Select Anti-Epileptic Drugs

Policy # 00541
Original Effective Date: 01/01/2017
Current Effective Date: 11/09/2020

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), and Diacomit®‡ (stiripentol) 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), and Diacomit (stiripentol) 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 greater than or equal to 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 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 greater than or equal to 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 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.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of Briviact (brivaracetam) and Spritam (levetiracetam) 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**.**

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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), and Epidiolex (cannabidiol) 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 4 years 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 is not approved in patients younger than 16 years of age. 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.

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.

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

Rationale/Source

Briviact, and Spritam 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 at least TWO alternative anti-epileptic agents will be ineffective or will cause an adverse reaction to the patient. For Sympazan, the patient selection criteria takes into account patients who may be unable to swallow liquids or tablets.

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 also represents a novel treatment for Dravet syndrome. It 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).

References

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Policy History

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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.

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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.

Next Scheduled Review Date: 10/2021

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.