Cannabidiol Prior Authorization Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
8/1/2023	4/1/2019

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Epidiolex® (cannabidiol) Oral solution	Treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Lennox-Gastaut Syndrome	Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that typically becomes apparent during infancy or early childhood. The syndrome has many causes, including genetic disorders, cortical malformations, tumors, encephalopathies following hypoxic-ischemic insults, meningitis, and head injuries. Affected children experience several different types of seizures; atonic, clonic, and atypical absence seizures are the most common. Children with LGS may develop cognitive dysfunction, delays in reaching developmental milestones, and behavioral problems. LGS is difficult to treat because no specific therapy is effective in all cases, and the disorder has proven particularly resistant to most therapeutic options. Valproate is generally considered first-line therapy, and if monotherapy is ineffective another drug such as lamotrigine or rufinamide is added to valproate therapy. Alternative adjunctive antiseizure medications include topiramate, clobazam, cannabidiol, fenfluramine, or felbamate. Additional therapies combined with drug therapy, for patients who do not respond, include the ketogenic diet and vagal nerve stimulation.(4,10)
Dravet Syndrome	Dravet syndrome (DS) is a severe form of epilepsy characterized by frequent, prolonged seizures and neurodevelopmental problems beginning in infancy. Mutations in the alpha-1 subunit of the voltage-gated sodium channel (*SCN1A*) gene are identified in 70-85% of patients with DS. Status epilepticus, or a seizure lasting longer than 5 minutes and sometimes 30 minutes or more, is common. Additional seizure types, including myoclonic, atypical absence, and complex partial seizures, appear before age 5 years. Mortality in DS is elevated above that found in the general epilepsy population, with an estimated mortality of 15-20% by adulthood. First-line treatment is typically valproate, with clobazam added if needed. Additional agents include stiripentol, topiramate, cannabidiol, and fenfluramine. For patients with symptoms refractory to drug therapy, ketogenic diet and vagal nerve stimulation may be beneficial.(7,8,9,15)
Tuberous Sclerosis Complex	Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by a mutation in either the *TSC1* gene or the *TSC2* gene. TSC is characterized by the development of a variety of benign tumors in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver. Seizures are the most frequent presenting neurologic feature of TSC, with more than 80% of patients developing seizures during

	childhood.(12) According to the 2012 International Tuberous Sclerosis Complex Consensus, first-line therapy is vigabatrin for infantile-onset seizures, and second-line therapy is adjunctive or alternative adrenocorticotropin hormone (ACTH).(12,13,14) Other anticonvulsants may be prescribed and depend on the specific type of seizure; for example, simple-partial or complex-partial seizures would be treated with oxcarbazepine or carbamazepine.(11,12,14)
Efficacy	Cannabidiol was studied for treatment of seizures associated with LGS in two published randomized, double-blind, placebo-controlled trials in patients age 2 to 55. Study 1 (GWPCARE4, N=171) compared cannabidiol 20 mg/kg/day vs. placebo.(2) Study 2 (GWPCARE3, N=225) compared cannabidiol 10 mg/kg/day and 20 mg/kg/day vs. placebo.(3) In both studies, LGS patients were inadequately controlled on at least one anti-epileptic drug (AED), with or without vagal nerve stimulation and/or ketogenic diet. In both trials, patients were required to have a minimum of 8 drop seizures (greater than or equal to 2 drop seizures per week) during a 4-week baseline evaluation period. The baseline period was followed by a 2-week titration period and a 12-week maintenance period.(2,3) During Study 1, 94% of patients were taking greater than 2 concomitant AEDs. Most frequently used concomitant AEDs (greater than 25%) were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%).(2) During Study 2, 94% of patients were taking greater than 2 concomitant AEDs. Most frequently used concomitant AEDs (greater than 25%) were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).(3) In both studies, the primary endpoint was percent change from baseline in frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over 14-weeks of treatment. In both studies, median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for cannabidiol vs. placebo: A reduction in drop seizures was observed within 4 weeks of initiating cannabidiol treatment; the reduction remained generally consistent over the 14-week treatment period. Median percent changes from baseline in drop seizure frequency per 28-day period (cannabidiol vs. placebo):(2,3) • Study 1- 20 mg/kg/day [-44%]; placebo [-22%] (p less than 0.01) • Study 2- 10 mg/kg/day [-37%], 20 mg/kg/day [-42%], placebo [-17%] (both doses p less than 0.01) An open-label extension study (GWPCARE5, N=681), evaluating the long-term safety and efficacy of cannabidiol, is being conducted in patients with LGS who completed either GWPCARE3 or GWPCARE4. Study completion date is June 2020, but an interim analysis has been issued. Median treatment duration was 38 weeks, with 208 patients receiving 48 weeks of treatment. Treatment-emergent adverse events were most commonly diarrhea (26.8%), somnolence (23.5%), and convulsion (23.1%). Sustained reductions in drop seizure (48-60%) and total seizures (48-57%) were observed through 48 weeks. Notably, 88% of patients/caregivers reported an improvement in the patient's overall condition per the patient-reported Subject/Caregiver Global Impression of Change (S/CGIC) scale.(5) A single, published, randomized, double-blind, placebo-controlled trial compared cannabidiol 20 mg/kg/day vs. placebo in patients ages 2-18 (N=120) with treatment-resistant DS, inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During a 4-week baseline period, patients were required to have greater than 4 convulsive seizures while on stable AED therapy. The baseline period was followed by a 2-week titration period and a 12-week maintenance period. During this study, 93% of patients were taking greater than 2 concomitant AEDs; most commonly used concomitant AEDs (greater than 25%) were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%). Baseline median convulsive seizure frequency was 13 per 28 days for the combined groups. The primary endpoint was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period. The median percent change in total convulsive seizure frequency per 28-day period (cannabidiol vs. placebo): 20 mg/kg/day [-39%], placebo [-13%]; p equal to 0.01. A reduction in

	convulsive seizures was observed within 4 weeks of initiating cannabidiol treatment; effect remained generally consistent over the 14-week treatment period.(6) A randomized, double-blind, placebo-controlled trial compared cannabidiol 25 mg/kg/day and 50 mg/kg/day (two times the recommended maintenance dosage) vs. placebo in patients aged 1-65 years (N=224) with treatment-resistant TSC, inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During a 4-week baseline period, patients were required to have greater than or equal to 8 seizures while on stable AED therapy. The baseline period was followed by a 4-week titration period and a 12-week maintenance period. During this study, all patients but one were taking 1-2 concomitant AEDs; most commonly used concomitant AEDs (greater than 25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%). Baseline median convulsive seizure frequency was 57 per 28 days for the combined groups. The primary efficacy measure was the percent change from baseline (reduction) in the frequency (per 28 days) of TSC-associated seizures over the 16-week treatment period. The median percentage change in total convulsive seizure frequency per 28-day period (cannabidiol vs. placebo): 25 mg/kg/day [-43%], placebo [-20%]; p less than 0.01. A reduction in convulsive seizures was observed within 4 weeks of initiating cannabidiol treatment; effect remained generally consistent over the 12-week maintenance period.(1)
Safety	Epidiolex carries no black box warnings. Epidiolex is contraindicated in patients with hypersensitivity to cannabidiol or any of the ingredients in Epidiolex.(1)

REFERENCES

Number	Reference
1	Epidiolex prescribing information. Jazz Pharmaceuticals, Inc. January 2023.
2	Thiele EA, Marsh ED, French JA, et al. Cannabidiol in Patients with Seizures Associated with Lennox-Gastaut syndrome (GWPCARE4): A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial. Lancet. 2018 Mar;391(10125):1085-1096.
3	Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. N Engl J Med. 2018;378:1888-1897.
4	Wheless JW. Lennox-Gastaut Syndrome. National Organization for Rare Disorders (NORD). Last updated 2020. Available at https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/.
5	Thiele E, Marsh E, Mazurkiewicz-Beldzinska M, et al. Cannabidiol in Patients with Lennox-Gastaut Syndrome: Interim Analysis of an Open-Label Extension Study. Epilepsia. 2019;60(3):i-vii.
6	Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017;376:2011-2020.
7	Sullivan J, Knupp K, Wirrell E, et al. Dravet Syndrome. National Organization for Rare Disorders (NORD). Last updated 2020. Available at https://rarediseases.org/rare-diseases/dravet-syndrome-spectrum/.
8	Andrade DM, Nascimento FA, et al. Dravet Syndrome: Management and Prognosis. UpToDate. Last updated November 2022. Literature review current through December 2022.
9	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.
10	Wilfong A, et al. Epilepsy Syndromes in Children. UpToDate. Last updated June 2022. Literature review current through December 2022.
11	Randle S, et al. Tuberous Sclerosis Complex: Management and Prognosis. UpToDate. Last updated August 2022. Literature review current through December 2022.
12	DiMario FJ, et al. Tuberous Sclerosis. National Organization for Rare Disorders (NORD). Last updated 2020. Available at https://rarediseases.org/rare-diseases/tuberous-sclerosis/.
13	Krueger DA, Northrup H, et al. International Tuberous Sclerosis Complex Consensus Group Recommendations for Tuberous Sclerosis Complex Surveillance and Management. Pediatr Neurol. 2012;49(4):P255-265.

Number	Reference
14	Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021;123:50.
15	International Consensus on Diagnosis and Management of Dravet Syndrome. Epilepsia. 2022 Jul;63(7):1761-1777.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Epidiolex	cannabidiol soln	100 MG/ML	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Epidiolex	cannabidiol soln	100 MG/ML	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of seizures associated with ONE of the following: A. Lennox-Gastaut syndrome (LGS) **OR** B. Dravet syndrome (DS) **OR** C. Tuberous sclerosis complex (TSC) **AND** 2. If the patient has an FDA approved indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The requested agent will NOT be used as monotherapy for seizure management **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The requested agent will NOT be used as monotherapy for seizure management **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

