

Policy Type: PA

Pharmacy Coverage Policy: EOCCO011

Description

Cannabidiol (Epidiolex) is an orally administered cannabinoid.

Length of Authorization

- Initial: Twelve months
- Renewal: Twelve months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cannabidiol (Epidiolex)	100 mg/mL oral solution	Lennox-Gastaut Syndrome Dravet Syndrome	20 mg/kg/day (round up to nearest pack size)
		Tuberous Sclerosis Complex	25 mg/kg/day (round up to nearest pack size)

Initial Evaluation

- I. Cannabidiol (Epidiolex) may be considered medically necessary when the following criteria below are met:
 - A. Member is one year of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - C. Documentation of the member's weight that has been measured in the past three months; **AND**
 - D. Cannabidiol (Epidiolex) will be used in combination with one or more anticonvulsant medications; **AND**
 - E. A diagnosis of one of the following:
 1. **Lennox-Gastaut Syndrome; OR**
 2. **Tuberous Sclerosis Complex; OR**
 3. **Dravet Syndrome; AND**
 - i. Cannabidiol (Epidiolex) will **not** be used in combination with fenfluramine (Fintepla); **AND**
 - F. Member's seizures are refractory to two or more anticonvulsant medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra], rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril])

- II. Cannabidiol (Epidiolex) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
 - A. Infantile Spasms

- B. Other non-FDA approved seizure disorder
- C. Substance use disorder
- D. Prader-Willi Syndrome
- E. Gastrointestinal disorders
- F. Parkinson's Disease/Essential tremors

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
- III. A diagnosis of one of the following:
 - A. **Lennox-Gastaut Syndrome; OR**
 - B. **Tuberous Sclerosis Complex; OR**
 - C. **Dravet Syndrome; AND**
 - 1. Cannabidiol (Epidiolex) will not be used in combination with fenfluramine (Fintepla); **AND**
- IV. Documentation of the member's weight that has been measured in the past three months; **AND**
- V. Cannabidiol (Epidiolex) will continue to be used in combination with at least one other anti-epileptic medication (i.e. used as adjunct therapy) such as clobazam, valproate, levetiracetam, rufinamide, topiramate, felbamate, stiripentol, zonisamide, vigabatrin or lamotrigine; **AND**
- VI. Documentation that the member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency].

Supporting Evidence

- I. Cannabidiol (Epidiolex) (CBD) is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS), or Tuberous Sclerosis Complex (TSC) in patients one year of age and older. It received initial approval for treatment of seizures associated with LGS and DS for patients two years of age and older. This approval was expanded in 2020 to include new indication of seizures associated with TSC in patients one year and older. Additionally, CBD also received approval for expanded age range (one year and older) for patients with LGS and DS.
- II. Differential diagnosis of LGS, DS, or TSC require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (SCN1A mutation for DS). Given the complexities of diagnosing and treating these conditions, supervision of treatment by a neurologist is required.
- III. CBD was studied in four Phase 3, double blind, randomized placebo-controlled clinical trials in patients with baseline characteristics of history of use of two or more antiepileptic drugs (AED). Efficacy of CBD for LGS was studied in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years old. Study 1 (N=171) compared a dose of Epidiolex 20 mg/kg/day with placebo, while Study 2 (N=225) used 10 mg/kg/day and 20 mg/kg/day doses with a match with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled

on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. At 14 weeks, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of CBD versus placebo with an observed reduction in drop seizures frequency within 4 weeks of initiating treatment.

- IV. Study 3 (N= 120) assessed efficacy and safety of CBD for the treatment of convulsive seizures (tonic, clonic, atonic, and tonic-clonic) associated with DS in patients refractory to at least 2 AEDs. The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for CBD 20 mg/kg/day treatment arm as compared to placebo (-39% versus -13%; $p= 0.01$).
- V. Participants in study 4 (N=224) were aged 1 to 65 years. Cannabidiol (Epidiolex) was evaluated at 25 mg/kg/day (CBD25) and 50 mg/kg/day (CBD50) doses with a matching placebo, for efficacy in treatment of seizures (focal, tonic, clonic, atonic or tonic-clonic) associated with TSC. At 16 weeks cut-off, Percent reduction (per 28 days) in TSC-associated seizure frequency was significantly higher for CBD25 cohort (48.6%) and CBD50 cohort (47.5%) vs placebo (27%; $p=0.0009$ and $p=0.0018$, respectively). Ninety-nine percent (N=199) of the patients from the initial 16-week controlled trial elected to continue into a 48-week open-label extension phase, wherein safety of CBD was assessed. Although most common adverse reactions (diarrhea, anorexia and somnolence) were mild to moderate the CBD50 cohort reported higher incidence of AE including liver function impairment (ALT and/or AST elevation).
- VI. CBD can cause dose-related elevations of liver transaminases (ALT and/or AST). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in CBD-treated patients compared with 1% in patients on placebo. Assessment of liver function (ALT, AST, total bilirubin) is recommended prior to initiating treatment with CBD, with dose changes, or with the addition of, or changes in, hepatotoxic medications.
- VII. During clinical trials for all FDA-approved indications, participants received CBD as an adjunct therapy. Majority of participants in these trials were receiving a median of 2 concomitant antiepileptic drugs (AED). Inclusion in clinical trial also required documentation of seizures above the minimum threshold (≥ 8 drop seizures per 28 days for LGS, ≥ 4 convulsive seizures per 28 days for DS, and ≥ 8 seizures per 28 days for TSC). Efficacy and safety of CBD as monotherapy has not been studied and remains unknown.

Investigational or Not Medically Necessary Uses

- I. There are ongoing trials for infantile spasms, substance use disorder, Prader-Willi Syndrome, gastrointestinal disorders, Parkinson's disease/essential tremors, and other seizure disorders, therefore these indications are considered investigational at this time.

References

1. Epidiolex [Prescribing Information]. Greenwich Biosciences: Carlsbad, CA; July 2020.
2. Arzimanoglou A, French J, Blume WT et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol*. 2009 Jan;8(1):82-93. PMID: 19081517.

3. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav.* 2017 May;70(Pt B):313-318. E-published ahead of print 2017 Jan 10. PMID: 28087250.
4. Kanner AM, Ashman E, Gloss D et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. *Neurology.* 2018; 0: 1-9. E-published ahead of print 2018 Jun 13. PMID: 29898974.
5. UpToDate, Inc. Dravet syndrome: Management and prognosis. *UpToDate* [database online]. Last updated September 2017.
6. UpToDate, Inc. Epilepsy syndromes in children. *UpToDate* [database online]. Last updated July 2018.
7. Wirrell EC, Laux L, Donner E et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations from a North American Consensus Panel. *Ped Neurol.* 2017 Mar; 68:18-34. e3. E published ahead of print 2017 Feb 4. PMID: 28284397.
8. Sahebkar F, Thiele E, Bebin EM, Bhathal H et al.; Cannabidiol (CBD) treatment in patients with seizures associated with tuberous sclerosis complex (TSC): a randomized, double-blind, placebo-controlled phase 3 trial (GWPCARE6), 2020, *Developmental Medicine and Child Neurology*; 62,13; conference abstract.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include new indication for cannabidiol (Epidiolex) for treatment of seizures associated with Tuberous Sclerosis Complex (TSC); updated policy format for consistency of requirements for coverage for each approved indication; added weight-based dosing and quantity limit; renewal criteria and supporting evidence section were updated	10/2020
Policy created	01/2019