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Drug Class Update with New Drug Evaluations: Antiepileptics

Date of Review: January 2019
Generic Name: cannabidiol
Generic Name: stiripentol

End Date of Literature Search: 08/01/2018
Brand Name (Manufacturer): Epidiolex® (GW Pharmaceuticals)
Brand Name (Manufacturer): Diacomit® (Biocodex Laboratories)
Dossier Received: Epidiolex®: Yes; Diacomit®: No

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for a new cannabinoid recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS). This update will also evaluate evidence for another new antiepileptic drug (AED), stiripentol, recently approved for treatment of DS. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.

Research Questions:
1. Is there new comparative evidence that antiepileptic drugs (AEDs) differ in efficacy or harms for management of seizures?
2. What is the safety and effectiveness of cannabidiol in reducing seizures in patients with LGS or DS?
3. What are the comparative harms of cannabidiol in patients with LGS or DS?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which cannabidiol may be beneficial or cause more harm?
5. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which stiripentol may be beneficial or cause more harm?

Conclusions:
- There is no new direct comparative evidence to evaluate drug treatment of epilepsy since the last AED literature scan completed March 2018.

Cannabidiol in Dravet Syndrome
- The safety and efficacy of cannabidiol in managing patients with DS was evaluated in one fair quality phase 3 trial.
- Moderate quality evidence found that compared with baseline, the median monthly reduction of convulsive seizures was significantly greater in the cannabidiol group (-38.9%) compared to the placebo group (-13.3%). The adjusted median difference (MD) between cannabidiol and placebo groups was

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-22.8% (95% CI -41.1 to -5.4; p = 0.01).[1] Absolute reduction in convulsive seizure frequency over the treatment period was not reported.

- Adverse events that occurred more frequently in the cannabidiol group versus the placebo group included diarrhea (31%), vomiting (15%), fatigue (20%), pyrexia (15%), somnolence (36%), and abnormal results on liver-function tests (20%) based on moderate quality evidence.[1] More subjects withdrew from the trial in the cannabidiol group (n=9) compared to the placebo group (n=3) primarily due to adverse effects.[1]

Cannabidiol in Lennox-Gastaut Syndrome

- The safety and efficacy of cannabidiol in managing patient with LGS was studied in 2 fair quality phase 3 randomized controlled trials (RCTs).
- Moderate quality evidence demonstrates the median reduction in monthly frequency of drop seizures was significantly greater in the cannabidiol 20 mg/kg/day group (42%) and 10 mg/kg/day group (37%) than in the placebo group (17%); [MD -21.6%; 95% CI -34.8 to -6.7; p = 0.005 and MD -19.2%; 95% CI -31.2 to -7.7; p =0.002, compared to placebo respectively].[2] Drop seizures were defined as atonic, tonic or tonic-clonic seizures involving the entire body, trunk, or head that led to or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.[2] Absolute reduction in drop seizure frequency over the 28 day treatment period was not reported. In the second phase 3 trial, moderate quality evidence shows that when used in addition to concurrent AED therapy, the cannabidiol group had a significantly greater reduction in monthly median drop seizure frequency (43.9%) compared to the placebo group (21.8%).[3] The estimated MD was -17.21 (95% CI -30.32 to 4.09; p = 0.014).[3]
- Adverse effects occurred in 74 (86%) of patients in the cannabidiol group and 59 (69%) of patients in the placebo group as reported in moderate quality evidence.[3] The most common adverse events occurring in greater than or equal to 10% of patients with cannabidiol compared to placebo included diarrhea (19%), somnolence (15%), pyrexia (13%), decreased appetite (13%) and vomiting (10%).[3]
- There is insufficient evidence to determine if any subgroups would particularly benefit or be harmed from treatment with cannabidiol. However, drug interactions should be monitored closely in certain patients taking cannabidiol. Patients taking clobazam concurrently with cannabidiol should be observed for excessive somnolence as cannabidiol can increase serum concentrations of clobazam and its active metabolite, n-desmethylclobazam.[4] Clobazam dose reduction may need necessary. Concomitant use of cannabidiol and valproate increases the incidence of liver enzyme elevations.[4] Discontinuation or reduction of cannabidiol and/or concomitant valproate should be considered.[4] Dose adjustment of cannabidiol is recommended in patients with moderate or severe (Child-Pugh B or C) hepatic impairment.[4]

Stiripentol in Dravet Syndrome

- Low to moderate quality data derived from two small, short term, RCTs indicate that stiripentol is significantly better than placebo with regards to 50% or greater reduction in seizure frequency. Only one French trial[5] is published and could be evaluated; the data from the second Italian trial were obtained from 2 systematic reviews.[6,7] A Cochrane meta-analysis of data pooled from the 2 trials showed a statistically significant higher proportion of stiripentol subjects (22/33; 67%) had 50% or greater reduction in seizure frequency compared to placebo (2/31; 6%) resulting in a risk ratio (RR) of 10.4% (95% CI 2.64 to 40.87; Absolute Risk Reduction (ARR)=61%; Numbers Needed to Treat (NNT)=2).[7]
- In the French trial, moderate quality evidence shows that adverse events were higher in the stiripentol group compared with the placebo group and were reported as being mild or moderate in severity.[5] The percentage of patients reporting adverse events in the stiripentol group was 100% (21 out of 21) compared with 25% (5 out of 20) in the placebo group.[5] The most frequently reported adverse events with stiripentol included nausea, drowsiness, loss of appetite, weight, somnolence, agitation, and aggression.[4]
- All clinical trials were conducted with stiripentol in combination with clobazam. Therefore, the stiripentol FDA-approved indication is treatment of seizures associated with DS in children aged 2 years and older taking clobazam.[8]

Recommendations:

- Implement prior authorization (PA) criteria to ensure medically appropriate utilization of cannabidiol and stiripentol (**Appendix 5**).
- Revise clobazam criteria to include Dravet Syndrome (based on 2012 NICE guidance)[9] and add renewal criteria.
- Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

Antiepileptic drug selection is based upon epileptic syndrome, seizure type, the adverse effect profile and patient preference. Approximately half of newly diagnosed epileptics are successfully treated with the first AED; however, treatment failure and drug intolerance can occur. Monotherapy is more likely to promote compliance, reduce potential for drug interactions, and is less costly but may not keep a patient seizure free. There are no controlled trials comparing different combinations of AEDs. The preferred oral and rectal AEDs included on the Oregon Medicaid FFS (Fee-For-Service) Preferred Drug List (PDL) are: carbamazepine, diazepam, divalproex, ethosuximide, ethotoin, gabapentin, lacosamide, levetiracetam, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproic acid, and zonisamide. Lamotrigine is classified as a voluntary medication due to its utilization in mental health treatment. Non-preferred AEDs are listed in **Appendix 1**. The utilization of clobazam, pregabalin, and topiramate is guided by prior authorization (PA) criteria to ensure they are prescribed for indications supported by the medial literature. The PA criteria for clobazam, pregabalin, and topiramate are presented in **Appendix 6**.

Background:

The International League Against Epilepsy (ILAE) defines epilepsy as a disease of the brain, diagnosis of which requires: (a) at least two unprovoked seizures occurring >24 hours apart; (b) one unprovoked seizure and a probability for further seizures of at least 60%, occurring over the next 10 years or (c) the diagnosis of an epilepsy syndrome.[10] The ILAE report states that it makes little sense to say that someone has an epilepsy syndrome but not epilepsy.[10] If evidence exists for an epilepsy syndrome, then epilepsy may be presumed to be present, even if the risk of subsequent seizures is low.[10] Exceptional syndromic cases may exist in which obvious behavioral seizures may not occur at all, as can be the case with continuous spike and waves during sleep.[10] Treatment-resistant epilepsy arises from a failure to achieve sustained seizure remission after trials of at least two AED regimens that are tolerated at therapeutic dosages.[11] Two types of severe seizure syndromes associated with epileptic encephalopathies, LGS and DS, are often refractory to pharmacotherapy. Both syndromes are associated with higher rates of mortality than the general epilepsy population, primarily due to status epilepticus and sudden unexpected death due to epilepsy.[12]

Lennox-Gastaut syndrome is commonly characterized by a triad of signs, which include multiple drug-resistant seizure types, slow spike-wave complexes on electroencephalographic (EEG) recordings, and intellectual disability.[13] The etiology of LGS is often divided into two groups: identifiable (e.g.; genetic, structural, or metabolic) in 65 to 75% of the patients and LGS of unknown cause in others.[13] LGS occurs most often in children less than 8 years of age with usual onset between ages 3 and 5 years, but can persist into adulthood.[14] The syndrome occurs in 2.8 per 100,000 live births and comprises 4%–10% of childhood epilepsy.[15] LGS is five times more common in boys.[15] Prognosis is poor, as less than 10% of patients achieve seizure freedom as adults. Most individuals with LGS develop co-morbid autism, intellectual disability and other behavioral concerns.[15] Drop seizures due to a loss of motor tone are characteristic of this disorder and often result in serious head injury.[16] Reduction in frequency of drop seizures is a major objective in management of patients with LGS.[13] Other types of seizures observed in LGS include: atypical absence seizures, nonconvulsive status epilepticus, myoclonic seizures, focal seizures, and unilateral clonic seizures.[13]

Six antiepileptic medications have FDA indications for the treatment of LGS, including lamotrigine, topiramate, felbamate, rufinamide, clobazam and clonazepam.[15] Direct comparative drug trials in patients with LGS have not been performed. Valproic acid is considered first-line therapy for LGS because it has efficacy in all types of seizures associated with LGS; however, it does not have a specific FDA indication for LGS.[13] The optimum treatment for LGS remains uncertain, and no study to date has shown any one drug to be highly efficacious.[13] There is potential for severe adverse drug reactions with many of the drugs

used to treat seizures in LGS, such as hepatic failure (felbamate, lamotrigine, and valproic acid), serious skin reactions (lamotrigine, clobazam, rufinamide), and hematologic abnormalities (felbamate, lamotrigine, topiramate, rufinamide).[12] The 2012 National Institute for Health Care and Excellence (NICE) guidelines on management of epilepsy state that carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine or vigabatrin should not be used to manage LGS as they may aggravate myoclonus or absence seizures.[9] The ketogenic diet is an effective and well tolerated treatment option for patients with LGS.[13] For patients with drug resistance, surgical intervention is an additional treatment strategy.[13]

Severe myoclonic epilepsy infancy (SMEI), also known as Dravet syndrome, is a rare genetic epilepsy syndrome characterized by refractory seizures beginning before the age of 1 year with poor neurodevelopmental outcomes and a high mortality rate.[17] It accounts for less than 5% of epilepsy cases presenting in the first year of life, and is estimated to affect 1 in 40,000 live births in the US.[18] It affects males and females in equal proportions.[19] Mutations in the voltage-gated sodium channel alpha-1 (SCN1A) gene are identified in 70 to 80% of patients with DS.[17] The most common presenting symptom is a hemiclonic or generalized seizure, often precipitated by fever, in an otherwise healthy infant between five and eight months of age.[17] Early seizures tend to be prolonged, recurrent, and may evolve into status epilepticus. Neurodevelopmental decline typically begins shortly after seizure onset. Between one and five years of age, patients with DS have refractory epilepsy characterized by multiple types of seizures, both febrile and afebrile, including convulsive seizures, myoclonic seizures, atypical absence seizures, and focal seizures.[17]

Drug resistance is a well-recognized feature of seizures in DS, and antiepileptic therapies have overall limited efficacy.[20] Pharmacologic therapy remains the mainstay of treatment, and ketogenic diet and neuromodulation are viable options in selected patients.[17] The goals of treatment are to reduce both the length and number of seizures and prevent status epilepticus, limit adverse effects of antiepileptics to promote better neurocognitive development, and improve quality of life. The most commonly used drugs in patients with DS include valproate, clobazam, topiramate, stiripentol, levetiracetam, and zonisamide.[17] Stiripentol recently received FDA approval for treatment of DS in the U.S. and is currently the only medication FDA-approved specifically for seizures in DS. The evidence for the safety and efficacy of stiripentol in treating DS are evaluated later in this update. National Institute for Health and Care Excellence (NICE) 2012 guidance on management of epilepsy recommends valproate and topiramate as first line agents for treatment of DS.[9] The NICE guidance recommends clobazam and stiripentol as second line medications to manage DS.[9] Phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, lamotrigine, vigabatrin, rufinamide, and tiagabine should be avoided as they can worsen seizures in patients with DS.[17]

Reduction in seizure frequency of 50% or more is generally accepted as demonstrating efficacy for FDA approval of new AEDs. A secondary endpoint measure utilized in the cannabidiol trials was the Caregiver Global Impression of Change (CGIC) scoring tool to assess improvement or worsening in seizure frequency by the patient's caregiver. The CGIC uses a 7-point Likert-like scale ranging from slightly improved, much improved, very much improved, slightly worse, much worse, very much worse or no change, (1 = very much improved; 7 = very much worse) to categorize changes in seizure frequency.[1]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 3 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or design of systematic review (e.g. network meta-analysis).

New Guidelines: No new guidelines have been published since the last AED review.

New Formulations or Indications: No new formulations or indications have been reported.

Randomized Controlled Trials: No new randomized controlled trials for the AED class were identified.

New FDA Safety Alerts:
Table 1. Description of New FDA Safety Alerts[21]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, Contraindications)	Addition or Change and Mitigation Principles (if applicable)
Topiramate	Trokendi XR®	1/2018	Warnings and Precautions	Risk of hyperammonemia with or without encephalopathy with topiramate appears dose-related and has been reported more frequently when topiramate is used concomitantly with valproic acid.
Topiramate	Topamax®	6/2018	Warnings and Precautions	Topiramate increases the risk of kidney stones. During adjunctive epilepsy trials, the risk for kidney stones in topiramate-treated adults was 1.5%, an incidence about 2 to 4 times greater than expected in a similar, untreated population. Metabolic acidosis was commonly observed in adult and pediatric patients treated with topiramate in clinical trials. The incidence of decreased serum bicarbonate in pediatric trials, for adjunctive treatment of Lennox-Gastaut syndrome or refractory partial onset seizures, was as high as 67% for topiramate (at approximately 6 mg/kg/day) vs. 10% for placebo. The incidence of a markedly abnormally low serum bicarbonate (i.e., absolute value <17 mEq/L and >5 mEq/L decrease from pretreatment) in these trials was up to 11% compared to <2% for placebo.
Lamotrigine	Lamictal®	7/2018	Warnings and Precautions	Hemophagocytic lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation.
Levetiracetam	Keppra®	7/2018	Warnings and Precautions	Hematologic abnormalities occurred in clinical trials and included decreases in white blood cell (WBC), neutrophil, and red blood cell (RBC) counts; decreases in hemoglobin and hematocrit; and increases in eosinophil counts. Cases of agranulocytosis, pancytopenia, and thrombocytopenia have been reported in the postmarketing setting.

NEW DRUG EVALUATION: Cannabidiol Oral Solution (Epidiolex®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Cannabidiol oral solution (100mg/ml) is FDA-approved for the adjunctive treatment of seizures associated with LGS or DS in patients 2 years of age and older. Cannabidiol is one of major non-psychoactive compounds derived from *Cannabis sativa* which has medicinal properties. The precise mechanism by which cannabidiol exerts its anticonvulsant effect in humans is unknown; the mechanism of action does not appear be related to interaction with cannabinoid receptors.[4] The proposed mechanisms of cannabidiol in the treatment of epilepsy include: 1) modulation of the endocannabinoid system by halting the degradation of anandamide, which may have a role in inhibiting seizures and 2) regulation of T-type calcium channels and nuclear peroxisome proliferator-activated receptor-ɣ, both of which have been implicated in seizure activity.[22] The initial dose of cannabidiol oral solution is 2.5 mg/kg twice daily by mouth. The dose can be increased after one week to the suggested maintenance dose of 5 mg/kg twice daily, and may be increased, if needed for further seizure control, up to a maximum of 10 mg/kg twice daily (20mg/kg/day).[4] Absorption of cannabidiol is enhanced when given with a high-fat meal. Therefore, the manufacturer recommends dosing cannabidiol consistently with respect to meals.[4] Dose adjustment of cannabidiol is recommended in patients with moderate or severe (Child-Pugh B or C) hepatic impairment.[4]

Three phase 3 trials were submitted to the FDA for approval of cannabidiol oral solution: GWPCARE1, GWPCARE3, and GWPCARE4. The fourth trial, GWPCARE2 was completed as of June 2017, but the results are not yet published. All three published trials are described and evaluated below in **Table 4**. GWPCARE1 was focused on DS while GWPCARE3 and GWPCARE4 focused on LGS. All 3 trials also enrolled patients into a long-term, open-label extension study to assess efficacy and safety. The cannabidiol new drug application was approved through orphan drug and fast track FDA designations.

Trials in DS
The first trial, GWPCARE1, was conducted in 120 children and young adults (2-18 years old) with DS who were taking a mean of 3 concomitant AEDs and whose seizures had not responded to an average of 4 AEDs. Subjects were enrolled at 23 centers in 4 countries: US (13), United Kingdom (3), France (4), and Poland (2). Patients were randomized to receive either cannabidiol 20 mg/kg/day or placebo in addition to baseline AEDs over 14 weeks.[1] Sixty-five percent of the subjects were taking clobazam, 55% were taking valproic acid, and 43% were taking stiripentol.[1] Median baseline convulsive seizure frequency was 13 seizures per month.[1] Convulsive seizures were defined as tonic, clonic, tonic-clonic, or atonic. Patients or caregivers recorded the number and type of convulsive seizures and non-convulsive seizures (myoclonic, partial, or absence) each day using an Interactive Voice Response System (IVRS) telephone diary during the study.

The primary efficacy measure was the percent change in monthly convulsive seizure frequency during the 14-week treatment period. Compared with baseline, the median monthly frequency of convulsive seizures decreased from a median of 12.4 seizures per month at baseline to 5.9 over the treatment period, representing a median change of -38.9% (interquartile range -69.5 to -4.8) from baseline in the cannabidiol group.[1] In the placebo group the median monthly convulsive-seizure frequency decreased from 14.9 to 14.1, representing a median change of -13.3% (interquartile range -52.5 to 20.2).[1] The adjusted median difference (MD) between cannabidiol and placebo groups was -22.8% which was statistically significant (95% CI -41.1 to -5.4; p = 0.01).[1] Key secondary endpoints were the proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of convulsive seizures, change in total seizure frequency, and change from baseline in the CGIC score at the end of treatment. A 50% reduction in convulsive seizures was found in 43% of the

treatment group, but this was not statistically significant from the 27% of subjects in the placebo group [odds ratio (OR) = 2.00; 95% CI 0.93 to 4.30; p = 0.08].[1] The median frequency of total seizures per month significantly decreased by 28.6% in the cannabidiol group versus a 9% decrease in the placebo group (MD: -19.2; 95% CI -39.25 to -1.17; p = 0.03).[1] On the CGIC scale, 37 of 60 caregivers (62%) judged their child's overall condition improved in the cannabidiol group, as compared with 20 of 58 caregivers (34%) in the placebo group (p=0.02).[1]

Trials in LGS

In the dose-ranging GWPCARE3 trial, 225 patients with LGS were randomly assigned to one of three treatment arms: oral cannabidiol 20 mg/kg/day, 10 mg/kg/day or placebo, in addition to baseline AED therapy.[2] The trial was conducted at 29 centers in 4 countries: US (20), UK (3), France (1) and Spain (5). Patients ranged in age from 2 to 55 years old and were taking a mean of 3 AEDs after prior failed treatment with an average of 6 AEDs.[2] The median baseline drop seizure frequency was 85 seizures per month.[2] Drop seizures were defined as atonic, tonic or tonic-clonic seizures involving the entire body, trunk, or head that led to or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface.[2] The primary outcome was median percent reduction in the frequency of drop seizures over 28 days during a 14 week treatment period compared to baseline. The reduction in frequency of drop seizures was significantly greater in the cannabidiol 20 mg/kg/day group (42%) and 10 mg/kg/day group (37%) than in the placebo group (17%) [MD -21.6%; 95% CI -34.8 to -6.7; p = 0.005 and MD -19.2%; 95% CI -31.2 to -7.7; p =0.002, compared to placebo respectively].[2] Key secondary endpoints were the proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of drop seizures, change in total seizure frequency, and change from baseline in the CGIC score at the end of treatment. All key secondary outcomes had statistically significant differences compared to placebo, results of these outcomes are presented in **Table 4**.

In the GWPCARE4 trial, 171 patients with LGS (2-55 years old) were randomized to cannabidiol 20 mg/kg/day or placebo in addition to current AEDs.[3] Patients were taking an average of 3 AEDs after prior trials with an average of 6 other AEDs, similar to the GWPCARE3 trial.[3] The median baseline drop seizure frequency for the population was 74 per month.[3] Twenty-four centers in 3 countries participated in the trial: US (17), Poland (6), and the Netherlands (1). The primary efficacy measure was the percent change in the monthly frequency of drop seizures during the 14 week treatment period. The cannabidiol group had a 44% reduction in drop seizure frequency compared to a 22% reduction in the placebo group (MD -17%; 95% CI -30.32 to 4.09; p = 0.014).[3] Key secondary endpoints were the proportion of patients in each treatment group that achieved a reduction of 50% or more in monthly frequency of drop seizures, change in total seizure frequency, and change from baseline in the CGIC score at the end of treatment. All key secondary outcomes had statistically significant differences compared to placebo, results of these outcomes are presented in **Table 4.**

Limitations of Clinical Trials:

Caregiver assessment in the GWPCARE 1 trial showed differences in palatability and distinct adverse effects (particularly somnolence and gastrointestinal upset) between cannabidiol and placebo which could have led to unblinding of treatment assignments.[1] The primary endpoint of seizure frequency and type of seizure was reported by caregivers via daily IVRS reports, which may have been biased by subjective reporting or caregiver error. The impact of concomitant AED therapy on safety and efficacy outcomes due to potential drug interactions is not clear and requires additional research. The patient population was primarily white, which makes generalizability difficult due to the lack of diverse patient population.

Finally, all 3 trials were manufacturer supported and manufacturer was responsible for trial design, trial management, site monitoring, trial pharmacovigilance, and statistical analysis. Each trial reported potential conflict of interests for the study authors in depth. GW Pharmaceuticals provided grant support paid to several of the authors' institutions. In addition, several authors serve on the advisory board for GW Pharmaceuticals and received fees paid to their department. Another author is a paid employee of GW Pharmaceuticals and holds a pending patent on the use of cannabinoids in the treatment of epilepsy.

Clinical Safety:
The most commonly observed adverse events in the controlled clinical trials conducted with cannabidiol that occurred with a greater incidence in cannabidiol-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia).[4] These events were generally mild to moderate in severity. Serious adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections.[4] In the trial that compared different doses of cannabidiol, the incidence of adverse events was lower in the 10 mg/kg per day group than the 20 mg/kg per day group.[2]

In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, some cases were observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate.[4] Resolution of transaminase elevations occurred with discontinuation or dosage adjustment of cannabidiol and/or concomitant valproate in about two-thirds of cases.[4] In about one-third of cases, transaminase elevations resolved without dose reduction or treatment discontinuation .[4] The FDA-approved labeling recommends serum transaminase (ALT and AST) and total bilirubin levels be obtained at baseline, at one, three, and six months after starting treatment, and periodically thereafter as clinically indicated. Testing is also recommended with changes in dose or with changes in other medications that affect liver function.[4] Cannabidiol should be discontinued or interrupted if symptoms or signs of liver dysfunction develop.[4] **Table 2** presents the most common adverse reactions reported in patients treated with cannabidiol compared to placebo as reported in the prescription labeling.

Table 2: Adverse Reactions in Patients Treated with Cannabidiol Oral Solution in Controlled Trials[4]

Adverse Reaction	Cannabidiol 10mg/kg/day (n=75)	Cannabidiol 20mg/kg/day (n=238)	Placebo (n=227)
Elevated Transaminases	8%	16%	3%
Decreased Appetite	16%	22%	5%
Diarrhea	9%	20%	9%
Somnolence	23%	25%	8%
Fatigue, malaise, asthenia	11%	12%	4%
Insomnia	11%	5%	4%
Rash	7%	13%	3%
Infections	41%	40%	31%

All AEDs include a warning that this class of drugs can increase the risk of suicidal thoughts or behavior.[4] This warning is based on a pooled analysis of 199 placebo controlled trials of 11 different AEDs that showed that patients randomized to 1 of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% CI 12. To 2.7) of suicidal thinking or behavior compared to patients randomized to placebo.[4] Anyone considering prescribing cannabidiol or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness.[4] Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior.[4]

Drug Interactions:
Dedicated drug-interaction trials evaluating concomitant administrations of CYP2C19 and CYP3A inhibitors and inducers with cannabidiol were not conducted during Phase 3 investigations. However, in 2 separate studies concentrations of clobazam and its active metabolite, N-desmethylclobazam, increased from 25%

to 63% and from 69% to 500%, respectively, with concurrent cannabidiol.[23,24] One study included 13 pediatric patients, 10 (77%) of whom experienced adverse effects of clobazam requiring dose reduction.[23] The other study included 203 serum concentrations from 27 adult and pediatric patients.[24] Cannabidiol doses were started at 5 mg/kg/day and titrated up to a goal of 25 mg/kg/day or to a maximum of 50 mg/kg/day.[24] In a pharmacokinetic study of healthy volunteers cannabidiol (750 mg twice daily) co-administered with clobazam increased the N-desmethylclobazam maximum serum concentration and AUC approximately 3-fold.[4] Clobazam is predominantly metabolized by CYP3A4 and CYP2C19, and cannabidiol potently inhibits CYP3A4 and CYP2C19 enzymes. Consequently, a pharmacokinetic interaction is suspected between clobazam and cannabidiol, as patients taking clobazam and cannabidiol have experienced increased sedation.[4] In the GWPCARE1 trial the most common adverse event was somnolence, reported in 22 patients (36%) in the cannabidiol group and 6 patients (10%) in the placebo group. Of the 22 patients in the cannabidiol group in whom somnolence was reported, 18 were taking clobazam, as compared with 5 of 6 patients in the placebo group.[1]

Cannabidiol causes dose-related increases in LFTs, and the majority of elevations in phase 3 trials occurred in patients taking concomitant valproate.[4] The incidence of LFT elevations greater than 3 times the upper limit of normal was 30% in patients taking concomitant valproate and clobazam, 21% in patients taking concomitant valproate (without clobazam), 4% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug.[4] Resolution of LFT elevations occurred with discontinuation of cannabidiol or a dose reduction of cannabidiol and/or concomitant valproate in about two-thirds of the cases.[4] In about one-third of the cases, LFT elevations resolved during continued treatment, without dose reduction of either drug.[4]

Look-alike / Sound-alike Error Risk Potential: No other medications identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in seizure frequency (all types)
2) Serious adverse events
3) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage change in seizure frequency from baseline over a month

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Unknown
Oral Bioavailability	Not available – high fat/high calorie meals increase extent of absorption
Distribution and Protein Binding	Volume of distribution ranges from 21,000 Liters to 42,000 Liters. Protein binding > 94%
Elimination	Excreted in feces (84%) with minor renal clearance (8%)
Half-Life	56-61 hours
Metabolism	Metabolized in the liver and the gut (primarily the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Devinsky O, et al.[1] (GWPCARE1) DB, PC, MC RCT Trial Design: 4 wk baseline, 14 wk treatment (2 weeks dose titration, 12 weeks maintenance), 10 day taper, 4 wk safety follow-up Total duration of subject participation: 3 mos Followed by open label extension study N= 120	1. CBD oral solution titrated to 20mg/kg divided twice daily 2. Placebo as an oral solution twice daily	Demographics: 1. Mean age: 9.8 yo 2. Gender: 52% male 3. Race: 78% White 4. Median baseline seizure frequency: 13 seizures per mo 5. Number of previous AEDs tried: 4 6. Median number of concomitant AEDs during study: 3 (65% clobazam; 55% valproic acid; 43% stiripentol) Key Inclusion Criteria: 1. Age 2 to 18 years with DS not controlled by current AED regimen 2. ≥4 seizures during 28 day baseline period 3. Stable on AED regimen at least 4 weeks prior to study enrollment Key Exclusion Criteria: 1. Unstable medical condition other than epilepsy 2. Significant abnormal lab values 3. ECG abnormalities 4. Prior use of cannabis within 3 months prior to study enrollment 5. Consumption of grapefruit juice 3 days prior to study enrollment and/or during study 6. Impaired hepatic function (ALT >5 ULN)	ITT: 1.61 2.59 PP: 1.52 2.56 Attrition: 1.9 (15%) 2.3 (5%)	Primary Endpoint: Median percentage change from baseline in convulsive seizure frequency over an average of 28 days 1. -38.9% 2. -14.9% Adjusted MD -22.8% (95% CI -41.1 to -5.4), p = 0.012 Secondary Endpoints: 1. Percent of patients with ≥50% reduction in convulsive seizure frequency during 4 week treatment period 1. 26 (43%) 2. 15 (27%) OR 2.00 (95% CI 0.93 to 4.30), p=0.08 2. Median percentage change in total seizure frequency per month 1. -28.6% 2. -9.0% Adjusted MD: -19.2% (95% CI -39.25 to -1.17), p=0.03 3. Overall improvement on CGIC scale 1. 37 (63.1%) 2. 20 (35.1%) p=0.02 95% CI - NR	 NA NS NA NA	AEs 1. 57 (93%) 2. 44 (75%) SAEs 1. 8 (16%) 2. 3 (5%) AE leading to withdrawal 1. 8 (13%) 2. 1 (1 %) Somnolence 1. 22 (36%) 2. 6 (10%) Loss of Appetite 1. 17 (28%) 2. 3 (5%) Diarrhea 1. 19 (31%) 2. 6 (10%) Elevated LFTs 1. 12 (20%) 2. 1 (1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Assigned 1:1 via IVRS; stratified by age group (2-5 yo, 6-12 yo, 13-18 yo). Performance Bias: High. Side effects of drugs could lead to unblinding. Caregiver assessment showed differences in palatability between study drug and placebo. Detection Bias: Unclear. Partially subjective end point of convulsive-seizure frequency reported by caregivers via IVRS. Attrition Bias: High. More drop out in the study drug arm compared to placebo (15% vs 5%) due to AEs. Reporting Bias: Low. Protocol available at NEJM website. Outcomes reported as prespecified. Other Bias: High. Funded by GW Pharmaceuticals, also responsible for trial design, trial management, site monitoring, data and statistical analysis. Author conflict of interest statements reported in depth. **Applicability**: Patient: Studied in children and young adults, cannot extrapolate results to adults >19 yo. Intervention: CBD dosed at maximum FDA-recommended dose based on safety analysis. Comparator: Placebo designed to be administered in same volume as study drug. Outcomes: Change in convulsive seizure frequency an appropriate outcome. Setting: 23 centers in 4 countries; primarily in US patients. US (13), UK (3), France (4), Poland (2)

2. Devinsky O et al.[2] (GWPCARE3) DB, PC, MC, RCT Duration: 14 weeks (2 weeks titration followed by 12 week maintenance period) Followed by open label extension study N=225	1. CBD oral solution 20mg/kg/day divided twice daily 2. CBD oral solution 10mg/kg divided twice daily 3. Placebo oral solution twice daily in a volume comparable to 20 mg/kg or 10mg/kg	<u>Demographics</u>: 1. Mean age 15 yo 2. Gender: 57% male 3. Race: 88% White 4. Median number of drop seizures per 28 days: 85 5. Number of previous AEDs tried: 6 6. Median number of concomitant AED: 3 (49% clobazam; 40% valproic acid) <u>Key Inclusion Criteria</u>: 1. Subjects with LGS aged 2 to 55 yo refractory to AED treatment 2. History of slow (<3.0 Hz) spike and wave pattern on EEG 3. Subject had at least 2 drop seizures per wk during 4 wk baseline period 4. Stable on one or more AEDs for 4 weeks prior to screening <u>Key Exclusion Criteria</u>: 1. Seizures due to progressive neurologic disease 2. Subjects with tuberous sclerosis with a progressive tumor 3. Anoxic episode requiring resuscitation within 6 mos of screening 4. Unstable medical condition 5. Prior use of cannabis within 3 mos prior to study enrollment	<u>ITT</u>: 1. 76 2. 73 3. 76 <u>PP</u>: 1. 67 2. 71 3. 74 <u>Attrition</u>: 1.9 (11.8%) 2.2 (2.7%) 3.2 (2.6%)	<u>Primary Endpoint</u>: Median percent change from baseline in the frequency of drop seizures over 28 days 1. -41.9% 2. -37.2% 3. -17.2% 1 vs 3: MD -21.6% (95% CI -34.8 to -6.7), p=0.005 2 vs 3: MD -19.2% (95% CI -31.2 to -7.7), p=0.002 <u>Secondary Endpoints</u>: 1.Percent of patients with ≥50% reduction in convulsive seizure frequency from baseline 1. 30 (39.5%) 2. 26 (35.6%) 3. 11 (14.5%) 1 vs 3: OR 3.85 (95% CI 1.75 to 8.47), p<0.001 2 vs 3: OR 3.27 (95% CI 1.47 to 7.26), p=0.003 2. Median percent change in total seizures (averaged over 28 days) 1. -38.4% 2. -36.4% 3. -18.5% 1 vs 3: MD 18.8% (95% CI 4.4 to 31.8), p=0.009 2 vs 3: MD 19.5% (95% CI 7.5 to 30.4), p=0.002 3. Overall Improvement from baseline on CGIC reported at last visit 1. 43 (57%) 2. 48 (66%) 3. 33 (44%)	NA 25%/4 21%/5 NA	<u>AEs</u> 1. 77 (94%) 2. 56 (84%) 3. 55 (72%) <u>SAEs</u> 1. 13 (17%) 2. 13 (18%) 3. 7 (9%) <u>Withdrawal due to SAEs</u> 1. 6 (8%) 2. 1 (1%) 3. 1 (1%) <u>Somnolence</u> 1. 30 (25%) 2. 21 (14%) 3. 5 (4%) <u>Decreased Appetite</u> 1. 26 (21%) 2. 13 (9%) 3. 4 (3%) <u>Diarrhea</u> 1. 15 (12%) 2. 10 (7%) 3. 8 (6%) <u>Elevated LFTs</u> 1. 11 (14%) 2. 3 (4%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 1:1:1 via computer-generated block randomization schedule with block sizes of 6. Stratified by age group (2-5 yo, 6-11 yo, 12-17 yo, 18-55 yo). <u>Performance Bias</u>: Unclear. Side effects of study drug could lead to unblinding. <u>Detection Bias</u>: Unclear. Patients and caregivers recorded number and type of seizures each day via an IVRS recording. <u>Attrition Bias</u>: High. Higher attrition observed with 20mg/kg/day dosing due to AEs. <u>Reporting Bias</u>: Outcomes reported as prespecified. <u>Other Bias:</u> High. Funded by GW Pharmaceuticals who were also responsible for study design, management, monitoring, statistical and data analysis. Author conflict of interest statements reported in depth **Applicability**: <u>Patient</u>: Study population did not display extensive diversity (88% white). Did not include patients older than 56 yo. <u>Intervention</u>: Assessed 2 dosing regimens of CBD. <u>Comparator</u>: Placebo designed to be administered in same volume as study drug. Placebo appropriate comparator as subjects continued with current AED regimen. <u>Outcomes</u>: Change in drop seizure frequency an appropriate outcome. <u>Setting</u>: Conducted at 29 centers in 4 countries: US (20); UK (3); France (1); Spain (5)

		6. Impaired hepatic function (ALT or AST >5 ULN) 7. History of suicidal behavior 8. Taking > 4 AEDs 9. Use of felbamate or long-term steroids or any medication known to exacerbate epilepsy 10. Use of corticotropins 6 mos prior to screening		1 vs 3: OR 1.83 (95% CI 1.02 to 3.30), p=0.04 2 vs 3: OR 2.57 (95% CI 1.41 to 4.66), p=0.002	13%/8 22%/5			
Thiele EA et al.[3] (GWPCARE4) DB, PC, MC, RCT Duration: 14 weeks (2 weeks titration followed by 12 week maintenance period) Followed by open label extension study N=171	1. CBD oral solution 20mg/kg/day divided twice daily 2. Placebo oral solution twice daily	Demographics: 1. Mean age: 15 yo 2. Gender: 51% male 3. Race: 90% White 4. Median number of drop seizures per 28 days: 74 5. Number of previous AEDs: 6 6. Median number of concomitant AEDs: 3 (50% clobazam; 40% valproic acid) Key Inclusion Criteria: 1. Subjects with LGS aged 2 to 55 yo refractory to at least 2 AEDs 2. History of slow (<2.5 Hz) spike and wave pattern on EEG 3. Experience ≥2 drop seizures per wk during 4 wk baseline period 4. Stable on one or more AEDs for 4 weeks prior to screening Key Exclusion Criteria: See criteria for GWPCARE 3	ITT: 1. 86 2. 85 PP: 1. 72 2. 84 Attrition: 1. 14 (16%) 2. 1 (1%)	Primary Endpoint: Median percent change in drop seizures frequency from baseline over 28 days 1. -43.9% 2. -21.8% MD -17 (95% CI -30.32 to -4.09), p=0.0135 Secondary Endpoints: 1. Percent of patients with ≥50% reduction in convulsive seizure frequency during 14 week treatment period 1. 38 (44%) 2. 20 (24%) OR 2.57 (95% CI 1.33 to 4.97), p=0.0043 2. Median percentage change in total seizure frequency 1. -41.2% 2. -13.7% MD -21.1 (95% CI-33.3 to -9.4), p=0.005 3. Improvement on CGIC scale 1. 49 (58%) 2. 29 (34%) OR 2.54 (95% CI 1.5 to 4.5), p=0.0012	NA 20%/5 NA	AEs 1. 74 (86%) 2. 59 (69%) AE leading to withdrawal 1. 12 (14%) 2. 1 (1%) SAEs 1. 20 (23%) 2. 4 (5%) Somnolence 1. 13 (15%) 2. 8 (9%) Loss of Appetite 1. 11 (13%) 2. 2 (2%) Diarrhea 1. 16 (19%) 2. 7 (8%) Elevated LFTs 1. 20 (23%) 2. 1 (1%)	NA for all	**Risk of Bias (low/high/unclear):** Selection Bias: Low. Randomized 1:1 IVRS. Performance Bias: Unclear. Side effects of study drug could lead to unblinding. Detection Bias: Unclear. Patients and caregivers recorded number and type of seizures each day via an IVRS recording. Attrition Bias: High. More discontinuations in study drug population vs. placebo due to AEs. Reporting Bias: Outcomes reported as prespecified. Other Bias: High. Funded by GW Pharmaceuticals who were also responsible for study design, management, monitoring, statistical and data analysis. Author conflict of interest statements reported in depth. **Applicability:** Patient: Patient population not very diverse (90% white). Patients > 55 yo not included. Intervention: CBD dosed at highest maximum dose deemed safe with acceptable AEs. Comparator: Placebo appropriate comparator as subjects continued with current AED regimen. Outcomes: Change in drop seizure frequency an appropriate outcome. Setting: 24 sites in 3 countries: US (17), Netherlands (1), and Poland (6)

Abbreviations [alphabetical order]: AE = adverse effect; AED = antiepileptic drug; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; CGIC = Caregiver Global Impression of Change; CBD = cannabidiol; CI = confidence interval; DB = double blind; DS = Dravet syndrome; ECG = electrocardiogram; EEG = electroencephalogram; ITT = intention to treat; IVRS = interactive voice response system; LGS = Lennox-Gastaut syndrome; MC = multi center; MD = median difference: Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SAE = serious adverse effect; UK = United Kingdom; ULN = upper limit of normal; US = United States; WK = week; YO = years old

NEW DRUG EVALUATION: Stiripentol capsules and powder for oral suspension (Diacomit®)
See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Stiripentol is structurally unrelated to all currently marketed antiepileptic products, and is classified as an aromatic allylic alcohol.[25] It is FDA-approved for treatment of seizures associated with DS in children aged 2 years and older taking clobazam.[8] The exact anticonvulsant mechanism of stiripentol is unknown, but possible actions include direct effects mediated through the gamma-aminobutyric acid (GABA) receptor and indirect effects involving inhibition of CYP450 activity with resulting increase in blood levels of clobazam and its active metabolite. The clinical development of the drug was delayed due to its inhibitory effect on hepatic enzymes. Stiripentol increases the plasma concentrations of many AEDs, including phenytoin, carbamazepine, phenobarbital, valproate, and clobazam. Studies of stiripentol in adults have been discontinued since 1995 due to lack of significant efficacy.[25]

Two, small, short-term, randomized placebo-controlled trials of stiripentol in DS were conducted in France and Italy over 15 years ago. These 2 trials led to the approval of stiripentol as an adjunctive treatment for DS in Europe (2007), Canada (2012), and Japan (2012) via orphan drug status.[26] The two studies combined involved a total of 65 children between 3 and 18 years of age with DS. The FDA approved stiripentol based on evidence from these 2 clinical trials. Stiripentol is only FDA-approved as an adjunctive therapy in combination with clobazam. There are no clinical data to support the use of stiripentol as monotherapy in DS.[8]

STICLO-France was conducted in 15 centers in France (n = 42)[5] and STICLO-Italy was conducted in 6 centers in Italy (n= 23).[6,7] The Italian study is not published, but individual data was reported in 2 separate systematic reviews published by CADTH[6] and Cochrane Collaboration[27] authors which evaluated evidence for the safety and efficacy of stiripentol in DS. The STICLO-France trial is described and evaluated below in **Table 5**. The two STICLO studies employed similar study designs to compare the efficacy and safety of stiripentol with placebo in patients aged 3 to 18 years old with a diagnosis of DS who were being treated concomitantly with clobazam (0.5mg/kg/day, maximum 20mg/day) and valproate (30 mg/kg/day).[6] Both studies included a one-month baseline period in which patients received stable doses of clobazam and valproate, and a two-month double-blind period (when stiripentol was administered orally at a dose of 50 mg/kg/day in combination with clobazam and valproate), followed by one month of open-label stiripentol therapy (plus clobazam and valproate) for all study participants.[6] During the double-blind period, the doses of clobazam or valproate were reduced in the event of serious adverse events: poor appetite or persistent weight loss for valproate, and drowsiness or hyperexcitability for clobazam.[6]

The primary efficacy endpoint for both studies was the proportion of responders during the double blind period. A responder was defined as a patient who had 50% or greater reduction in the monthly frequency of generalized clonic or tonic-clonic seizures during the treatment period compared to baseline.[5] In both studies, the percentage of responders was statistically significantly higher in the stiripentol groups compared with placebo. In STILCO-France, 15 of 21 (71%) stiripentol-treated patients were responders compared to 1 out of the 20 (5%) patients in the placebo group ($p<0.0001$; 95% CI 42.2 to 85.7; ARR=66; NNT=2).[5] In STILCO-Italy, 8 of 12 (67%) of stiripentol-treated patients were responders versus 1 of 11 (9%) in the placebo arm ($p<0.009$; 95% CI not reported; ARR=58; NNT=2).[6,27] In the Cochrane meta-analysis, a statistically significant higher proportion of stiripentol subjects (22/33; 67%) had 50% or greater reduction in seizure frequency compared to placebo (2/31; 6%) resulting in a risk ratio (RR) of 10.4% (95% CI 2.64 to 40.87; ARR=61%; NNT=2).[27]

Trial Limitations

The STILCO-France study has a number of methodological flaws that impact the reliability of interpreting the data reported from this trial. Additional adequately powered studies with long-term follow-up are needed to establish the long-term efficacy and tolerability of stiripentol in the treatment of patients with DS.

- Power calculations were not performed prior to study initiation. Investigators inappropriately determined a between-treatment difference for the primary outcome for statistical testing after the study was under way.[6]
- The small sample size limits the identification of infrequent or rare adverse events or clinical effectiveness in the broader population.
- The short-term follow-up duration (2 months) of the trial limits the ability to assess the impact of stiripentol on developmental delay, cognitive impairment, and behavioral disorders. Long-term follow-up is also necessary to evaluate survival and adverse events related to treatment of DS with stiripentol.[7]
- Although the study reported a decrease in seizure frequency with stiripentol versus placebo, the benefit of stiripentol may be overestimated due to a known pharmacokinetic drug–drug interaction of stiripentol with clobazam.[6] Plasma levels of norclobazam (an active metabolite of clobazam) during the double-blind period were noticeably elevated over baseline levels in the stiripentol groups, but not the placebo groups.[6] The combination of the relatively low dose of clobazam used (20mg/kg/day), plus the pharmacokinetic drug–drug interaction that elevated levels of norclobazam in the stiripentol groups, may have overestimated the benefit of stiripentol.[6]
- Treatment adherence to the study drug was evaluated for 22 out of 41 patients. Nineteen patients did not return all the bottles: 11 in the stiripentol group and 8 in the placebo group.[6]
- The frequency of study discontinuation was higher in the placebo group compared with the stiripentol group. However, since it is unclear how missing data were handled, it is unclear to what extent this differential dropout affects the study results.[6]
- Parents and caregivers recorded patients' seizure frequency in a diary; however, this method has not been validated and the reliability of this method is questionable; also it was not clear if, prior to the patient enrollment in the study, parents and caregivers received training on how to recognize and accurately report seizures.[6] Patient and caregiver adherence to daily reporting of seizure frequency was not reported.[6]
- There were no definitions of the analyzed populations, which created confusion as it which populations were used to assess (intention-to-treat or per protocol population.[6]

Clinical Safety:

In STILCO-France, adverse events were higher in the stiripentol group compared with the placebo group and were reported as being mild or moderate in severity.[5] The percentage of patients reporting adverse events in the stiripentol group was 100% (21 out of 21) compared with 25% (5 out of 20) in the placebo group.[5] The most frequently reported adverse events with stiripentol included nausea, drowsiness, loss of appetite, weight, somnolence, agitation, and aggression.[4] **Table 5** outlines the adverse effects that occurred in 5% or more of patients treated with stiripentol and more frequently than placebo as reported in the manufacturer's prescribing information.

Table 5. Adverse effects that occurred in 5% or more of patients treated with stiripentol and more frequently than placebo[8]

Adverse Effect	Stiripentol 50 mg/kg/day (n =33), %	Placebo (n=31), %
Nausea	15	3
Fatigue	9	3
Decreased weight	27	6
Decreased appetite	46	10
Somnolence	67	23
Agitation	27	16
Insomnia	12	7
Aggression	9	0

Drug Interaction with Clobazam

Doses of the co-administered antiepileptic drugs in the double-blind period were allowed to be decreased due to adverse events.[6] In STILCO-France, 11 (52.4%) patients in the stiripentol group and 3 (15%) patients in the placebo group had to reduce their doses of clobazam or valproate.[6] At the end of the double-blind period, the steady-state plasma concentrations of clobazam and its metabolite, norclobazam, increased from baseline in the stiripentol groups.[6] Compared with clobazam, the increase in norclobazam was of a greater magnitude: from a median of 0.74 mg/L to 4.14 mg/L in STICLO-France.[6] In contrast, in the placebo groups, there was little change in the plasma concentrations of either clobazam or norclobazam from baseline to the double-blind period.[6]

Look-alike / Sound-alike Error Risk Potential: Nothing reported.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Proportion of patients with decrease in seizures
2) Serious adverse events
3) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Proportion of responders, defined as a patient who had 50% or greater reduction in the monthly frequency of seizures during the treatment period compared to baseline

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Unknown: possible GABA receptor agonist
Oral Bioavailability	Rapid; well absorbed – time to peak absorption is 2-3 hours
Distribution and Protein Binding	Protein binding – 99%
Elimination	Renal excretion – 90%
Half-Life	Half-life ranges from 4.5 to 13 hours and increases with increasing doses (dose-dependent)
Metabolism	Main liver cytochrome P450 CYP isoenzymes involved in metabolism are considered to be CYP1A2, CYP2C19, and CYP3A4

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Chiron MD et al.[5] DB, PC, MC Duration: 2 months followed by open label extension for 1 month 15 French centers from 1996 through 1998	1. Stiripentol 50mg/kg to 100mg/kg per day divided 2-3 times per day 2. Placebo	Demographics: -Mean age: 9 yo -Median number of monthly seizures: 18 -Gender 1. Male: 28% 2. Male: 55% Key Inclusion Criteria: -Age ≥3 yo with DS taking valproate and clobazam -≥4seizures per month Key Exclusion Criteria: -Children receiving other AEDs except for progabide (not approved in the US) and intra-rectal diazepam -Asthma patients treated with theophylline -Parents unable to accurately record number of seizures	ITT: 1. 21 2. 20 PP: 1. 20 2. 16 Attrition: 1.1 (5%) 2.4 (20%)	Primary Endpoint: Proportion of responders (responders defined as ≥50% reduction in frequency of seizures during the second month of treatment compared to baseline); ITT population 1. 15 (71%) 2. 1 (5%) Difference: 66% 95% CI 42.2 to 85.7 p<0.0001 Secondary Endpoints: Change in mean number of seizures during first month of treatment compared to baseline 1. -15.18 2. +5.32 p=0.001 95% CI NR Change in mean number of seizures during second month of treatment compared to baseline 1. -12.75 2. -4.7 p<0.002 95% CI NR Number of seizure-free patients (ITT population) 1. 9 (43%) 2. 0 (0%) 95% CI NR p=0.0013	66%/2 NA NA 43%/3	Drowsiness 1 .15 (68%) 2. 2 (10%) Loss of appetite 1. 7 (32%) 2. 1 (5%) Weight loss 1. 6 (28%) 2. 0 (0%) Neutropenia 1. 3 (14%) 2. 0 (0%) All AEs 1. 21 (100%) 2. 5 (25%) SAEs 1. 6 (28%) 2. 3 (15%) Withdrawals due to SAEs 1. 1 (5%) 2. 2 (10%) 95% CI or p value NR for all outcomes	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Baseline demographics not evenly matched in terms of gender. Randomization completed using a computer-generated list. Performance Bias: Unclear. Adherence unable to assess based on bottle return by patient's family. Active drug matched in appearance to placebo. Differences in AEs could have potentially resulted in unblinding. Study protocol unavailable. Detection Bias: Unclear. Double blind trial design, no additional details provided. Seizure frequency documented by caregiver in a diary. Differences in AEs could have potentially resulted in unblinding. Attrition Bias: High. More dropouts in placebo arm (20% vs 5%). Not clear how missing data was handled. Reporting Bias: Unclear. Study protocol unavailable; however published report includes all expected outcomes. Other Bias: Trial funded by manufacturer. **Applicability**: Patient: Restricted to DS patients aged 3-18 yo Intervention: Stiripentol dose is used in clinical practice combined with clobazam and valproate. FDA approval is only for stiripentol in combination with clobazam. Trial is a short term assessment (2 months) which limits long term assessment of AEs and efficacy. Comparator: Placebo Outcomes: Frequency of seizures is appropriate, other outcome such as frequency of status epilepticus and health related quality of life not assessed. Setting: 15 sites in France

Abbreviations AEs = adverse effects: AEDS= anti-epileptic drugs; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; DS = Dravet syndrome; ITT = intention to treat; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; SAEs = serious adverse effects; SMEI = severe myoclonic epilepsy in infancy; YO = years old

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Appendix 1: Current Preferred Drug List

Route	Form	Brand	Generic	PDL	Carveout
PO	ORAL SUSP	CARBAMAZEPINE	carbamazepine	Y	
PO	TABLET	CARBAMAZEPINE	carbamazepine	Y	
PO	TAB CHEW	CARBAMAZEPINE	carbamazepine	Y	
PO	TAB ER 12H	CARBAMAZEPINE ER	carbamazepine	Y	
PO	TABLET	EPITOL	carbamazepine	Y	
PO	ORAL SUSP	TEGRETOL	carbamazepine	Y	
PO	TABLET	TEGRETOL	carbamazepine	Y	
PO	TAB ER 12H	TEGRETOL XR	carbamazepine	Y	
RC	KIT	DIASTAT	diazepam	Y	
RC	KIT	DIASTAT ACUDIAL	diazepam	Y	
RC	KIT	DIAZEPAM	diazepam	Y	
PO	TABLET DR	DEPAKOTE	divalproex sodium	Y	Y
PO	TAB ER 24H	DEPAKOTE ER	divalproex sodium	Y	Y
PO	CAP DR SPR	DEPAKOTE SPRINKLE	divalproex sodium	Y	Y
PO	CAP DR SPR	DIVALPROEX SODIUM	divalproex sodium	Y	Y
PO	TABLET DR	DIVALPROEX SODIUM	divalproex sodium	Y	Y
PO	TAB ER 24H	DIVALPROEX SODIUM ER	divalproex sodium	Y	Y
PO	CAPSULE	ETHOSUXIMIDE	ethosuximide	Y	
PO	SOLUTION	ETHOSUXIMIDE	ethosuximide	Y	
PO	CAPSULE	ZARONTIN	ethosuximide	Y	
PO	SOLUTION	ZARONTIN	ethosuximide	Y	
PO	TABLET	PEGANONE	ethotoin	Y	
PO	CAPSULE	GABAPENTIN	gabapentin	Y	
PO	TABLET	GABAPENTIN	gabapentin	Y	
PO	CAPSULE	NEURONTIN	gabapentin	Y	
PO	TABLET	NEURONTIN	gabapentin	Y	
PO	TABLET	VIMPAT	lacosamide	Y	
PO	TABLET	LAMICTAL	lamotrigine	Y	Y
PO	TABLET	LAMOTRIGINE	lamotrigine	Y	Y
PO	TABLET	SUBVENITE	lamotrigine	Y	Y
PO	TABLET	KEPPRA	levetiracetam	Y	
PO	SOLUTION	KEPPRA	levetiracetam	Y	
PO	TABLET	LEVETIRACETAM	levetiracetam	Y	
PO	SOLUTION	LEVETIRACETAM	levetiracetam	Y	
PO	TABLET	ROWEEPRA	levetiracetam	Y	
PO	CAPSULE	CELONTIN	methsuximide	Y	

PO	TABLET	OXCARBAZEPINE	oxcarbazepine	Y	
PO	ORAL SUSP	OXCARBAZEPINE	oxcarbazepine	Y	
PO	TABLET	TRILEPTAL	oxcarbazepine	Y	
PO	ORAL SUSP	TRILEPTAL	oxcarbazepine	Y	
PO	ELIXIR	PHENOBARBITAL	phenobarbital	Y	
PO	TABLET	PHENOBARBITAL	phenobarbital	Y	
PO	TAB CHEW	DILANTIN	phenytoin	Y	
PO	ORAL SUSP	DILANTIN-125	phenytoin	Y	
PO	ORAL SUSP	PHENYTOIN	phenytoin	Y	
PO	TAB CHEW	PHENYTOIN	phenytoin	Y	
PO	CAPSULE	DILANTIN	phenytoin sodium extended	Y	
PO	CAPSULE	PHENYTEK	phenytoin sodium extended	Y	
PO	CAPSULE	PHENYTOIN SODIUM EXTENDED	phenytoin sodium extended	Y	
PO	TABLET	MYSOLINE	primidone	Y	
PO	TABLET	PRIMIDONE	primidone	Y	
PO	TABLET	BANZEL	rufinamide	Y	
PO	TABLET	GABITRIL	tiagabine HCl	Y	
PO	TABLET	TIAGABINE HCL	tiagabine HCl	Y	
PO	TABLET	TOPAMAX	topiramate	Y	
PO	TABLET	TOPIRAMATE	topiramate	Y	
PO	CAPSULE	DEPAKENE	valproic acid	Y	Y
PO	CAPSULE	VALPROIC ACID	valproic acid	Y	Y
PO	SOLUTION	DEPAKENE	valproic acid (as sodium salt)	Y	Y
PO	SOLUTION	VALPROIC ACID	valproic acid (as sodium salt)	Y	Y
PO	CAPSULE	ZONEGRAN	zonisamide	Y	
PO	CAPSULE	ZONISAMIDE	zonisamide	Y	
PO	TB CHW DSP	LAMICTAL	lamotrigine	V	Y
PO	TAB DS PK	LAMICTAL (BLUE)	lamotrigine	V	Y
PO	TAB DS PK	LAMICTAL (GREEN)	lamotrigine	V	Y
PO	TAB DS PK	LAMICTAL (ORANGE)	lamotrigine	V	Y
PO	TAB RAPDIS	LAMICTAL ODT	lamotrigine	V	Y
PO	TB RD DSPK	LAMICTAL ODT (BLUE)	lamotrigine	V	Y
PO	TB RD DSPK	LAMICTAL ODT (GREEN)	lamotrigine	V	Y
PO	TB RD DSPK	LAMICTAL ODT (ORANGE)	lamotrigine	V	Y
PO	TAB ER 24	LAMICTAL XR	lamotrigine	V	Y
PO	TB ER DSPK	LAMICTAL XR (BLUE)	lamotrigine	V	Y
PO	TB ER DSPK	LAMICTAL XR (GREEN)	lamotrigine	V	Y
PO	TB ER DSPK	LAMICTAL XR (ORANGE)	lamotrigine	V	Y

PO	TB CHW DSP	LAMOTRIGINE	lamotrigine	V	Y
PO	TAB DS PK	LAMOTRIGINE	lamotrigine	V	Y
PO	TAB DS PK	LAMOTRIGINE (BLUE)	lamotrigine	V	Y
PO	TAB DS PK	LAMOTRIGINE (GREEN)	lamotrigine	V	Y
PO	TAB DS PK	LAMOTRIGINE (ORANGE)	lamotrigine	V	Y
PO	TAB ER 24	LAMOTRIGINE ER	lamotrigine	V	Y
PO	TAB RAPDIS	LAMOTRIGINE ODT	lamotrigine	V	Y
PO	TB RD DSPK	LAMOTRIGINE ODT (BLUE)	lamotrigine	V	Y
PO	TB RD DSPK	LAMOTRIGINE ODT (GREEN)	lamotrigine	V	Y
PO	TB RD DSPK	LAMOTRIGINE ODT (ORANGE)	lamotrigine	V	Y
PO	TAB DS PK	SUBVENITE (BLUE)	lamotrigine	V	Y
PO	TAB DS PK	SUBVENITE (GREEN)	lamotrigine	V	Y
PO	TAB DS PK	SUBVENITE (ORANGE)	lamotrigine	V	Y
PO	SOLUTION	BRIVIACT	brivaracetam	N	
PO	TABLET	BRIVIACT	brivaracetam	N	
PO	SOLUTION	EPIDIOLEX	cannabidiol	N	
PO	CPMP 12HR	CARBAMAZEPINE ER	carbamazepine	N	
PO	CPMP 12HR	CARBATROL	carbamazepine	N	
PO	TABLET	ONFI	clobazam	N	
PO	ORAL SUSP	ONFI	clobazam	N	
PO	TABLET	APTIOM	eslicarbazepine acetate	N	
PO	TABLET	POTIGA	ezogabine	N	
PO	ORAL SUSP	FELBAMATE	felbamate	N	
PO	TABLET	FELBAMATE	felbamate	N	
PO	ORAL SUSP	FELBATOL	felbamate	N	
PO	TABLET	FELBATOL	felbamate	N	
PO	SOLUTION	GABAPENTIN	gabapentin	N	
PO	TAB ER 24H	GRALISE	gabapentin	N	
PO	SOLUTION	NEURONTIN	gabapentin	N	
PO	TABLET ER	HORIZANT	gabapentin enacarbil	N	
PO	SOLUTION	VIMPAT	lacosamide	N	
PO	TAB DS PK	VIMPAT	lacosamide	N	
PO	TAB ER 24H	KEPPRA XR	levetiracetam	N	
PO	TAB ER 24H	LEVETIRACETAM ER	levetiracetam	N	
PO	TAB ER 24H	ROWEEPRA XR	levetiracetam	N	
PO	TAB SUSP	SPRITAM	levetiracetam	N	
PO	TAB ER 24H	OXTELLAR XR	oxcarbazepine	N	
PO	TABLET	FYCOMPA	perampanel	N	

PO	TAB DS PK	FYCOMPA	perampanel	N
PO	ORAL SUSP	FYCOMPA	perampanel	N
PO	CAPSULE	LYRICA	pregabalin	N
PO	SOLUTION	LYRICA	pregabalin	N
PO	ORAL SUSP	BANZEL	rufinamide	N
PO	CAPSULE	DIACOMIT	stiripentol	N
PO	CAP SPR 24	QUDEXY XR	topiramate	N
PO	CAP SPRINK	TOPAMAX	topiramate	N
PO	CAP SPRINK	TOPIRAMATE	topiramate	N
PO	CAP SPR 24	TOPIRAMATE ER	topiramate	N
PO	CAP ER 24H	TROKENDI XR	topiramate	N
PO	POWD PACK	SABRIL	vigabatrin	N
PO	TABLET	SABRIL	vigabatrin	N
PO	POWD PACK	VIGABATRIN	vigabatrin	N
PO	POWD PACK	VIGADRONE	vigabatrin	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2018 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 1, 2018

1	Carbamazepine	10556
2	Diazepam/	17408
3	divalproex.mp. or Valproic Acid/	11954
4	Ethosuximide/	914
5	ethotoin.mp.	48
6	Anticonvulsants/ or gabapentin.mp.	51267
7	lacosamide.mp.	567
8	lamotrigine.mp.	4601
9	levetiracetam.mp.	2576
10	methsuximide.mp.	99
11	oxcarbazepine.mp.	1642
12	Phenobarbital/	17758
13	Phenytoin/	13251
14	Primidone/	1285
15	rufinamide.mp.	195
16	tiagabine.mp.	895
17	topiramate.mp.	3974
18	Valproic Acid/	11749
19	zonisamide.mp.	1131
20	brivaracetam.mp.	146
21	clobazam.mp.	810
22	esclicarbazepine.mp.	2
23	felbamate.mp.	681
24	perampanel.mp.	218
25	Pregabalin/	1645
26	Vigabatrin/	1551
27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	105876
28	Epilepsy/	70268
29	27 and 28	19230
30	limit 29 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	121
31	limit 30 to yr = 2018-current	3

Appendix 3: Prescribing Information Highlights for Epidiolex® and Diacomit®

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution, CV
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older (1)

DOSAGE AND ADMINISTRATION

- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- EPIDIOLEX is to be administered orally. (2.2)
- The recommended starting dosage is 2.5 mg/kg taken 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). (2.2)
- 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). See Full Prescribing Information for titration. (2.2)
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.5, 8.6)

DOSAGE FORMS AND STRENGTHS

Oral solution: 100 mg/mL (3)

CONTRAINDICATIONS

Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX (4)

WARNINGS AND PRECAUTIONS

- 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. (5.1)
- 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. (5.2)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.3)
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart EPIDIOLEX if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Greenwich Biosciences at 1-833-424-6724 (1-833-GBIOSCI) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Moderate or strong inhibitors of CYP3A4 or CYP2C19: Consider dose reduction of EPIDIOLEX. (7.1)
- Strong inducer of CYP3A4 or CYP2C19: Consider dose increase of EPIDIOLEX. (7.1)
- Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 (e.g., clobazam). (7.2)
- Substrates of CYP1A2 and CYP2B6 may also require dose adjustment. (7.2)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 9/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DIACOMIT safely and effectively. See full prescribing information for DIACOMIT.

DIACOMIT (stiripentol) capsules, for oral use
DIACOMIT (stiripentol) powder, for oral suspension
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
DIACOMIT is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. There are no clinical data to support the use of DIACOMIT as monotherapy in Dravet syndrome. (1)

----------DOSAGE AND ADMINISTRATION----------
- The dosage of DIACOMIT is 50 mg/kg/day, administered by mouth in 2 or 3 divided doses. (2.2)
- Reduce dose or discontinue dose gradually. (2.3)
- Capsules must be swallowed whole with a glass of water during a meal. Capsules should not be broken or opened. (2.4)
- Powder for suspension should be mixed in a glass of water and should be taken immediately after mixing during a meal. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsule: 250 mg or 500 mg (3)
- Powder for Oral Suspension: 250 mg or 500 mg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- *Somnolence:* Monitor for somnolence, particularly when DIACOMIT is used concomitantly with other CNS depressants; If somnolence occurs during co-administration with clobazam, consider an initial reduction of clobazam by 25%. (5.1)
- *Decreased Appetite and Decreased Weight:* the weight of patients and the growth rate of pediatric patients should be carefully monitored. (5.2)
- *Neutropenia and Thrombocytopenia:* Blood counts should be obtained prior to starting treatment with DIACOMIT and then every 6 months. (5.3)
- *Withdrawal*: DIACOMIT should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.4)
- *Risks in Patients with Phenylketonuria (PKU)*: DIACOMIT powder for suspension contains phenylalanine; consider total daily intake before prescribing to patients with PKU. (5.5)
- *Suicidal Behavior and Ideation*: Monitor for suicidal thoughts or behaviors. (5.6)

----------ADVERSE REACTIONS----------
Adverse reactions that occurred in at least 10% of DIACOMIT-treated patients and more frequently than on placebo were somnolence, decreased appetite, agitation, ataxia, weight decreased, hypotonia, nausea, tremor, dysarthria, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BIOCODEX at 1-877-356-7787 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- DIACOMIT increases the plasma concentration of clobazam and its metabolite through metabolic inhibition of CYP3A4 and CYP2C19. Consider dose reduction of clobazam in case of adverse reactions. (7.1)
- Substrates of CYP2C8, CYP2C19, P-gp and BCRP may require a dose reduction. (7.1)
- Substrates of CYP1A2, CYP2B6 and CYP3A4 may require a dose adjustment. (7.1)
- Strong inducers of CYP1A2, CYP3A4 or CYP2C19: Consider dose increase of DIACOMIT (7.2).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2018

Appendix 4: Key Inclusion Criteria

Population	Patients with epilepsy
Intervention	Drugs listed in **Appendix 1**
Comparator	Active or placebo comparisons of drugs listed in **Appendix 1.**
Outcomes	Change in seizure frequency Quality of life Adverse drug effects
Timing	Any study duration: literature search from 1/1/18 to 8/1/18
Setting	Outpatient

Cannabidiol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cannabidiol

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is this an FDA approved indication? (Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older).	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Are baseline liver function tests on file (serum transaminases and total bilirubin levels)? LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver. Note: dosage adjustment is recommended for patients with moderate or severe hepatic impairment. See Table 1 for dosing recommendations.	**Yes:** Go to # 5 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No**: Pass to RPh. Deny; medical appropriateness
5. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent LFT's documented in patient records?	**Yes:** Go to # 2 Document results here: Date of lab work_____ AST_____ ALT_____ Total Bilirubin_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment[1]

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. June 2018.

P&T/DUR Review: 11/18 (DM)
Implementation: TBD

Stiripentol

Goal(s):

- To ensure appropriate drug use and restrict to indications supported by medical literature.

Length of Authorization:

Up to 12 months

Requires PA:

- Stiripentol capsules and powder for oral suspension

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 2 years of age and older taking clobazam?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
4. Are baseline white blood cell (WBC) and platelet counts on file within the past 3 months? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Approve for 12 months Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records? Note: Labs should be assessed every six months while receiving stiripentol therapy.	**Yes:** Go to # 2 Document results here: Date of lab work_____ WBC_____ Platelets_____	**No:** Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 11/18 (DM)
Implementation: TBD

Clobazam

Goal(s):

Length of Authorization:

- 12 months

Requires PA:

- Clobazam

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	**Yes:** Go to #3	**No:** Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny for lack of treatment response.

Limitations of Use:

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.[1]

1.National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: *11/18 (DM); 3/18; 7/16; 3/15; 5/12*
Implementation: *8/16, 8/12*

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	

P&T Review: *11/18 (DM); 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

Pregabalin

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature.

Length of Authorization:

- 90 days to lifetime (criteria-specific)

Requires PA:

Pregabalin and pregabalin extended release

Covered Alternatives

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for pregabalin immediate release?	**Yes:** Go to # 3	No: Go to #4
3. Does the patient have a diagnosis of epilepsy?	**Yes:** Approve for lifetime	**No:** Go to # 4
4. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Approve for 90 days to lifetime	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; not funded by the OHP.
6. Has the patient tried and failed gabapentin therapy for 90 days or have contradictions or intolerance to gabapentin?	**Yes**: Approve for 90 days	**No:** Pass to RPh. Deny and recommend trial of gabapentin for 90 days

Renewal Criteria		
1. Does the patient have documented improvement from pregabalin?	**Yes**: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Non-funded		
Fibromyalgia	X	

P&T Review: *1/19; 11/18 (DM); 7/18; 3/17; 3/15; 5/09; 9/07; 11/07*
Implementation: *10/18, 4/18/15; 1/11; 1/10*