09-J3000-08

Original Effective Date: 09/15/18

Reviewed: 04/13/22

Revised: 05/15/22

Subject: Cannabidiol (Epidiolex®)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Cannabidiol (Epidiolex), a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant, was approved by the U.S. Food and Drug Administration (FDA) in June 2018 for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients 2 years of age and older. Lennox-Gastaut syndrome is a form of severe epilepsy that begins in childhood. It is characterized by multiple types of seizures and intellectual disability. People with LGS begin having frequent seizures in early childhood, usually between ages 3 and 5. Approximately 90% of patients have seizures persist into adulthood. Dravet syndrome is a rare genetic form of severe epilepsy primarily due to loss-of-function mutations in the SCN1A gene. People with Dravet syndrome begin having seizures in the first year of life, persisting into adulthood.

Lennox-Gastaut Syndrome

The safety and efficacy of cannabidiol was evaluated in a randomized trial of subjects 2 to 55 years old with LGS and seizures inadequately controlled with standard epileptic therapy. Subjects were eligible if they had an electroencephalogram that showed a pattern of slow (<3.0 Hz) spike-and-wave complexes, which is characteristic of the disorder; and had at least two types of generalized seizures, including drop seizures, for at least 6 months. A drop seizure was defined as an epileptic seizure (atonic, tonic, or tonic–clonic) involving the entire body, trunk, or head that leads or could lead to a fall, injury, or slumping in a chair. Eligible patients were taking between one and four antiepileptic drugs and had at least two drop seizures each week during the baseline period.

Subjects (n=225) were randomized to receive cannabidiol oral solution at a dose of either 20 mg per kilogram of body weight (n=76) or 10 mg per kilogram (n=73) or matching placebo (n=76), administered in two equally divided doses daily for 14 weeks. The primary outcome was the percentage change from baseline in the frequency of drop seizures (average per 28 days) during the treatment period. During the

28-day baseline period, the median number of drop seizures was 85 in all trial groups combined. The median percent reduction from baseline in drop-seizure frequency during the treatment period was 41.9% in the 20-mg cannabidiol group, 37.2% in the 10-mg cannabidiol group, and 17.2% in the placebo group (P=0.005 for the 20-mg cannabidiol group vs. placebo group, and P=0.002 for the 10-mg cannabidiol group vs. placebo group).

The most common adverse events among the patients in the cannabidiol groups were somnolence, decreased appetite, and diarrhea; these events occurred more frequently in the higher-dose group. Six patients in the 20-mg cannabidiol group and 1 patient in the 10-mg cannabidiol group discontinued the trial medication because of adverse events and were withdrawn from the trial. Fourteen patients who received cannabidiol (9%) had elevated liver aminotransferase concentrations.

Dravet Syndrome

The safety and efficacy of cannabidiol was evaluated in a randomized trial of 120 subjects aged 2 to 18 years with Dravet syndrome and drug-resistant seizures. Subjects were randomized to receive either cannabidiol oral solution at a dose of 20 mg per kilogram of body weight per day or placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. The median frequency of convulsive seizures per month decreased from 12.4 to 5.9 with cannabidiol, as compared with a decrease from 14.9 to 14.1 with placebo (adjusted median difference between the cannabidiol group and the placebo group in change in seizure frequency, −22.8 percentage points; 95% CI, −41.1 to −5.4; P=0.01). The percentage of patients who had at least a 50% reduction in convulsive-seizure frequency was 43% with cannabidiol and 27% with placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The patient's overall condition improved by at least one category on the seven-category Caregiver Global Impression of Change scale in 62% of the cannabidiol group as compared with 34% of the placebo group (P=0.02). The frequency of total seizures of all types was significantly reduced with cannabidiol (P=0.03), but there was no significant reduction in nonconvulsive seizures. The percentage of patients who became seizure-free was 5% with cannabidiol and 0% with placebo (P=0.08).

Adverse events that occurred more frequently in the cannabidiol group than in the placebo group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver-function tests. There were more withdrawals from the trial in the cannabidiol group.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of cannabidiol (Epidiolex) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with one of the following:
    a. Lennox-Gastaut Syndrome

b. Dravet Syndrome

c. Tuberous Sclerosis Complex

2. Member's diagnosis has been confirmed by a neurologist specializing in epilepsy - documentation from the medical record must be provided
3. Cannabidiol is prescribed by or in consultation with a neurologist specializing in epilepsy
4. Dosage does not exceed:
    a. Initial: 2.5 mg/kg twice daily (5 mg/kg daily)
    b. Maintenance:
        i. Lennox-Gastaut Syndrome, Dravet Syndrome: 10 mg/kg twice daily (20 mg/kg daily)
        ii. Tuberous Sclerosis Complex: 12.5 mg/kg twice daily (25 mg/kg/day)

Approval duration: 1 year

Continuation of cannabidiol (Epidiolex) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of Lennox-Gastaut Syndrome, Dravet Syndrome, or Tuberous Sclerosis Complex, **OR** the member has previously met all indication-specific criteria.
2. Member has had a beneficial response to treatment with cannabidiol - documentation from the medical record must be provided
3. Dose does not exceed
    a. Lennox-Gastaut Syndrome, Dravet Syndrome: 10 mg/kg twice daily (20 mg/kg daily)
    b. Tuberous Sclerosis Complex: 12.5 mg/kg twice daily (25 mg/kg/day)

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- EPIDIOLEX is to be administered orally.
- Lennox-Gastaut Syndrome or Dravet Syndrome:
    - The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
    - After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
    - Patients who are tolerating 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20

mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions

- Tuberous Sclerosis Complex:
    - The starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
    - Increase the dose in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day). For patients in whom a more rapid titration to 25 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day.
    - The effectiveness of doses lower than 12.5 mg/kg twice daily has not been studied in patients with TSC.
- When discontinuing, the dose should be decreased gradually. As with all antiepileptic drugs, abrupt discontinuation should be avoided when possible, to minimize the risk of increased seizure frequency and status epilepticus

Dose Adjustments

- Because of the risk of hepatocellular injury, obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment

Drug Availability

- Oral solution: 100 mg/mL

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Hypersensitivity to cannabidiol

Precautions/Warnings

- Hepatocellular injury
- Somnolence and sedation
- Suicidal behavior and ideation
- Hypersensitivity reactions
- Withdrawal of antiepileptic drugs

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

G40.811	Lennox-Gastaut Syndrome Not Intractable, With Status Epilepticus
G40.812	Lennox-Gastaut Syndrome Not Intractable, Without Status Epilepticus
G40.813	Lennox-Gastaut Syndrome Intractable, With Status
G40.814	Lennox-Gastaut Syndrome Intractable, Without Status
G40.83	Dravet Syndrome
G40.833	Dravet Syndrome, Intractable, With Status Epilepticus
G40.834	Dravet Syndrome, Intractable, Without Status Epilepticus
Q85.1	Tuberous Sclerosis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2022 [cited 4/1/22]. Available from: http://www.clinicalpharmacology.com/.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 4/1/22]. Available from: http://clinicaltrials.gov/.
3. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018 May 17;378(20):1888-1897.

4. Devinsky O, Cross JH, Laux L, Marsh E, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017 May 25;376(21):2011-2020.
5. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 4/1/22].
6. Greenwich Biosciences. Epidiolex (cannabidiol) oral solution. 2022 [cited 4/1/22]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8bf27097-4870-43fb-94f0-f3d0871d1eec /.
7. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2022 [cited 4/1/22]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 04/13/22.

GUIDELINE UPDATE INFORMATION:

09/15/18	New Medical Coverage Guideline.
05/15/19	Review and revision to guideline; updated references.
07/15/20	Review and revision to guideline; updated references.
12/15/20	Updated position statement to include new FDA approved indication.
07/15/21	Review and revision to guideline; updated references.
05/15/22	Review and revision to guideline; updated references.