RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	cannabidiol
Policy Number:	RxA.370
Drug(s) Applied:	Epidiolex®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2020
Line of Business Policy Applies to:	All lines of business

Background

Cannabidiol (Epidiolex®) is a cannabinoid. It is indicated, in patients 2 years of age and older, for the treatment of seizures associated with:

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Cannabidiol (Epidiolex®)	Dravet Syndrome & Lennox-Gastaut Syndrome	Initial dose is 2.5 mg/kg PO twice a day (5mg/kg/day). Maintenance dose is 5 mg/kg PO twice a day (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 twice a day (20 g/kg/day)

Dosage Forms

- Oral solution: 100 mg/mL

Clinical Policy

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

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 2 years of age or older;

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
Commercial :12 months
Medicaid :12 months
HIM :12 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance , 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
Commercial :12 months
Medicaid :12 months
HIM :12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AEDs: Antiepileptic Drugs
DS: Dravet Syndrome
FDA: Food and Drug Administration
LGS: Lennox-Gastaut Syndrome

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
topiramate (Topamax®, Trokendi® XR, 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). 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.	**LGS** Age ≥ 17: 400 mg/day Age 2 – 16: 25 mg/day **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 2030%. 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
Banzel (rufinamide)	**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. 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.	3,200 mg/kg/day
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	**LGS** ≤ 30 kg: 0.2 mg/kg/day > 30 kg:

	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**ǂ Initial dose is 0.2 to 0.3 mg/kg/day PO. Max target dose is 0.5 to 2 mg/kg/day PO.	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 (®, Depakote®, ®)	**LGS**ǂ 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**ǂ 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.	**LGS** 60 mg/kg/day or 3,000 mg/day **DS** 60 mg/kgday
levetiracetam (Spritam®, Keppra®)	**LGS**ǂ 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**ǂ 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

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. ǂ 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

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.

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1) Policy description table was updated 2) Dosing Information was updated to replace BID with "twice a day" 3) Continuation therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance" 4) Approval duration updated for both indications and both initial & continued therapies 5) Appendix B, therapeutic alternatives was updated to remove brand drug names: Stavzor, Depakene due to discontinuation 6) References were updated	07/28/2020	09/14/2020