PRIOR AUTHORIZATION POLICY

POLICY: Antiseizure Medications – Epidiolex Prior Authorization Policy
- Epidiolex® (cannabidiol oral solution – Greenwich Biosciences)

REVIEW DATE: 02/07/2024

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 callostomy).[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.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Epidiolex. All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Epidiolex as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Epidiolex to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Epidiolex is recommended in those who meet the following criteria:

FDA-Approved Indications

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 tried 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 tried 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 tried 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 tried 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 tried 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Epidiolex is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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