LOUISIANA BLUE

Select Anti-Epileptic Drugs

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider the following anti-epileptic drugs: Sympazan™‡ (clobazam film), Epidiolex®‡ (cannabidiol solution), Briviact®‡ (brivaracetam), Spritam®‡ (levetiracetam), Diacomit®‡ (stiripentol), Xcopri®‡ (cenobamate), Fintepla®‡ (fenfluramine), Eprontia™‡ (topiramate solution), Elepsia™‡ XR (levetiracetam), Ztalmy®‡ (ganaxolone), brand Primidone 125 mg tablets, and Libervant™‡ (diazepam) to be **eligible for coverage**** when the patient selection criteria for the specific drug are met.

Patient Selection Criteria

Coverage eligibility for Sympazan (clobazam film), Epidiolex (cannabidiol solution), Briviact (brivaracetam), Spritam (levetiracetam), Diacomit (stiripentol), Xcopri (cenobamate), Fintepla (fenfluramine), Eprontia (topiramate solution), Elepsia XR (levetiracetam), Ztalmy (ganaxolone), brand Primidone 125 mg tablets, and Libervant (diazepam), will be considered when the following patient selection criteria are met for the requested drug:

- For Sympazan requests:
  - Patient has a diagnosis of Lennox-Gastaut syndrome; AND
  - Patient is ≥ 2 years of age; AND
  - Patient meets ONE of the following:
    - Patient has tried and failed (e.g., intolerance or inadequate response) both GENERIC clobazam oral suspension and GENERIC clobazam tablets unless there is clinical evidence or patient history that suggests the use of the required generic products will be ineffective or cause an adverse reaction to the patient; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

        - Patient meets BOTH of the following:
            - Patient is unable to swallow tablets or suspensions (e.g., has dysphagia or has a gastrostomy tube [G-tube]); AND
            - Patient is not currently taking any medication in tablet, capsule, or suspension form.
- For Epidiolex requests:
    - Patient is ≥ 1 year of age and meets ONE of the following:
        - Patient has a diagnosis of Dravet syndrome; OR
        - Patient has a diagnosis of Lennox-Gastaut syndrome; OR
        - Patient has a diagnosis of tuberous sclerosis complex.
- For Briviact or Spritam requests:
    - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO alternative anti-epileptic agents for the condition being treated (ONE of which MUST be generic levetiracetam) unless there is clinical evidence or patient history that suggests the use of at least TWO alternative anti-epileptic agents (ONE of which MUST be generic levetiracetam) will be ineffective or cause an adverse reaction to the patient.
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Diacomit requests:
    - Patient has a diagnosis of Dravet syndrome; AND
    - Patient is ≥ 2 years of age; AND
    - Patient is currently taking clobazam and will continue concomitant clobazam while on Diacomit unless there is clinical evidence or patient history that suggests the use of clobazam will be ineffective or cause an adverse reaction to the patient.
- For Xcopri requests:
    - Patient has a diagnosis of partial onset seizures; AND
    - Patient is ≥ 18 years of age; AND
    - Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following GENERIC products for the condition: lacosamide, divalproex, lamotrigine, oxcarbazepine, topiramate, valproic acid, gabapentin, levetiracetam, pregabalin, or zonisamide unless there is clinical evidence or patient history that suggests the use of these GENERIC products will be ineffective or cause an adverse reaction to the patient.
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Fintepla requests:
    - Patient has a diagnosis of Dravet syndrome OR Lennox-Gastaut syndrome; AND
    - Patient is ≥ 2 years of age.

- For Eprontia requests:
  - Patient meets ONE of the following:
    - Patient has a diagnosis of partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome AND the patient is 2 years of age or older; OR
    - Patient will utilize the requested drug for the prevention of migraine headaches AND the patient is 12 years of age or older; AND
  - Patient meets ONE of the following:
    - Patient has tried and failed (e.g., intolerance or inadequate response) at least one GENERIC alternative for the treatment of the patient's condition unless there is clinical evidence or patient history that suggests the use of the GENERIC products will be ineffective or cause an adverse reaction to the patient; OR
      *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
    - Patient meets BOTH of the following
      - Patient is unable to swallow tablets or capsules (e.g., has dysphagia or has a gastrostomy tube [G-tube]); AND
      - Patient is not currently taking any medication in tablet or capsule form.

      *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Elepsia XR requests:
  - Patient has a diagnosis of partial-onset seizures; AND
  - Patient is ≥12 years of age; AND
  - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO alternative anti-epileptic agents for the condition being treated (one of which MUST be GENERIC levetiracetam) unless there is clinical evidence or patient history that suggests the use of at least TWO alternative anti-epileptic agents (one of which MUST be GENERIC levetiracetam) will be ineffective or case an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Ztalmy requests:
  - Patient is 2 years of age or older; AND
  - Patient has a diagnosis of CDKL5 deficiency that has been confirmed on genetic testing; AND

  - Patient has tried and failed (e.g., intolerance or inadequate response) at least TWO alternative antiepileptic therapies unless there is clinical evidence or patient history that suggests the use of at least TWO alternative anti-epileptic therapies will be ineffective or cause an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Motpoly XR requests:
  - Patient has a diagnosis of partial onset seizures; AND
  - Patient has tried and failed (e.g., intolerance or inadequate response) TWO of the following GENERIC products for the condition (one of which MUST be generic lacosamide): lacosamide, divalproex, lamotrigine, oxcarbazepine, topiramate, valproic acid, gabapentin, levetiracetam, pregabalin, or zonisamide unless there is clinical evidence or patient history that suggests the use of these GENERIC products (one of which MUST be generic lacosamide) will be ineffective or cause an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For brand Primidone 125 mg requests:
  - There is clinical evidence or patient history that suggests the generic 50 mg or scored 250 mg GENERIC primidone tablets will be ineffective or cause an adverse reaction to the patient.
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- For Libervant requests:
  - Patient is 2 to 5 years of age; AND
  - Patient has a diagnosis of epilepsy.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Briviact (brivaracetam), Spritam (levetiracetam), Xcopri (cenobamate), Ztalmy (ganaxolone), Elepsia XR (levetiracetam), and Motpoly XR (lacosamide) when the patient has not tried and failed at least two alternative anti-epileptic agents to be **not medically necessary**.**

Based on review of available data, the Company considers the use of Sympazan (clobazam film) when the patient is able to swallow and has not tried and failed the available generic products to be **not medically necessary**.**

Based on review of available data, the Company considers the use of brand Primidone 125 mg tablets when the patient is able to tolerate the available generic products to be **not medically necessary**.**

Based on review of available data, the Company considers the use of Eprontia (topiramate oral solution) when the patient has not tried and failed at least ONE GENERIC alternative and is able to swallow tablets or capsules to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Sympazan (clobazam), Diacomit (stiripentol), Epidiolex (cannabidiol), Xcopri (cenobamate), Fintepla (fenfluramine), Eprontia (topiramate oral solution), Ztalmy (ganaxolone), Elepsia XR (levetiracetam), Motpoly XR (lacosamide), and Libervant (diazepam) when the patient selection criteria are not met (except those noted to be **not medically necessary****) to be **investigational.***

Background/Overview

Diacomit is an antiepileptic drug with an unknown mechanism of action that is indicated for the treatment of seizures associated with Dravet syndrome in patients ≥2 years of age taking clobazam. There are no clinical data supporting the use of Diacomit as monotherapy in Dravet syndrome. The recommended dosage of Diacomit is 50 mg/kg/day, administered in two or three divided doses with a maximum recommended dose of 3,000 mg. If Diacomit treatment is discontinued, the drug should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. It is available in capsules that must be swallowed whole and a powder that may be mixed with water. Both dosage forms should be taken with a meal.

Sympazan is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older. It is an oral film formulation of clobazam, which was previously only available as a generic oral suspension, generic tablets, and brand Onfi®‡ tablets and suspension. Sympazan was approved for the same indication as the other products based on bioavailability studies comparing clobazam tablets to Sympazan. The dosing of Sympazan is the same as the other clobazam products and is based on body weight and response. The Sympazan films should be dissolved on top of the tongue and may provide an option for administration in patients who are unable to swallow liquids or tablets. In patients who are able to swallow, there is no noted advantage of Sympazan over the generic products.

Epidiolex is the first cannabidiol product to be approved by the FDA and is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex in patients 1 year of age and older. Cannabidiol is a major phytocannabinoid found in cannabis that accounts for up to 40% of the plant's extract, but it does not have psychoactive properties like tetrahydrocannabinol (THC), another major component of cannabis extract. The

recommended dose of Epidiolex for Lennox-Gastaut syndrome and Dravet syndrome is 5 mg/kg/day titrated weekly in increments of 5 mg/kg/day up to a therapeutic dose of 10 mg/kg/day or a maximum dose of 20 mg/kg/day. The recommended dose for seizures associated with tuberous sclerosis complex is 5 mg/kg/day titrated in weekly increments of 5 mg/kg/day up to a therapeutic dose of 25 mg/kg/day.

The conditions that Epidiolex is approved for, Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex, can be severe and difficult to treat. Lennox-Gastaut syndrome is a severe epileptic and developmental encephalopathy that is associated with a high rate of morbidity and mortality. Affected individuals experience several different types of seizures which may change as the patient grows older. Currently, the FDA approved drugs for Lennox-Gastaut syndrome are Felbatol®‡ (felbamate), lamotrigine, Banzel®‡ (rufinamide), topiramate, and Onfi. In addition, valproic acid is a mainstay in treatment and levetiracetam, zonisamide, and Fycompa®‡ (perampanel) are also used in the treatment of this condition. None of the therapies are effective in all cases, and the disorder is resistant to most therapeutic options. Dravet syndrome is a rare genetic epileptic encephalopathy marked with frequent and/or prolonged seizures. Affected individuals face a 15-20% mortality rate due to sudden unexpected death in epilepsy (SUDEP), prolonged seizures, and seizure-related accidents. Antiepileptic drugs are the mainstay of therapy and most patients require two or more drugs to control their seizures. In most cases, the seizures are refractory to medications. Because there were previously no FDA approved treatment options for Dravet syndrome, a North American consensus expert panel recommended Onfi and valproic acid as first-line options. Other therapies that may be used are topiramate, clonazepam, levetiracetam, and zonisamide. Tuberous sclerosis complex is an inherited neurocutaneous disorder with varying expression of pleomorphic disease features that involve many organ systems. The most common and difficult aspect of tuberous sclerosis complex to manage is the detection and treatment of seizures. Although many patients can be treated with traditional anti-seizure medications such as oxcarbazepine and carbamazepine, approximately 60 percent of patients with epilepsy develop medically intractable epilepsy for which Epidiolex is a potential option.

Briviact is indicated for the treatment of partial-onset seizures in patients 1 month of age and older with epilepsy. Briviact has a similar structure and mechanism of action as levetiracetam, which is available in generic form as tablets, an oral solution, and an injection. Briviact is also available in these dosage forms, but the Briviact injection has only been studied in up to 4 days of consecutive use. Levetiracetam is indicated in a broader patient population than Briviact. Briviact is a controlled substance while levetiracetam is not a controlled substance. Given the lack of any clinically significant breakthrough in the treatment of the indicated condition, it joins the ranks of multiple other drugs that are indicated for the treatment of partial onset seizures, including, but not limited to topiramate, lamotrigine, gabapentin, zonisamide, pregabalin, oxcarbazepine, levetiracetam, levetiracetam extended release, divalproex, Aptiom®‡ (eslicarbazepine), Potiga®‡ (ezogabine), Vimpat®‡ (lacosamide), Oxtellar XR™‡ (oxcarbazepine extended release), and Fycompa.

Spritam is indicated for adjunctive therapy in the treatment of partial onset seizures in patients with epilepsy 4 years of age and older, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy. Spritam contains the active ingredient levetiracetam, which is available in generic form as a tablet, an oral solution, and as an injectable. Spritam is a tablet that disintegrates when taken with a sip of liquid. The clinical efficacy of Spritam was based on studies that were previously done with levetiracetam tablets. Given the various dosage forms of levetiracetam available, coupled with multiple alternative options for treatment, Spritam offers minimal additional clinical value in current treatment regimens as compared to other existing products on the market. Various options exist for partial onset seizures (mentioned in the above paragraph). Other treatment options for juvenile myoclonic epilepsy include, but are not limited to drugs such as valproate, levetiracetam, lamotrigine, topiramate, etc. Other treatment options for primary generalized tonic-clonic seizures include, but are not limited to valproate, phenytoin, carbamazepine, lamotrigine, topiramate, levetiracetam, etc.

Xcopri is a novel tetrazole-derived compound that joins the armamentarium of medications approved as adjunctive treatment of partial onset seizures in adults. It is administered once daily with or without food at a target dose of 200 mg. The dose must be titrated slowly starting at an initial dose of 12.5 mg once daily due to the increased risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Unlike many of the alternative anti-epileptic drugs that have been available for some time, Xcopri was approved based on Phase II clinical trials and a Phase III trial is ongoing. Treatment guidelines have not been updated to include Xcopri.

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age and older. It is the third drug to receive the indication for Dravet syndrome from the FDA and is the only one that carries a boxed warning. The warning concerns increased risk of valvular heart disease and pulmonary arterial hypertension (PAH) based on experience with the active ingredient, fenfluramine, when it was approved for weight loss. At the time of approval, no patient using the drug for Dravet syndrome had developed valvular heart disease or PAH. However, because of the risk, Fintepla is categorized as a schedule IV controlled substance and has a Risk Evaluation and Mitigation Strategy (REMS) program. The REMS program requires patients to be counseled on the risks of valvular heart disease and PAH and to be monitored with echocardiograms prior to, during, and after treatment with Fintepla. The dose of Fintepla is weight based and should be started at 0.1 mg/kg by mouth twice daily and titrated to a maximum of 0.35 mg/kg twice daily for both indications.

Eprontia is a liquid formulation of topiramate that is indicated for the treatment of epilepsy in patients 2 years of age and older or the preventive treatment of migraine in patients 12 years of age and older. It was approved based on bioavailability studies comparing topiramate sprinkle capsules to Eprontia and thus does not present a clinical advantage over the generically available topiramate products (tablets, sprinkle capsules, and extended release tablets). In addition, there are numerous other generic treatment options available for the treatment of epilepsy and the prevention of migraines (see above paragraphs for examples).

Elepsia XR is another extended release formulation of levetiracetam and is approved for the adjunctive treatment of partial onset seizures in patients 12 years of age and older. It was approved based on bioavailability studies comparing levetiracetam extended release tablets to Elepsia XR extended release tablets and thus does not present a clinical advantage over the generically available levetiracetam extended release tablets. In addition, there are numerous other generic treatment options available for the treatment of partial onset seizures (see above paragraphs for examples).

Ztalmy is a neuroactive steroid gamma-aminobutyric acid type A ($GABA_A$) receptor positive modulator indicated for the treatment of seizures associated with cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder (CDD). It has a novel mechanism and is the first drug to be approved for the treatment of this rare condition. Ztalmy is an oral suspension containing 50 mg/mL of ganaxolone and should be administered three times daily in a weight-based fashion for patients weighing up to 28 kg. In patients weighing 28 kg or more, the dose should be 1800 mg/day divided into three doses. CDD is a rare, X-linked developmental epileptic encephalopathy caused by mutations in the *CDKL5* gene. The disorder can manifest in a broad range of clinical symptoms, including early-onset, intractable epilepsy, and neurodevelopmental delay. The epilepsy associated with CDD is particularly severe and refractory, often requiring numerous treatments. Many anti-epileptic drugs are often used off-label for treatment, but none (except Ztalmy) have been prospectively studied.

Motpoly XR is an extended release formulation of lacosamide. It is indicated for the treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg. It was approved based on bioavailability studies comparing Motpoly XR to immediate release lacosamide in healthy adults and thus does not present a clinical advantage over the generically available lacosamide products. Additionally, there are numerous other generic treatment options available for the treatment of partial onset seizures (see above paragraphs for examples).

Primidone has been available for the treatment of seizures since the early 1950s and was approved by the Food and Drug Administration (FDA) prior to the requirement for efficacy to be demonstrated in clinical trials. It is available in generic formulations including a 50 mg tablet and 250 mg scored tablet. The branded 125 mg product is an option for patients unable to achieve therapeutic target levels using variations in the generic products.

Libervant is a diazepam buccal film indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age. The dose is dependent on the patient's weight, and different strengths of films are available for patient weights up to 30 kg. Alternatives to this product include generically available diazepam rectal gel as well as a nasally administered diazepam product and a nasally administered midazolam product.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Diacomit was approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.

Sympazan was approved in November 2018 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age or older.

Epidiolex was approved in June 2018 for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. In 2020, the indication was updated to include seizures associated with tuberous sclerosis complex and the minimum age was lowered to 1 year old.

Briviact was approved in February 2016 for use in adjunctive therapy in the treatment of partial onset seizures. The label was expanded in September 2017 to allow for use as monotherapy for the treatment of partial onset seizures. In May 2018, the label was further expanded to include pediatric patients 4 years of age and older. In September 2021, the label was expanded again to include pediatric patients 1 month of age and older.

Spritam was approved in July of 2015 for the treatment of partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures.

Xcopri was approved in November 2019 for the treatment of partial onset seizures in adults.

Fintepla was approved in June 2020 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. In March 2022, the label was expanded to include treatment of Lennox-Gastaut syndrome in patients 2 years of age and older.

Eprontia was approved in November 2021 as initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older; as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older; and for the preventive treatment of migraine in patients 12 years of age and older.

Elepsia XR was approved in December 2018 as adjunctive therapy for the treatment of partial onset seizures in patients 12 years of age and older.

Ztalmy was approved in March 2022 for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older.

Motpoly XR was approved in May 2023 for the treatment of partial-onset seizures in adults and in pediatric patients weighing at least 50 kg.

Libervant was approved in April 2024 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Briviact, Spritam, Sympazan, Eprontia, Elepsia XR, and Motpoly XR

Briviact, Spritam, Eprontia, Elepsia XR, and Motpoly XR do not offer any new clinical significance in the treatment of their respective disease(s) as equally efficacious, less expensive alternative products are available on the market. For these products, the patient selection criteria take into consideration clinical evidence or patient history that suggests alternative anti-epileptic agents will be ineffective or will cause an adverse reaction to the patient. For Sympazan and Eprontia, the patient selection criteria take into account patients who may be unable to swallow liquids or tablets.

Epidiolex

Epidiolex represents a novel treatment agent with an unknown mechanism of action. Its efficacy in Lennox-Gastaut syndrome was established in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years who were inadequately controlled on at least one antiepileptic drug and had a minimum of 8 drop seizures during a 4-week baseline period. Study 1 (n=171) compared a dose of Epidiolex 20 mg/kg/day with placebo and Study 2 (n=255) compared a dose of Epidiolex 20 mg/kg/day with placebo. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures over the 14-week treatment period. This percent change was found to be significantly greater for both dosage groups of Epidiolex than with placebo. A reduction in drop seizures was observed within 4 weeks of initiating treatment and the effect remained generally consistent over the 14-week treatment period. In study 1 the Epidiolex group had a median reduction of 44% vs a 22% reduction in the placebo group ($p=0.01$). In Study 2, the Epidiolex group had a median reduction of 42% vs a 17% reduction in the placebo group ($p<0.01$).

The effectiveness of Epidiolex for the treatment of seizures associated with Dravet syndrome was demonstrated in a single randomized, double-blind, placebo-controlled trial in 120 patients aged 2 to 18 years with a diagnosis of treatment resistant Dravet syndrome and inadequate control on at least one concomitant antiepileptic drug. During the 4-week baseline period, patients were required to have at least 4 convulsive seizures while on stable antiepileptic drug therapy. The baseline period was followed by a 2-week titration period and a 12-week maintenance period. The primary efficacy

measure was the percent change from baseline in the frequency (per 28 days) of convulsive seizures over the 14-week treatment period. The median percent change from baseline in the frequency of convulsive seizures was significantly greater in the Epidiolex group than in the placebo group with a reduction of 39% seen in the Epidiolex group vs a 13% reduction in the placebo group (p=0.01).

The effectiveness of Epidiolex for the treatment of seizures associated with tuberous sclerosis complex was demonstrated in a randomized, double-blind, placebo-controlled trial in 224 patients aged 1-65 years with a diagnosis of tuberous sclerosis complex and seizures inadequately controlled with at least one concomitant antiepileptic drug. During the 4 week baseline period, patients had at least 8 seizures with at least 1 seizure occurring in at least 3 of the 4 weeks. The baseline period was followed by a 4-week titration period and a 12-week maintenance period. The primary efficacy measure was the change in seizure frequency over the 16-week treatment period compared with baseline. The percentage change from baseline in the frequency of seizures was significantly greater for patients treated with Epidiolex than with placebo with a reduction of 43% in the Epidiolex group and 20% in the placebo group (p<0.01).

Diacomit
Diacomit was approved based on 2 multicenter, placebo-controlled, double-blind, randomized studies conducted according to similar protocols. It should be noted that neither of these studies included patients in the United States. To be enrolled in either study, patients were required to be 3 years to <18 years of age, have Dravet syndrome, and be inadequately controlled on clobazam and valproate, with at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy. Eligible patients were enrolled in a 1-month baseline period during which they continued to receive their optimized antiepileptic treatment. Following this 1-month baseline, patients were randomly allocated to receive either Diacomit or placebo, added to their treatment with clobazam and valproate. Duration of double-blind treatment was 2 months. The frequency of generalized clonic or tonic-clonic seizures during the study was recorded by patients and/or their caregivers, using a diary. Although patients with Dravet syndrome have several different types of seizures, only generalized clonic or tonic-clonic seizures were recorded, as other seizure types can be difficult to recognize by patients and/or their caregivers as seizures. The primary efficacy endpoint for both studies was the responder rate. A responder was defined as a patient who experienced a greater than 50% decrease in the frequency (per 30 days) of generalized clonic or tonic-clonic seizures during the double-blind treatment period compared to the 4-week baseline period. In Study 1 (n=41), 21 patients were randomized to Diacomit and 20 patients to placebo. In Study 2 (n=23), 12 patients were randomized to Diacomit and 11 patients to placebo. In both studies, a statistically significantly higher number of patients responded to therapy in the Diacomit group vs the placebo group (Study 1: Diacomit 71% response vs 5% response for placebo [p<0.0001]. Study 2: Diacomit 67% response vs 9.1% response for placebo (p=0.0094).

Xcopri
The efficacy of Xcopri for the treatment of partial-onset seizures was established in two multicenter, randomized, double-blind, placebo-controlled, phase II studies in adult patients (Study 1 and Study 2). Patients enrolled in the studies had partial-onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs. During an 8-week baseline period, patients were required to have at least 3 or 4 partial-onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks. In these studies, patients had a mean duration of epilepsy of approximately 24 years and a median baseline seizure frequency of 8.5 seizures per 28 days. More than 80% of patients were taking 2 or more concomitant AEDs.

Study 1 compared doses of Xcopri 200 mg/day with placebo and Study 2 compared doses of Xcopri 100 mg/day, 200 mg/day, and 400 mg/day with placebo. After the 8-week baseline period, patients in both studies were randomized to a treatment arm consisting of an initial titration phase (6 weeks) and subsequent maintenance phase (6 weeks for Study 1 and 12 weeks for Study 2). It should be noted that the titration used in both studies began at a higher dose and was titrated faster than the currently approved dosing regimen recommends. The primary efficacy outcome in both studies was the percent change from baseline in seizure frequency per 28 days in the treatment period. In Study 1, the median percent change was -55.6% in the Xcopri 200 mg/day group and -21.5% in the placebo group ($p<0.0001$). In Study 2, the median percent change was -24.3% in the placebo group, -36.3% in the Xcopri 100 mg/day group ($p=0.006$), -55.2% in the Xcopri 200 mg/day group ($p<0.001$), and -55.3% in the Xcopri 400 mg/day group ($p<0.001$).

Fintepla
The effectiveness of Fintepla for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older was established in two randomized, double-blind, placebo-controlled trials in patients 2 to 18 years of age.

Study 1 (n=117) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of Fintepla with placebo in patients who were not receiving stiripentol. Study 2 (n=85) compared a 0.4 mg/kg/day dose of Fintepla with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both. In both studies, patients had a clinical diagnosis of Dravet syndrome and were inadequately controlled on at least one AED or other antiseizure treatment including vagal nerve stimulation or a ketogenic diet. Both trials had a 6-week baseline period, during which patients were required to have a minimum of 6 convulsive seizures while on stable AED therapy. The baseline period was followed by randomization into a 2-week (Study 1) or 3-week (Study 2) titration period and a subsequent 12-week maintenance period, where the dose of Fintepla remained stable.

The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the combined titration and maintenance periods. In both studies, this reduction in convulsive seizure frequency was statistically significantly greater for all

dose groups of Fintepla compared to placebo. In study 1, the 0.2 mg/kg/day dose was associated with a -31.7% difference in frequency compared to placebo and the 0.7 mg/kg/day dose was associated with a -70% difference. In study 2, the Fintepla group experienced a -59.5% difference in frequency of convulsive seizures compared to placebo.

The effectiveness of Fintepla for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled study in 263 patients aged 2-35 years of age. The study compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of Fintepla with placebo. Patients had a diagnosis of Lennox-Gastaut syndrome and were inadequately controlled in at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The study had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures while on stable AED therapy. The baseline period was followed by randomization into a 2-week titration period and a subsequent 12-week maintenance period, where the dose of Fintepla remained stable.

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. This endpoint was found to be significantly greater for the 0.7 mg/kg/day group compared with placebo with a reduction of 23.7% in the treatment group compared to a reduction of 8.7% in the placebo group (p=0.0037). The 0.2 mg/kg/day group did not experience statistically significant percent reduction from baseline in drop seizure frequency per 28 days.

Ztalmy
The effectiveness of Ztalmy for the treatment of seizures associated with CDD in patients 2 years of age and older was established in a single, double-blind, randomized, placebo-controlled study in patients 2 to 19 years of age. Patients enrolled in the study (n=50 for Ztalmy and 51 for placebo) had molecular confirmation of a pathogenic or likely pathogenic mutation in the CDKL5 gene, seizures inadequately controlled by at least 2 previous treatment regimens, and a minimum of 16 major motor seizures per 28 days during a retrospective 2-month period prior to screening. Patients were randomized in a 1:1 ratio to receive either Ztalmy or placebo. Following a 21-day titration period, patients in the Ztalmy arm weighing 28 kg or less received a maintenance dosage of 21 mg/kg three times daily (maximum of 1800 mg) while those weighing more than 28 kg received a maintenance dosage of 600 mg three times daily. The majority (96%) of patients were taking between 1 to 4 concomitant anti-epileptic drugs with valproate, levetiracetam, clobazam, and vigabatrin being the most frequently used. The primary efficacy endpoint was the percentage change in the 28-day frequency of major motor seizures from a 6-week prospective baseline phase during the 17-week double-blind phase. Patients treated with Ztalmy had a significantly greater reduction in the 28-day frequency of major motor seizures (median percent change of -31 from baseline) compared to placebo (median percent change of -7 from baseline). This difference was statistically significant with a p-value of 0.0036.

Libervant
Safety and effectiveness of Libervant in pediatric patients 2 to 5 years of age are supported by evidence from adequate and well-controlled studies of diazepam rectal gel in adult and pediatric patients, adult bioavailability studies comparing Libervant with diazepam rectal gel, adult and pediatric Libervant pharmacokinetic data, and an open-label safety study of Libervant including patients 2 years to 5 years of age.

References

1. Briviact [package insert]. UCB. Smyrna, Georgia. Updated September 2021.
2. Spritam [package insert]. Aprecia Pharmaceuticals. East Windsor, New Jersey. Updated February 2016.
3. UpToDate. Treatment of Juvenile Myoclonic Seizures. Accessed November 2016.
4. UpToDate. Overview of Management of Epilepsy in Adults. Accessed November 2016.
5. Briviact Drug Evaluation. Express Scripts. Updated March 2016.
6. Sympazan [package insert]. Aquestive Therapeutics. Warren, NJ. Updated November 2018.
7. Epidiolex [package insert]. Greenwich Biosciences, Inc. Carlsbad, CA. Updated August 2020.
8. Antiepileptics- Clobazam Products PA Policy. Express Scripts. Updated November 2018.
9. Epidiolex Drug Evaluation. Express Scripts. Updated July 2018.
10. Diacomit [package insert]. Biocodex Inc. Redwood City, CA. Updated March 2019.
11. Diacomit Drug Evaluation. Express Scripts. Updated October 2018.
12. Tuberous Sclerosis Complex: Management and prognosis. UpToDate. Updated September 2020.
13. Xcopri [package insert]. SK Life Science, Inc. Paramus, NJ. Updated October 2020.
14. Xcopri Drug Evaluation. Express Scripts. Updated January 2020.
15. Fintepla [package insert]. Zogenix, Inc. Emeryville, CA. Updated March, 2022.
16. Fintepla Drug Evaluation. Express Scripts. Updated July 2020.
17. Elepsia XR [package insert]. Tripoint Therapeutics, LLC. Westfield, New Jersey. Updated March 2021.
18. Eprontia [package insert]. Azurity Pharmaceuticals, Inc. Wilmington, MA. Updated April 2022.
19. Ztalmy [package insert]. Marinus Pharmaceuticals, Inc. Radnor, PA. Updated June 2022.
20. Motpoly [package insert]. Aucta Pharmaceuticals, Inc. Piscataway, NJ. Updated May 2023.
21. Primidone tablet [package insert]. TruPharma LLC. Tampa, FL. Updated March 2023.
22. Libervant [package insert]. Aquestive Therapeutics. Warren, NJ. Updated November 2024.

Policy History

Original Effective Date: 01/01/2017
Current Effective Date: 01/13/2025

12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. New policy.
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Updated background information to include new pediatric indication for Briviact. Coverage eligibility unchanged.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Added Sympazan and Epidiolex to policy with criteria and relevant background information.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Added Diacomit to the policy with criteria and relevant background information.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. Updated criteria for Epidiolex to include tuberous sclerosis complex and patients over 1 year of age along with relevant background information.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. Added new drug, Xcopri, with relevant criteria and background information.
03/04/2021	Medical Policy Committee review
03/10/2021	Medical Policy Implementation Committee approval. Added new drug, Fintepla, with relevant criteria and background information.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Added new drug, Elepsia XR, with relevant criteria and background information.
06/02/2022	Medical Policy Committee review
06/08/2022	Medical Policy Implementation Committee approval. Updated background information to include approval for Briviact in patients 1 month of age and older. Updated criteria and background to include new indication for Fintepla. Updated criteria and background information to include new drug, Eprontia
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. Updated criteria and background information to include new drug, Ztalmy.
08/03/2023	Medical Policy Committee review
08/09/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/07/2023	Medical Policy Committee review
12/13/2023	Medical Policy Implementation Committee approval. Updated criteria and background information to include new drug, Motpoly XR. Also updated Xcopri criteria to include lacosamide generic.

Policy # 00541
Original Effective Date: 01/01/2017
Current Effective Date: 01/13/2025

04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Added new single source brand primidone product to policy with relevant criteria and background information.
12/05/2024	Medical Policy Committee review
12/11/2024	Medical Policy Implementation Committee approval. Added new drug, Libervant, with relevant criteria and background information.

Next Scheduled Review Date: 12/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.