Clinical Policy: Cannabidiol (Epidiolex)

Reference Number: DE.PMN.164
Effective Date: 01.23
Last Review Date: 01.23
Line of Business: Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Cannabidiol (Epidiolex®) is a cannabinoid.

FDA Approved Indication(s)

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

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Epidiolex is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Seizures Associated with Dravet Syndrome, Lennox-Gastaut Syndrome, or Tuberous Sclerosis Complex (must meet all)**:**

1. Diagnosis of DS, LGS, or TSC;
2. Age ≥ 1 year;
3. Will be used as adjunctive therapy (*see Appendix B*) with at least one other antiepileptic drug (AED);
4. For LGS, failure of two of the following, unless clinically significant adverse effects are experienced or all are contraindicated: clobazam, clonazepam, lamotrigine, rufinamide, topiramate;
5. Dose does not exceed any of the following (a or b):
   a. For DS or LGS: 20 mg/kg per day;
   b. For TSC: 25 mg/kg per day.

Approval duration:
Medicaid – 12 months

B. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Seizures Associated with Dravet Syndrome, Lennox-Gastaut Syndrome, or Tuberous Sclerosis Complex (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Epidiolex for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Epidiolex will continue to be used as adjunctive therapy (*see Appendix B*) with at least one other AED;
4. If request is for a dose increase, new dose does not exceed any of the following (a or b):
   a. For DS or LGS: 20 mg/kg per day;
   b. For TSC: 25 mg/kg per day.

Approval duration:
Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policies CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AED: antiepileptic drug
DS: Dravet syndrome
FDA: Food and Drug Administration
LGS: Lennox-Gastaut syndrome
TSC: tuberous sclerosis complex

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
LGS, DS		
topiramate (Topamax®, Qudexy® XR)	**LGS** • Adults and Adolescents 17 years and older: Initial dose is 25 to 50 mg/day orally. Maintenance dose is 200 to 400 mg/day orally (divided and given twice daily).	LGS: Age ≥ 17: 400 mg/day Age 2 – 16: 25 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• Children and Adolescents 2 to 16 years: Initial dose is 1 to 3 mg/kg/day (max: 25 mg/day) orally once daily in the evening. Maintenance dose is 5 to 9 mg/kg/day orally. **DS**‡ Initial dose is 0.5 to 2 mg/kg/day orally. Max target dose is 8 to 12 mg/kg/day orally.	DS: 8 to 12 mg/kg/day
lamotrigine (Lamictal® CD, ODT, XR, & Subvenite®)	**LGS**‡ • Patients receiving enzyme-inducing AEDs (e.g., carbamazepine, phenobarbital, phenytoin, primidone) NOT to include valproate: ○ Adults and Adolescents: Initial dose is 50 mg orally daily. Maintenance dose is 300 to 500 mg/day orally given in 2 divided doses. ○ Children 2 to 12 years: Initial dose is 0.6 mg/kg/day orally in 2 divided doses. Maintenance dose is 5 to 15 mg/kg/day (max 400 mg/day) orally given in 2 divided doses. • Patients receiving valproate: ○ Adults and Adolescents: Initial dose is 25 mg orally every other day is given for 2 weeks. Maintenance dose is 100 to 400 mg/day orally, given in 1 to 2 divided doses. ○ Children 2 to 12 years: Dosage depends on weight. **DS**‡ Avoid lamotrigine and other sodium channel agents since they can exacerbate seizures associated with Dravet Syndrome.	With valproate: 100 mg/day With enzyme-inducing drugs: 400 mg/day
felbamate (Felbatol®)	**LGS** Adolescents and Children 2 - 14 years: Add felbamate at 15 mg/kg/day orally in 3-4 divided doses while reducing doses of other AEDs by 20-30%. Increase felbamate dose by 15 mg/kg/day increments at weekly intervals to 45 mg/kg/day orally. Max dose is 3,600 mg/day orally.	3,600 mg/day
rufinamide (Banzel®)	**LGS** • Adults and Adolescents ≥ 17 years: Initial dose is 400-800 mg/day orally in 2 equally divided doses. Target and max dose is 3,200 mg/day orally given in 2 equally divided doses.	3,200 mg/kg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• Children and Adolescents 1-16 years: Initial dose is 10 mg/kg/day orally given as 2 equally divided doses. Maintenance target dose is 45 mg/kg/day or 3,200 mg/day orally, whichever is less, given in 2 equally divided doses. **DS** Avoid rufinamide and other sodium channel agents since they can exacerbate seizures associated with Dravet Syndrome.	
clobazam (Onfi®)	**LGS** For Adults, Adolescents, & Children older than 2 years: • Patients weighing > 30 kg: Initial dose is 5 mg orally twice daily. Max dose is 20 mg orally twice daily. Dosing should be individualized based upon efficacy and tolerability. • Patients weighing ≤ 30 kg: Initial dose is 5 mg orally once daily. Max dose is 10 mg orally twice daily. Dosing should be individualized based upon efficacy and tolerability. **DS**‡ Initial dose is 0.2 to 0.3 mg/kg/day PO. Max target dose is 0.5 to 2 mg/kg/day PO.	LGS: ≤ 30 kg: 0.2 mg/kg/day > 30 kg: 20 mg/day DS: 2 mg/kg/day
clonazepam (Klonopin®)	**LGS** For Adults, Adolescents, & Children: • Patients weighing > 30 kg: Initial dose is 1.5 mg/day orally, given in three equally divided doses. Max dose is 20 mg/day orally, given in three equally divided doses. • Patients weighing ≤ 30 kg: Initial dose is 0.01 to 0.03 mg/kg/day orally, given in three equally divided doses. Max dose is 0.1 to 0.2 mg/kg/day orally, given in three equally divided doses.	≤ 30 kg: 0.2 mg/kg/day > 30 kg: 20 mg/day
valproic acid (Depakene®, Depakote®, Stavzor®)	**LGS**‡ Initial dose is 7 to 10 mg/kg/day PO, given three to four times daily for nonenteric-coated capsules or syrup, BID for delayed-release tablets, and QD for the extended release preparation. A typical adult starting dose is 500 mg QD. The max dose is 60 mg/kg/day or 3,000 mg/day. **DS**‡	LGS: 60 mg/kg/day or 3,000 mg/day DS: 60 mg/kg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Initial dose is 10 to 15 mg/kg/day PO, given in two to three equally divided doses. Max target dose is 25 to 60 mg/kg/day PO, given in two to three equally divided doses, depending on achieved blood levels.	
levetiracetam (Spritam®, Keppra®)	**LGS**‡ Initial dose is 5 mg/kg/day PO, given in two or three equal doses per day. Max dose is 20 to 80 mg/kg/day PO, according to effectiveness and tolerability. **DS**‡ Initial dose is 10 to 20 mg/kg/day PO, divided twice daily or three times daily. Max dose is 60 to 80 mg/kg/day PO, divided twice daily or three times daily.	80 mg/kg/day
TSC		
AED examples for partial seizures	carbamazepine (Tegretol®), felbamate (Felbatol®), gabapentin (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), oxcarbazepine (Trileptal®), phenytoin (Dilantin®), tiagabine (Gabitril®), topiramate (Topamax®), valproic acid (Depakene®), divalproex sodium (Depakote®), vigabatrin (Sabril®), zonisamide (Zonegran®)	Varies according to the agent used
AED examples for generalized onset seizures	carbamazepine (Tegretol®), lamotrigine (Lamictal®), levetiracetam (Keppra®), phenytoin (Dilantin®), primidone (Mysoline®), topiramate (Topamax®), valproic acid (Depakene®), divalproex sodium (Depakote®)	Varies according to the agent used
Afinitor Disperz® (everolimus)	**TSC-associated partial-onset seizures** 5 mg/m^2 PO QD; adjust dose to attain trough concentration of 5-15 ng/mL	Based on trough concentration

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
‡ *Off-label*

Appendix C: Contraindications / Boxed Warnings

- Contraindication(s): hypersensitivity to cannabidiol or any of the ingredients in the product
- Boxed warning(s): none reported

Appendix D: General Information

- DS, also called severe myoclonic epilepsy of infancy, is a severe form of epilepsy. Per the United Kingdom National Institute for Health and Care Excellence (NICE) Anti-Epileptic

Pharmacologic Treatment Guidelines (published on January 2012 and updated on April 2018), the recommended first-line anti-epileptic drugs to treat DS are sodium valproate and topiramate. Clobazam and stiripentol are listed as adjunctive anti-epileptic drugs. Except for stiripentol, these drugs are not FDA-approved for treatment of DS.

- LGS is another severe form of epilepsy. Per American Academy of Neurology and the American Epilepsy Society Anti-Epileptic Pharmacologic Treatment Guidelines, the recommended treatment for drop seizures associated with LGS is lamotrigine and topiramate (Level A).
  - A Cochrane Database of Systematic Review 2013 article concluded that the optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious; rufinamide, lamotrigine, topiramate and felbamate may be helpful as add-on therapy, and clobazam may be helpful for drop seizures. Until further research has been undertaken, clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.
- Seizures associated with TSC are a rare neurocutaneous genetic disorder, with a prevalence of one in 6,000 to 10,000. Mutations in either TSC1 or TSC2 lead to over-activation of the mammalian target of rapamycin (mTOR) pathway and relatively uncontrolled cell growth that causes growth of benign tumors (hamartomas) in various organs, such as the brain, kidneys, skin, heart, lungs and bones, with epilepsy being the most common neurological symptom in TSC. While vigabatrin is the recommended first-line therapy for TSC-associated infantile spasms, anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies per the Tuberous Sclerosis Complex Surveillance and Management Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference and the 2019 UK guidelines for management and surveillance of TSC. Patients with TSC can present with almost any seizure type including tonic, atonic or tonic-clonic seizures, with about two-thirds having refractory focal-onset (previously referred to as partial-onset) epilepsy; focal seizures and epileptic spasms are the most prevalent.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
DS, LGS	Initial dose is 2.5 mg/kg PO BID (5 mg/kg/day). Maintenance dose is 5 mg/kg PO BID (10 mg/kg/day) to 10 mg/kg PO BID (20 mg/kg/day). Dosage adjustment is recommended for patients with moderate or severe hepatic impairment.	20 mg/kg/day
TSC	Initial dose is 2.5 mg/kg PO BID (5 mg/kg/day). Increase the dose in weekly increments of 2.5 mg/kg BID (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg BID (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.	25 mg/kg/day

VI. Product Availability

Oral solution: 100 mg/mL (100 mL)

VII. References

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	01.23	01.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.