Clinical Policy Title:	cannabidiol
Policy Number:	RxA.370
Drug(s) Applied:	Epidiolex®
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All line of business

Background

Cannabidiol (Epidiolex®) is a cannabinoid. It is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
cannabidiol (Epidiolex®)	Seizures associated with Dravet Syndrome & Lennox-Gastaut Syndrome	The recommended starting dosage is 2.5 mg/kg by mouth 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). Based on individual clinical response and tolerability, Epidiolex® can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).	20 mg/kg/day orally.
	Seizures associated with tuberous sclerosis complex	The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). Increase the dose weekly by 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).	25 mg/kg/day PO.

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. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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 ≥ 1 years;
4. Obtain baseline complete blood count (CBC), serum transaminase and total bilirubin prior to initiating therapy;
5. For LGS, failure of two of the following, unless contraindicated or clinically significant adverse effects are experienced: Banzel® (rufinamide), clobazam, clonazepam, felbamate, lamotrigine, topiramate, valproic acid;
6. For DS, failure of at least two of the following, unless contraindicated or clinically significant adverse effects are experienced: clobazam, levetiracetam, topiramate, and valproic acid;
7. Maximum dose does not exceed 20 mg/kg/day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

B. Tuberous sclerosis complex (must meet all)**:**

1. Diagnosis of TSC;
2. Prescribed by or in consultation with a neurologist;
3. Age 1 years of age or older;
4. Obtain baseline complete blood count (CBC), serum transaminase and total bilirubin prior to initiating therapy;
5. For TSC, failure of two of the following, unless contraindicated or clinically significant adverse effects are experienced: carbamazepine, oxcarbazepine, and vigabatrin.;
6. Maximum dose does not exceed 25 mg/kg/day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in section I (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy, 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:
   a. 10 mg/kg orally twice daily (20 mg/kg/day) for DS and LGS;
   b. 12.5 mg/kg twice daily (25 mg/kg/day) for TSC.

Approval duration

Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

AEDs: Antiepileptic Drugs
DS: Dravet Syndrome
FDA: Food and Drug Administration
LGS: Lennox-Gastaut Syndrome
TSC: Tuberous sclerosis complex

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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**[ǂ] 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: o Adults and Adolescents: Initial dose is 50 mg orally daily. Maintenance dose is 300 to 500 mg/day orally given in 2 divided doses. o 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: o 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. o 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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: o 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. o 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: o 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. o 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
valproic acid (Depakote®)	**LGS‡** Initial dose is 7 to 10 mg/kg/day PO, given three to four times daily for nonenteric-coated capsules or syrup, twice a day for delayed-release tablets, and once daily for the extended-release preparation. A typical adult starting dose is 500 mg once daily. The max dose is 60 mg/kg/day or 3,000 mg/day. **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 equally divided doses, depending on achieved blood levels.	**LGS** 60 mg/kg/day or 3,000 mg/day **DS** 60 mg/kg/day
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

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

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

- Hepatocellular Injury: Epidiolex® can cause transaminase elevations. Concomitant use of valproate and higher doses of Epidiolex® increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations.
- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on Epidiolex®.
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts.
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart Epidiolex® if hypersensitivity occurs.
- Withdrawal of Antiepileptic Drugs: Epidiolex® should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus.

References

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Review/Revision History	Review/Revision 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	07/28/2020	09/14/2020
1) for both indications and both initial & continued therapies.		

2) Appendix B, therapeutic alternatives were updated to remove brand drug names: Stavzor, Depakene due to discontinuation. 3) References were updated.		
Policy was reviewed: 1) Background was updated to include "…or tuberous sclerosis complex in patients 1 year of age and older". 2) Dosing Information indication was updated from "Dravet Syndrome & LennoxGastaut Syndrome" to "Seizures associated with Dravet Syndrome & Lennox-Gastaut Syndrome". 3) Dosing Information dosing regimen for indication Seizures associated with Dravet Syndrome & Lennox-Gastaut Syndrome was updated to include "Based on individual clinical response and tolerability, Epidiolex® can be increased…". 4) Dosing Information was updated to include indication , "Seizures associated with tuberous sclerosis complex" and its respective dosing information and maximum dose. 5) Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 6) Initial Approval Criteria I.A.3 age criteria was updated from "Age ≥ 2 years" to "Age ≥ 1 years".	05/31/2021	09/14/2021

7) Initial Approval Criteria I.A.4 was updated to include “Obtain baseline complete blood count (CBC), serum transaminase and total bilirubin prior to initiating therapy”. 8) Initial Approval Criteria I.A.4 was updated to remove “Will be used as adjunctive therapy (see Appendix B) with at least one other antiepileptic drug”. 9) Initial Approval Criteria I.A.5 was updated to include generic drug names srufinamide and valproic acid. 10) Initial Approval Criteria I.A.6 was updated to include “For DS, failure of at least two of the following, unless contraindicated or clinically significant adverse…”. 11) Initial Approval Criteria I.B was updated to include indication “Tuberous sclerosis complex”. 12) Continued Therapy Approval Criteria II.A was updated from “Dravet Syndrome or Lennox-Gastaut Syndrome” to “All indications in section I”. 13) Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 14) Continued Therapy Approval Criteria II.A.3 was updated from “If request is for a dose increase, new dose does not exceed 10 mg/kg orally twice daily (20 mg/kg/day)” to “If request is for a dose increase, new dose does not exceed…”.		

15) Continued Therapy Approval Criteria II.A.3 was updated to include sub-criteria a and b; “10 mg/kg orally twice daily (20 mg/kg/day) for DS and LGS” and “12.5 mg/kg twice daily (25 mg/kg/day) for TSC”; respectively. 16) Appendix A was updated to include abbreviation TSC. 17) Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 18) Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 19) Appendix D was updated to remove “Dravet Syndrome (DS), also called severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy…” and “Lennox-Gastaut syndrome (LGS) is another severe form of epilepsy…”. 20) Appendix D was updated to include “Hepatocellular Injury: Epidiolex® can cause transaminase elevations…” , “Somnolence and Sedation: Monitor for somnolence and sedation and advise patients…”, “Suicidal Behavior and Ideation: Monitor patients		

for suicidal behavior and thoughts…", "Hypersensitivity Reactions: Advise patients to seek immediate medical care…", and "Withdrawal of Antiepileptic Drugs: Epidiolex® should be gradually withdrawn…". 21) References were reviewed and updated.		