and

2. Diagnosis of seizures associated with Dravet Syndrome (DS); and
3. Used as adjunctive therapy; and
4. Prescribed by or in consultation with a neurologist; and
5. For brand Onfi® and brand Sympazan® only, inadequate response or inability to tolerate generic clobazam tablets or oral suspension

INITIAL CRITERIA: Fenfluramine (Fintepla®) is approved when ALL of the following are met:

1. Diagnosis of Dravet Syndrome; and
2. Member is 2 years of age or older; and
3. Inadequate response or inability to tolerate ONE of the following:
    a. Clobazam*; or
    b. Valproic acid; or
    c. Divalproex sodium; or
    d. Topiramate; or
    e. Levetiracetam; and
4. Prescribed by or in consultation with a neurologist

Initial authorization duration: 2 years

CONTINUATION CRITERIA: Cannabidiol (Epidiolex®), Stiripentol (Diacomit®), clobazam (Onfi®, Sympazan®), or fenfluramine (Fintepla®) is re-approved when ALL of the following are met:

1. Documentation of reduction in seizure activity or intensity; and
2. Stiripentol (Diacomit®) only, used in combination with clobazam*; and
3. Prescribed by or in consultation with a neurologist

Continuation authorization duration: 2 years

Lennox-Gastaut Syndrome (LGS)

INITIAL CRITERIA: Cannabidiol (Epidiolex®) is approved when ALL of the following are met:

1. Member is 1 years of age or older; and
2. Baseline CBC, serum transaminases and total bilirubin obtained prior to initiating therapy; and
3. Diagnosis of Lennox-Gastaut syndrome (LGS); and
4. Inadequate response or inability to tolerate ONE of the following:

    a. Valproic acid; or
    b. Lamotrigine; or
    c. Topiramate; or
    d. Felbamate; or
    e. Rufinamide*; or
    f. Clobazam*; and

5. Documentation of concurrent use with additional anti-epileptic(s); and
6. Prescribed by or in consultation with a neurologist

INITIAL CRITERIA: Rufinamide (Banzel®) tablet or suspension is approved when ALL of the following are met:

1. Diagnosis of seizures associated with Lennox-Gastaut Syndrome (LGS); and
2. Used as adjunctive therapy; and
3. Member is 1 year of age or older; and
4. Inadequate response or inability to tolerate ONE of the following generics:
    a. Valproic acid; or
    b. Lamotrigine; or

c. Topiramate; or
d. Felbamate; or
e. Clobazam*; and

5. Prescribed by or in consultation with a neurologist; and
6. For rufinamide (Banzel®) suspension only; ONE of the following:
    a. Drug will be administered via nasogastric or gastronomy tube; or
    b. Member is unable to swallow an intact capsule or tablet

INITIAL CRITERIA: Fenfluramine (Fintepla®) is approved when ALL of the following are met:

1. Diagnosis of seizures associated with Lennox-Gastaut Syndrome (LGS); and
2. Member is 2 years of age or older; and
3. Inadequate response or inability to tolerate ONE of the following generics:
    a. Valproic acid; or
    b. Lamotrigine; or
    c. Topiramate; or
    d. Felbamate; or
    e. Clobazam; and
4. Prescribed by or in consultation with a neurologist

Initial authorization duration: 2 years

INITIAL CRITERIA: Clobazam (Onfi®, Sympazan®) tablets, films or oral suspension is approved when ALL of the following are met:

1. Member is 2 years of age and older; and
2. Diagnosis of seizure associated with Lennox-Gastaut Syndrome; and
3. Prescribed by or in consultation with a neurologist; and
4. For Brand Onfi® and brand Sympazan® only, inadequate response or inability to tolerate generic clobazam tablets or oral suspension

Initial authorization duration: 2 years

CONTINUATION CRITERIA Cannabidiol (Epidiolex®) , clobazam (Onfi®, Sympazan®), rufinamide (Banzel®), or fenfluramine (Fintepla®) is re-approved when there is documentation of reduction in seizure activity or intensity.

Continuation authorization duration: 2 years

Seizures associated with tuberous sclerosis complex

INITIAL CRITERIA: Cannabidiol (Epidiolex®) is approved when ALL of the following are met:

1. Member is 1 years of age or older; and
2. Baseline CBC, serum transaminases and total bilirubin obtained prior to initiating therapy; and
3. Diagnosis of seizures associated with tuberous sclerosis complex; and
4. Inadequate response or inability to tolerate ONE of the following:
    a. Vigabatrin*; or
    b. Carbamazepine; or
    c. Oxcarbazepine; and
5. Documentation of concurrent use with additional anti-epileptic(s); and
6. Prescribed by or in consultation with a neurologist

Initial authorization duration: 2 years

CONTINUATION CRITERIA: Cannabidiol (Epidiolex®) is re-approved when there is documentation of reduction in seizure activity or intensity.

Continuation authorization duration: 2 years

Refractory complex partial seizure or infantile spasms

INITIAL CRITERIA: Vigabatrin (Sabril®) is approved when ALL of the following are met:

1. One of the following:
    a. BOTH of the following:
        i. Diagnosis of refractory complex partial seizures as adjunctive therapy; and
        ii. Member is 2 years of age or older; or
    b. BOTH of the following:
        i. Diagnosis of infantile spasms; and
        ii. Member is 1 month to 2 years of age; and
2. For brand Sabril® only, inadequate response or inability to tolerate generic vigabatrin or vigadrone; and
3. Prescribed by or in consultation with a neurologist

Initial authorization duration: 2 years

CONTINUATION CRITERIA: Vigabatrin (Sabril®) is re-approved when there is documentation of reduction in seizure activity of intensity

Continuation authorization duration: 2 years

*Please note: prior authorization required

Black Box Warning as shown in the drug Prescribing Information:

Onfi®, Sympazan® (clobazam): Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation. The use of benzodiazepines, including ONFI and SYMPAZAN, , exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing ONFI and SYMPAZAN, and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Abrupt discontinuation or rapid dosage reduction of ONFI and SYMPAZAN, after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue ONFI and SYMPAZAN, or reduce the dosage.

Fintepla® (fenfluramine): 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.

Sabril® (vigabatrin): SABRIL causes progressive and permanent bilateral concentric visual field constriction in a high percentage of patients. In some cases, SABRIL may also reduce visual acuity. Risk increases with total dose and duration of use, but no exposure to SABRIL is known that is free of risk of vision loss. Risk of new and worsening vision loss continues as long as SABRIL is used, and possibly after discontinuing SABRIL. Unless a patient is formally exempted, periodic vision assessment is required for patients on SABRIL. However, this assessment cannot always prevent vision damage. SABRIL can cause permanent vision loss. SABRIL is available only through a restricted program called the SHARE Program.

Guidelines:

Refer to the specific manufacturer's prescribing information for administration and dosage details and any applicable Black Box warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, the applicable drug(s) identified in this policy is (are) covered under the prescription drug benefits of the Company's products when the medical necessity criteria listed in this pharmacy policy are met. Any services that are experimental/investigational or cosmetic are benefit contract exclusions for all products of the Company.

References:

Banzel® (rufinamide) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc.; December 2021. Available from: https://www.banzel.com/~/media/Files/BanzelPatient/BanzelPI.pdf. Accessed April 20, 2023.

Diacomit® (stripentol) [package insert]. Beauvais, France. Biocodex. July 2022. Available from: https://www.diacomit.com/pdf/PI-Diacomit-2018.pdf. Accessed April 20, 2023.

"Dravet Syndrome." Genetic and Rare Diseases Information Center, U.S. Department of Health and Human Services, December 2016, rarediseases.info.nih.gov/diseases/10430/dravet-syndrome.

"Epidiolex (Cannabidiol) Dosing, Indications, Interactions, Adverse Effects, and More." Medscape Drugs & Diseases - Comprehensive Peer-Reviewed Medical Condition, Surgery, and Clinical Procedure Articles with Symptoms, Diagnosis, Staging, Treatment, Drugs and Medications, Prognosis, Follow-up, and Pictures, 26 June 2018, reference.medscape.com/drug/epidiolex-cannabidiol-1000225#10.

Epidiolex® (cannabidiol) [package insert]. Cambridge, United Kingdom. GW Pharmaceuticals Co. Ltd. January 2023. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=8bf27097-4870-43fb-94f0-f3d0871d1eec&type=display. Accessed April 20, 2023.

Fintepla® (fenfluramine) oral solution [prescribing information]. Emeryville, CA: Zogenix, Inc.; March 2023. Available from: https://www.fintepla.com/pdf/Fintepla-prescribing-information.pdf. Accessed April 20, 2023.

"Lennox-Gastaut Syndrome - Genetics Home Reference - NIH." U.S. National Library of Medicine, National Institutes of Health, July 2019, ghr.nlm.nih.gov/condition/lennox-gastaut-syndrome.

Onfi® (clobazam) [prescribing information]. Deerfield, IL: Lundbeck; January 2023. Available from: https://www.lundbeck.com/upload/us/files/pdf/Products/ONFI_PI_US_EN.pdf. Accessed April 20, 2023.

Sabril® (vigabatrin) [prescribing information]. Deerfield, IL: Lundbeck; October 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020427s010s011s012,022006s011s012s013lbl.pdf. Accessed April 20, 2023.

Sympazan® (clobazam) [prescribing information]. Warren, NJ: Aquestive Therapeutics; March 2021. Available from: https://www.sympazan.com/pdfs/pi.pdf. Accessed April 20, 2023.

Applicable Drugs:

Inclusion of a drug in this table does not imply coverage. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

Brand Name	Generic Name
Epidiolex®	Cannabidiol
Diacomit®	Stiripentol
Onfi®, Sympazan®	Clobazam
Banzel®	Rufinamide
Fintepla®	Fenfluramine
Sabril®	Vigabatrin

Cross References:

Off-Label Use Rx.01.33
Applicable Age Edits Rx.01.2

P&T Approval Date:	March 16, 2023
Policy Effective Date:	July 01, 2023
Next Required Review Date:	March 16, 2024