Epidiolex® (cannabidiol)

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Medicaid Testimony

- Epidiolex® (cannabidiol) is the first and only FDA-approved, prescription cannabidiol 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. The recommended maintenance dose for LGS and Dravet is 10mg/kg/day to 20mg/kg/day and the maintenance dose for TSC is 25mg/kg/day.
- The Silver Scripts Nevada Medicaid policy for approval of Epidiolex mentions the inclusion of chart notes confirming the presence of at least four convulsive seizures per month. In fact, in seizures associated with LGS, Dravet syndrome and TSC, Epidiolex has been shown to be effective in a wide range of seizure types: atonic, tonic, tonic-clonic, clonic, simple partial, complex partial and secondary generalized tonic-clonic seizures.
- Cannabidiol, the active ingredient in Epidiolex, is highly purified and structurally distinct from other antiepileptic drugs. Although the exact mechanisms of action are unknown, it does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors. In contrast to THC, it does not have psychoactive or euphoric properties.
- The efficacy and safety profile of Epidiolex for the treatment of seizures associated with LGS and Dravet were evaluated in three randomized, double-blind, placebo-controlled, multicenter 14-week trials, where Epidiolex or placebo were added to the patient's current anti-epileptic drugs.
- Epidiolex achieved its primary endpoint of statistically significant median percent change in convulsive and/or drop seizure frequency from baseline in these three studies vs placebo. The treatment effect was established during the first 4 weeks of initiating treatment and was sustained throughout the study period. Results showed 39-44% reduction in median monthly convulsive and/or drop frequency over baseline across all three trials.
- In addition, the secondary endpoint of the proportion of 50% responders was greater among patients receiving Epidiolex compared with placebo across all three trials.
- Tuberous sclerosis complex (TSC) is a highly variable genetic disorder that is characterized by the formation of benign hamartomas in virtually every organ of the body. Patients with TSC commonly experience treatment-resistant epilepsy that can begin in infancy and persist throughout life, with multiple seizure-types. TSC may be associated with highly variable, multi-organ manifestations, neuropsychiatric disorders, intellectual deficits, and significantly increased resource utilization compared with healthy controls.
- The efficacy and safety of add-on Epidiolex for the treatment of seizures associated with TSC was evaluated in a 16-week, randomized, double-blind, placebo-controlled, multicenter trial. Doses of 25 mg/kg/day and 50 mg/kg/day equally and significantly reduced seizures (49% and 48% mean reduction, respectively, compared to baseline) vs. placebo (27% reduction) in the intention to treat analysis (p=.0009, p= 0.018, respectively). While the TSC clinical trial included a 50mg/kg/day arm, greater efficacy was not observed compared with 25mg/kg/day; however, a greater incidence of AEs was observed. Thus, we did not seek approval for this dose.
- As described in the USPI, the most common adverse reactions that occurred in Epidiolex-treated patients with an incidence at least 10% and greater than placebo for those with LGS and Dravet were somnolence, decreased appetite, diarrhea, transaminase elevations, fatigue, malaise, asthenia, rash, insomnia, sleep disorder, poor-quality sleep and infections; those with TSC were diarrhea, transaminase elevations, decreased appetite, somnolence, pyrexia, and vomiting
- Details regarding the contraindication for hypersensitivity and warnings and precautions for hepatocellular injury, somnolence/sedation, suicidal behavior/ideation, and withdrawal of antiepileptic drugs are provided in the Epidiolex full Prescribing Information.
- In summary, Epidiolex has been demonstrated as effective for the treatment of seizures associated with Lennox-Gastaut, Dravet Syndrome or Tuberous sclerosis complex in patients 1 year of age and older with a well characterized safety profile.

References

1. Epidiolex U.S. Prescribing Information, Greenwich Biosciences, 2022
2. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55 (suppl 4):4-9.
3. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(suppl 2):3-9.
4. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017;68:18-34.e13.

5. Doring JH, Lampert A, Hoffmann GF, Ries M. Thirty years of orphan drug legislation and the development of development of drugs to treat rare seizure conditions: a cross sectional analysis. *PLoS One* 2016; **11:** e0161660.
6. Cross JH, Auvin S, Falip M, Striano P, Arzimanoglou A. Expert opinion on the management of Lennox-Gastaut syndrome: treatment algorithms and practical considerations. *Front Neurol*. 2017;8:505.
7. Devinsky O. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *NEJM*. 2017;376(21)2011-2020.
8. Thiele E. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet.* 2018; http://dx.doi.org/10.1016/S0140-6736(18)30136-3.
9. Devinsky O et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. NEJM. 2018; 378: 1888-1897.
10. Atakan Z. *Ther Adv Psychopharmacol.* 2012;2(6):241-254.
11. GW Pharmaceuticals announces receipt of notices. https://globenewswire.com/news-release/2018/03/13/1421662/0/en/GW-Pharmaceuticals-Announces-Receipt-of-Notices-of-Allowance-by-the-United-States-Patent-and-Trademark-Office-USPTO-for-Five-New-Epidiolex-cannabidiol-Patents.html. 2018. Accessed May 4, 2018
12. Bih CI, Chen T, Nunn AV, et al. Molecular Targets of Cannabidiol in Neurological Disorders. Neurotherapeutics (2015) 12:699–730.
13. Thiele E, Bebin EM, Bhathal H, et al. GWPCARE6 Study Group. Add-On Cannabidiol (CBD) Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Randomized, Double blind, Placebo Controlled Phase 3 Trial. JAMA Neurology 2021;78(3):285-292.