Drug Coverage Policy

Effective Date.....5/15/2024
Coverage Policy Number.....IP0410
Policy Title.....Epidiolex

Antiseizure Medications – Epidiolex

- Epidiolex® (cannabidiol oral solution – Greenwich Biosciences)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW
Epidiolex, a cannabinoid, is indicated in patients ≥ 1 year of age for the **treatment of seizures associated with**:[1]

- **Dravet syndrome**.
- **Lennox-Gastaut syndrome**.
- **Tuberous sclerosis complex**.

Disease Overview
Dravet syndrome is a rare genetic epileptic encephalopathy marked with frequent and/or prolonged seizures.[2,3] The seizures generally begin in the first year of life in an otherwise healthy

infant. Affected individuals can develop many seizure types: myoclonic, tonic-clonic, absence, atypical absence, atonic, focal aware or impaired awareness (previously called partial seizures), and status epilepticus.[3] Two or more antiseizure medications (ASMs) are often needed to control the seizures; most of the seizures are refractory to medications. The goals of treatment are cessation of prolonged convulsions, reduction in overall seizure frequency, and minimization of treatment side effects.[4,5]

Lennox-Gastaut syndrome, a severe epileptic and developmental encephalopathy, is associated with a high rate of morbidity and mortality.[6,7] Lennox-Gastaut syndrome most often begins between 3 and 5 years of age.[6-9] Affected children experience several different types of seizures, most commonly atonic seizures (sudden loss of muscle tone and limpness) and tonic seizures.[6,9] The three main forms of treatment of Lennox-Gastaut syndrome are ASMs, dietary therapy (typically the ketogenic diet), and device/surgery (e.g., vagus nerve stimulation, corpus callosotomy).[9] None of the therapies are effective in all cases of Lennox-Gastaut syndrome and the disorder has proven particularly resistant to most therapeutic options.

Tuberous sclerosis complex is a rare, genetic disease that causes non-cancerous (benign) tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin.[10] It can result in a combination of symptoms including seizures, impaired intellectual development, autism, behavioral problems, skin abnormalities, and kidney disease. Seizures affect most individuals with tuberous sclerosis complex at some point during their life and can be difficult to control.

Clinical Efficacy in Other Refractory Seizures

In 2014, an expanded access program was initiated to provide Epidiolex to patients with treatment-resistant epilepsy.[14] Of the 840 patients included in a published review, 192 patients were diagnosed with Dravet syndrome or Lennox-Gastaut syndrome, and 648 patients were diagnosed with other conditions, including CDKL5 deficiency disorder, Dup15q, Aicardi, and Doose syndromes; febrile infection-related epilepsy syndromes; tuberous sclerosis complex; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and myoclonic absence. The patients enrolled in the study had severe, intractable, childhood-onset treatment-resistant epilepsy and were on stable doses of ASMs for 4 weeks before starting Epidiolex as add-on therapy. The initial dose of Epidiolex was 2 to 10 mg/kg/day (taken as two divided doses) and gradually titrated until intolerance or to a maximum dose of 25 mg/kg/day or 50 mg/kg/day, depending upon treatment site. Of those enrolled in the expanded access program, 892 patients were evaluated and included in the safety analysis set and 840 patients were included in the efficacy analysis set. Through 192 weeks, the median percentage reduction in seizure frequency across visit windows ranged from 50% to 67% for convulsive seizures and 46% to 66% for total seizures. In a cohort of 132 patients (72 children, 60 adults) with treatment-resistant epilepsy, bi-weekly seizure frequency decreased from a mean of 144.4 at entry to 52.2 at 12 weeks ($P = 0.01$) and remained stable thereafter.[15] Of note, patients with a diagnosis of Lennox-Gastaut syndrome or Dravet syndrome were initially excluded because of preferential enrollment into the randomized clinical trials; once these trials were closed for enrollment, patients with these syndromes were also enrolled. In a separate cohort of patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes ($n = 46$), the percent change in median convulsive seizure frequency decreased from baseline to Week 12 by 51.4% and by 59.1% at Week 48.[16] There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and Week 12 ($P = 0.00001$), with no difference in seizure percent change between Weeks 12 and 48. Of the 55 patients in the safety group, 27% of patients withdrew by Week 144 due to adverse effects ($n = 4$), lack of efficacy ($n = 9$), withdrawn consent ($n = 1$), and lost to follow-up ($n = 1$).

Guidelines/Recommendations

Dravet Syndrome
At this time, there are three drugs approved for the treatment of seizures associated with Dravet syndrome: Epidiolex, Diacomit® (stiripentol capsules, powder for oral suspension), and Fintepla® (fenfluramine oral solution).[1,11,17] An expert panel considers valproic acid and clobazam to be the first-line treatment for Dravet syndrome.[4] If seizure control is suboptimal, Diacomit and topiramate are second-line treatment. Ketogenic diet is moderately effective and can also be considered second-line. The Dravet Foundation states that Diacomit, Epidiolex, and Fintepla are considered first-line agents for the treatment of Dravet syndrome.[2] If control is still inadequate, other therapies to consider are clonazepam, levetiracetam, and zonisamide.[2,4] Sodium channel blockers (e.g., carbamazepine, oxcarbazepine, lamotrigine, and phenytoin) can worsen seizures in Dravet syndrome. Additionally, vigabatrin and tiagabine may increase the frequency of myoclonic seizures and should be avoided.

Lennox-Gastaut Syndrome
Currently, the FDA-approved drugs for this condition are Epidiolex, Fintepla, felbamate, Banzel® (rufinamide tablet, oral suspension), lamotrigine, topiramate, and clobazam.[12] Despite the lack of level I or level II evidence, valproic acid remains a mainstay in treatment.[8,9,13] If valproic acid does not provide adequate seizure control, which is almost always the case, lamotrigine should be added as the first adjunctive therapy.[7] If the combination regimen of valproic acid and lamotrigine does not provide adequate control, then Banzel should be initiated and either valproic acid or lamotrigine should be discontinued. If seizure control is still not achieved, the next adjunctive therapies to consider are topiramate, clobazam, and felbamate. There is limited evidence for the use of levetiracetam, zonisamide, and Fycompa® (perampanel tablet, oral suspension). Where possible, no more than two ASMs should be used concomitantly; use of multiple ASMs raise the risk of side effects and/or drug-drug interactions.

Medical Necessity Criteria

Epidiolex is considered medically necessary when ONE of the following are met:

1. **Dravet Syndrome.** Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient meets ONE of the following (a or b):
       - **a)** Patient has failure, contraindication or intolerance, or is concomitantly receiving at least two other antiseizure medications; OR
         Note: Examples of other antiseizure medications include valproic acid, topiramate, clonazepam, levetiracetam, zonisamide.
       - **b)** Patient has failure, contraindication or intolerance, or is concomitantly receiving one of Fintepla, Diacomit or clobazam; AND
     - **iii.** The medication is prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

2. **Lennox-Gastaut Syndrome.** Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has failure, contraindication or intolerance, or is concomitantly receiving at least two other antiseizure medications; AND

Note: Examples of other antiseizure medications include lamotrigine, topiramate, Banzel, felbamate, clobazam, valproic acid, levetiracetam, zonisamide, Fycompa, vigabatrin.

iii. The medication is prescribed by or in consultation with a neurologist.

B) Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

3. **Tuberous Sclerosis Complex.** Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has failure, contraindication or intolerance, or is concomitantly receiving at least two other antiseizure medications; AND
       Note: Examples of other antiseizure medications include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin, everolimus.
     - **iii.** The medication is prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

Other Uses with Supportive Evidence

4. **Treatment-Refractory Seizures/Epilepsy [specific rare conditions]** (i.e., CDKL5 deficiency disorder; Dup15q, Aicardi, or Doose syndromes; febrile infection-related epilepsy syndromes; Sturge-Weber syndrome; lissencephaly; cortical malformation/dysplasia; and epilepsy with myoclonic absences). Approve if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets the following (i, ii, and iii):
     - **i.** Patient is ≥ 1 year of age; AND
     - **ii.** Patient has failure, contraindication or intolerance, or is concomitantly receiving at least two other antiseizure medications; AND
       Note: Examples of other antiseizure medications include valproic acid, lamotrigine, topiramate, clonazepam, levetiracetam, zonisamide, Banzel, felbamate, clobazam, Fycompa, vigabatrin.
     - **iii.** The medication is prescribed by or in consultation with a neurologist.
   - **B)** Patient is Currently Receiving Epidiolex. Approve for 1 year if the patient is responding to therapy (e.g., reduced seizure severity, frequency, and/or duration) as determined by the prescriber.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven (criteria will be updated as new published data are available).

References

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3. Shafer PO. Epilepsy Foundation – Dravet Syndrome. Updated August 2020. Available at: https://www.epilepsy.com/learn/types-epilepsy-syndromes/dravet-syndrome. Accessed on February 5, 2024.
4. Wirrell EC, Laux L, Donner, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. *Pediatr Neurol*. 2017;68:18-34.
5. Knupp KG1, Wirrell EC. Treatment Strategies for Dravet Syndrome. *CNS Drugs*. 2018;32(4):335-350.
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13. Cherian KA. Lennox-Gastaut syndrome treatment & management. Updated August 2020. Available at: https://emedicine.medscape.com/article/1176735-treatment. Accessed on February 5, 2024.
14. Szaflarski JP, Devinsky O, Lopez M, et al. Long-term efficacy and safety of cannabidiol in patients with treatment-resistant epilepsies: Four-year results from the expanded access program. *Epilepsia*. 2023;64(3):619-629.
15. Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav*. 2018;87:131-136.
16. Devinsky O, Verducci C, Thiele EA, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy Behav*. 2018;86:131-137.
17. Fintepla® oral solution [prescribing information]. Smyrna, GA: UCB; December 2023.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	**Updated** coverage policy title from Cannabidiol to Antiseizure Medications – Epidiolex. **Added** criterion for Dravet Syndrome allowing for	5/1/2024

	treatment with Epidiolex if there is either failure, contraindication or intolerance to, or concomitantly receiving Fintepla, Diacomit or clobazam. **Removed** criterion for Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex and Treatment-Refractory Seizures/ Epilepsy requiring a contraindication, intolerance or not a candidate for all alternative formulary anti-epileptic medications.	

The policy effective date is in force until updated or retired.