

Clinical Policy: Cannabidiol (Epidiolex)

Reference Number: CP.PMN.164

Effective Date: 07.17.18

Last Review Date: 08.19

Line of Business: Commercial, HIM, 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, in patients 2 years of age and older, for the treatment of seizures associated with:

- Dravet Syndrome (DS)
- Lennox-Gastaut Syndrome (LGS)

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. Dravet Syndrome or Lennox-Gastaut Syndrome (must meet all):

1. Diagnosis of DS or LGS;
2. Prescribed by or in consultation with a neurologist;
3. Age \geq 2 years;
4. Will be used as adjunctive therapy (*see Appendix B*) with at least one other antiepileptic drug;
5. For LGS, failure of two of the following, unless contraindicated or clinically significant adverse effects are experienced: Banzel®, clobazam, clonazepam, felbamate, lamotrigine, topiramate;
6. Dose does not exceed 20 mg/kg/day.

Approval duration:

Medicaid/HIM – 12 months

Commercial – Length of Benefit

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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Dravet Syndrome or Lennox-Gastaut Syndrome (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. If request is for a dose increase, new dose does not exceed 10 mg/kg orally twice daily (20 mg/kg/day).

Approval duration:

Medicaid/HIM – 12 months

Commercial – Length of Benefit

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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration

DS: Dravet Syndrome

LGS: Lennox-Gastaut Syndrome

AEDs: antiepileptic drugs

Appendix B: Therapeutic Alternatives for adjunctive treatment of Lennox-Gastaut Syndrome
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
topiramate (Topamax [®] , Trokendi [®] XR, Qudexy [®] XR)	<p>LGS</p> <ul style="list-style-type: none"> • 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). • Children and Adolescents 2 to 16 years: Initial dose is 1 to 3 mg/kg/day (max: 25 mg/day) 	<p>LGS: Age ≥ 17: 400 mg/day Age 2 – 16: 25 mg/day</p> <p>DS: 8 to 12 mg/kg/day</p>

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	<p>orally once daily in the evening. Maintenance dose is 5 to 9 mg/kg/day orally.</p> <p>DS[†] Initial dose is 0.5 to 2 mg/kg/day orally. Max target dose is 8 to 12 mg/kg/day orally.</p>	
<p>lamotrigine (Lamictal[®] CD, ODT, XR, & Subvenite[®])</p>	<p>LGS</p> <ul style="list-style-type: none"> • Patients receiving enzyme-inducing AEDs (e.g., carbamazepine, phenobarbital, phenytoin, primidone) NOT to include valproate: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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. <p>DS Avoid lamotrigine and other sodium channel agents since they can exacerbate seizures associated with Dravet Syndrome.</p>	<p>With valproate: 100 mg/day With enzyme-inducing drugs: 400 mg/day</p>
<p>felbamate (Felbatol[®])</p>	<p>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.</p>	<p>3,600 mg/day</p>
<p>Banzel[®] (rufinamide)</p>	<p>LGS</p> <ul style="list-style-type: none"> • 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. • Children and Adolescents 1-16 years: Initial dose is 10 mg/kg/day orally given as 2 equally 	<p>3,200 mg/kg/day</p>

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	<p>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.</p> <p>DS Avoid Rufinamide and other sodium channel agents since they can exacerbate seizures associated with Dravet Syndrome.</p>	
<p>clobazam (Onfi®)</p>	<p>LGS For Adults, Adolescents, & Children older than 2 years:</p> <ul style="list-style-type: none"> • 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. <p>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.</p>	<p>LGS: ≤ 30 kg: 0.2 mg/kg/day > 30 kg: 20 mg/day</p> <p>DS: 2 mg/kg/day</p>
<p>clonazepam (Klonopin®)</p>	<p>LGS For Adults, Adolescents, & Children:</p> <ul style="list-style-type: none"> • 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. 	<p>≤ 30 kg: 0.2 mg/kg/day > 30 kg: 20 mg/day</p>
<p>valproic acid (Depakene®, Depakote®, Stavzor®)</p>	<p>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.</p> <p>DS[†] 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</p>	<p>LGS: 60 mg/kg/day or 3,000 mg/day</p> <p>DS: 60 mg/kg/day</p>

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	equally divided doses, depending on achieved blood levels.	
levetiracetam (Spritam [®] , Keppra [®])	<p>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.</p> <p>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.</p>	80 mg/kg/day

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 components of the product, which includes sesame seed oil
- Boxed warning(s): None reported

Appendix D: General Information

- Dravet Syndrome (DS), also called severe myoclonic epilepsy of infancy (SMEI), 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 Dravet Syndrome are sodium valproate and topiramate. Clobazam and stiripentol are listed as adjunctive anti-epileptic drugs. To note, stiripentol is approved in Canada, Japan, and European countries, but not FDA-approved in the United States. Sodium valproate is also not FDA-approved for treatment of Dravet Syndrome.
- Lennox-Gastaut syndrome (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 Lennox-Gastaut Syndrome 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Dravet Syndrome & Lennox-Gastaut Syndrome	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.	10 mg/kg PO BID (20 mg/kg/day)

VI. Product Availability

Oral solution: 100 mg/mL

VII. References

1. Epidiolex Prescribing Information. Carlsbad, CA: Greenwich Biosciences, Inc; December 2018. Available at: www.epidiolex.com. Accessed May 19, 2019.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available at: <http://www.clinicalpharmacology-ip.com/>.
3. National Institute of Neurological Disorders and Stroke. Dravet Syndrome Information Page. Available at: <https://www.ninds.nih.gov/Disorders/All-Disorders/Dravet-Syndrome-Information-Page>. Accessed July 2, 2018.
4. Wirrell EC. Treatment of dravet syndrome. *Can J Neurol Sci.* 2016 Jun;43 Suppl 3:S13-8.
5. National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. Available at: <https://www.nice.org.uk/guidance/CG137/chapter/Appendix-E-Pharmacological-treatment>. Accessed July 2, 2018.
6. Ferrie CD, Patel A. Treatment of lennox-gastaut syndrome. *Eur J Paediatr Neurol.* 2009 Nov;13(6):493-504.
7. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. July 10, 2018; 91 (2)
8. National Institute of Neurological Disorders and Stroke. Lennox-Gastaut Syndrome Information Page. Available at: <https://www.ninds.nih.gov/Disorders/All-Disorders/Lennox-Gastaut-Syndrome-Information-Page>. Accessed May 19, 2019.
9. Panebianco M, Prabhakar H, Marson AG. Rufinamide add-on therapy for refractory epilepsy. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD011772.
10. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD003277.
11. Wirrell EC. Treatment of Dravet Syndrome. *Can J Neurol Sci.* 2016 Jun;43 Suppl 3:S13-8. doi: 10.1017/cjn.2016.249. <https://www.ncbi.nlm.nih.gov/pubmed/27264138>
12. Kim HJ, Kim SH, MD, Kang HC, et al. Adjunctive Levetiracetam Treatment in Pediatric Lennox-Gastaut Syndrome. *Pediatr Neurol.* 2014 Oct;51(4):527-31. doi: 10.1016/j.pediatrneurol.2014.06.004. Epub 2014 Jun 25. <https://www.ncbi.nlm.nih.gov/pubmed/25266616>

13. Grosso S, Franzoni E, Coppola G, et al. Efficacy and safety of levetiracetam: an add-on trial in children with refractory epilepsy. *Seizure*. 2005 Jun;14(4):248-53.
<https://www.ncbi.nlm.nih.gov/pubmed/15911359>
14. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. *Neurol Sci*. 2018 Mar;39(3):403-414. doi: 10.1007/s10072-017-3188-y. Epub 2017 Nov 9.
<https://www.ncbi.nlm.nih.gov/pubmed/29124439>

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	07.17.18	08.18
No significant changes: clarified redirection language to “at least one” other antiepileptic drug from “other antiepileptic drugs.”	10.23.18	
No significant changes; added HIM line of business; for Lennox-Gastaut Syndrome, per SDC added requirement for failure of two of the following, unless contraindicated or clinically significant adverse effects are experienced: Banzel, clobazam, clonazepam, felbamate, lamotrigine, topiramate, consistent with prior clinical guidance.	03.04.19	
3Q 2019 annual review: no significant changes; references reviewed and updated.	05.19.19	08.19

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

©2018 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.