# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210365Orig1s000

# RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

**Division of Risk Management (DRISK)**
**Office of Medication Error Prevention and Risk Management (OMEPRM)**
**Office of Surveillance and Epidemiology (OSE)**
**Center for Drug Evaluation and Research (CDER)**

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| **Application Type** | NDA |
| **Application Number** | 210365 |
| **PDUFA Goal Date** | June 27, 2018 |
| **OSE RCM #** | 2017-1581 |
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| **Reviewer Name(s)** | Yasmeen Abou-Sayed, PharmD |
| **Team Leader** | Donella Fitzgerald, PharmD |
| **Deputy Division Director** | Jamie Wilkins Parker, PharmD |
| **Review Completion Date** | May 10, 2018 |
| **Subject** | Evaluation of Need for a REMS |
| | |
| **Established Name** | Cannabidiol |
| **Trade Name** | Epidiolex |
| **Name of Applicant** | Greenwich Biosciences Research Ltd. |
| **Therapeutic Class** | Anti-convulsant |
| **Formulation(s)** | Oral Solution |
| **Dosing Regimen** | 5 mg/kg twice daily (10 mg/kg/day), can be increased up to 10 mg/kg twice daily (20 mg/kg/day) if needed |

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# EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Epidiolex (cannabidiol) is necessary to ensure the benefits outweigh its risks. Greenwich Biosciences submitted a New Drug Application (NDA 210365) for cannabidiol with the proposed indication for the adjunctive treatment of seizures associated with Dravet Syndrome (DS) and the adjunctive treatment of seizures associated with Lennox Gastaut Syndrome (LGS). The risks associated with cannabidiol include hepatic adverse events. The applicant did not submit a REMS with this application.

DRISK and the Division of Neurology Products (DNP) agree that a REMS is not necessary to ensure the benefits of cannabidiol outweigh its risks. DS and LGS are both rare, severe, refractory epilepsies associated with higher rates of morbidity and mortality than the general epilepsy population, and an unmet treatment need remains. Most adverse events associated with cannabidiol use are mild to moderate in severity. Drug-induced liver toxicity with cannabidiol has the potential to be serious, however it can be communicated via labeling, as other anti-epileptic drugs used to treat these conditions are associated with this risk and prescribers should be familiar with monitoring for it.

# 1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) (b) (4) (cannabidiol) is necessary to ensure the benefits outweigh its risks. Greenwich Biosciences Research Ltd. (Greenwich) submitted a New Drug Application (NDA) 210365 for cannabidiol with the proposed indication for the adjunctive treatment of seizures associated with Dravet Syndrome (DS) and the adjunctive treatment of seizures associated with Lennox Gastaut Syndrome (LGS) in patients aged 2 and older. This application is under review in the Division of Neurology Products (DNP). The applicant did not submit a REMS with this application.

# 2 Background

## 2.1 PRODUCT INFORMATION

Epidiolex (cannabidiol), a new molecular entity[a], is an anti-epileptic drug (AED) derived from the cannabis plant, and is the first in its class. Cannabidiol's anticonvulsant properties are thought to be mediated by the endocannabinoid system by reducing neuro hyperexcitability through modulation of intracellular calcium via the orphan G protein-coupled receptor (GPR55) and the transient receptor potential channel (TRPV1), as well as modulation of adenosine-mediated signaling. However, it does not activate the cannabinoid type 1 (CB1) receptor associated with psychoactivity.[1] Metabolism of cannabidiol is primarily via enzymes CYP3A4 and CYP2C219. Additionally, cannabidiol is a direct broad-spectrum inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. The proposed indication is for the adjunctive treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

patients aged 2 and older. Cannabidiol is proposed as a 100 mg/ml oral solution to be titrated up to 5 mg/kg twice daily (10 mg/kg/day), and can be increased up to 10 mg/kg twice daily (20 mg/kg/day) if needed. The medication will be administered in the inpatient and outpatient setting for chronic maintenance therapy.[b] Currently, U.S. federal law prohibits the use of cannabidiol and it is classified as a Schedule I controlled substance. Cannabidiol is not currently approved in any jurisdiction. Cannabidiol was granted orphan-drug designation for the treatment of both DS (2013) and LGS (2014). This application has been granted priority review.

### 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 210365 relevant to this review:

- 10/27/2017: Greenwich submitted the final submission to complete the rolling submission for NDA 210365.
- 12/20/2017: Priority review designation for NDA 210365 granted.
- 2/20/2018: A Mid-Cycle Communication with Sponsor was held in which the Agency indicated at this time, a REMS was not likely to be required.
- 4/3/2018: A Late-Cycle Communication with Sponsor was held in which the Agency indicated at this time, a REMS was not likely to be required.
- 4/19/2018: A Peripheral and Central Nervous System Drugs Advisory Committee Meeting was convened to discuss the benefit-risk profile of cannabidiol. The members of the panel voted 13-0, that the benefit-risk profile of cannabidiol was favorable for the treatment of seizures associated with Lennox Gastaut Syndrome and Dravet syndrome in patients 2 years of age and older.

## 3 Therapeutic Context and Treatment Options

### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Cannabidiol is proposed to serve as adjunctive treatment for two epilepsy indications – Dravet Syndrome (DS), and Lennox Gastaut Syndrome (LGS).

DS, which formerly was known as severe myoclonic epilepsy of infancy, is an early-onset genetic epilepsy with onset typically in the first year of life. In 70 to 80 percent of DS patients, the syndrome is caused by de novo mutations in the alpha-1 subunit of the voltage-gated sodium channel gene. It is a rare disorder, affecting approximately 1 in 15,700 individuals and affects both males and females equally.[c] Patients initially present typically with a prolonged, often febrile, clonic seizure in the setting

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

of normal cognitive and motor development prior to seizure onset. Febrile and afebrile seizures, including status epilepticus, repeatedly occur in the weeks and months after the initial event, and cognitive and motor decline begins shortly thereafter. Refractory epilepsy featuring multiple seizure types and neurodevelopmental problems persist and the majority of older children and young adults with DS have lifelong persistent motor system dysfunction, gait and postural abnormalities, and cognitive and behavioral impairment.[d] There is an increased risk of premature mortality due to sudden unexpected death in epilepsy (SUDEP), with children suffering from seizure disorders in general at risk for death at a four-fold higher rate than children without epilepsy.[2]

Lennox Gastaut Syndrome is also an epilepsy characterized by severe childhood onset seizures with intellectual disability. This epilepsy syndrome tends to have a later onset than DS, usually between the ages of three to five years, and may occur after an earlier presentation of infantile seizures or other severe seizure disorder. The incidence of LGS is estimated to be between 1 and 28 per 1,000,000, with the annual incidence estimated to be 2 per 100,000 children.[3] The syndrome is characterized by multiple seizure types, most commonly atonic, axial tonic, and atypical absence seizures. Approximately 40% of LGS cases are of unknown etiology, with the remainder being due to multiple causes including encephalopathies following hypoxic-ischemic insults, meningitis, head injuries, and genetic disorders (particularly chromosomal syndromes or de novo mutations).[4] Mental retardation and psychotic symptoms are common in this patient population and children with this syndrome are often difficult to manage medically. Patients have a poor seizure and neurologic prognosis and mortality is high, with up to 0.5-1% of patients with severe refractory epilepsies dying due to SUDEP annually.[5]

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Dravet syndrome is a pharmacoresistant epilepsy with most patients continuing to have seizures even on polypharmacy. Valproic Acid (VPA) and Clobazam (CLB) are identified as first line therapy by experts in the field and clinical practice, although neither has a specific indication for DS.[6,7] Topiramate and the Ketogenic Diet are identified as recommended second line therapies for patients who do not respond to Valproic Acid or Clobazam. [10,11] Third line therapies for DS include clonazepam, levetiracetam, zonisamide, ethosuximide, and vagal nerve stimulation, all with limited results. Rescue medications used to help stop status epilepticus include – clonazepam, diazepam, lorazepam, and midazolam. Ninety six percent of DS patients will continue to have seizures even when treated with first and second line therapies, reinforcing the intractable nature of this patient population and the high unmet medical need. Commonly used anticonvulsants carbamazepine, oxcarbazepine, phenytoin, and lamotrigine may exacerbate seizures in patients with DS and should be avoided.[6]

Lennox Gastaut Syndrome is an equally pharmacoresistant epilepsy, with no optimal therapy indicated for LGS patients. First line therapies include valproic acid, clobazam, clonazepam, and nitrazepam. Second line treatments include lamotrigine, topiramate, felbamate, and rufinamide. Third line therapies

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

include vigabatrin, and zonisamide, with other non-medical interventions such as the ketogenic diet, corpus callostomy, vagal nerve stimulation, and focal cortical resection.[8,9,10]

These two treatment-resistant epilepsies impair quality of life and contribute to long-term cognitive and behavioral disorders. These patients often receive high doses of multi-AED regimens that cause significant side effects, with many patients continuing to experience frequent seizures despite polypharmacy. Status epilepticus, which leads to a third of deaths in these patient populations, demonstrates the need for improved seizure control.[6,11]

# 4 Benefit Assessment

The clinical development program supporting the efficacy of CBD-OS is comprised of three pivotal Phase 3 clinical trials: a single randomized, placebo-controlled, double-blind trial in DS (GWEP1332-B [National Clinical Trial (NCT) 02091375], part A was a pharmacokinetic/tolerability/dose-finding study), and 2 randomized, double-blind, placebo-controlled trials in LGS (GWEP1414 [NCT02224560] and GWEP1423 [NCT02224690]). All 3 pivotal trials consisted of a 4-week baseline period, followed by a 14-week treatment period comprised of a 2-week titration (dose escalation) period and a 12-week maintenance (stable dosing) period. Patients who discontinued cannabidiol had their dose tapered over a 10-day period, to avoid an abrupt change in blood levels (however no adverse events associated with anti-epileptic drug withdrawal were seen in cannabidiol), with a safety follow-up 4 weeks after final dose. All three trials evaluated a dose of 20 mg/kg/day, divided twice daily, cannabidiol vs. placebo as adjunctive therapy, with LGS trial GWEP1414 also including a 10 mg/kg/day dose arm to assess whether there may be a minimally effective dose. Trial patients could elect to continue in an open-label extension study (GWEP1415) to continue to evaluate safety in cannabidiol. GWEP1415's primary objective is to evaluate the long-term safety and tolerability of cannabidiol. All patients titrated up to a daily dose of 20 mg/kg/day, and could receive treatment for up to 3 years. By the cutoff date for the NDA submission, 644 patients had enrolled in this trial (278 with DS, and 366 with LGS). Patients had to have been taking 1 or more AEDs which had been maintained at a stable dose for at least 4 weeks prior to screening. All medications or nonpharmacological interventions for epilepsy (including ketogenic diet and VNS) were to remain stable throughout the trial. Seizure counts were recorded daily during the baseline and treatment period using an interactive voice response system (IVRS) telephone diary.

GWEP1332-B studied the efficacy of cannabidiol in 120 male and female DS patients between the ages of 2 and 18 years. To qualify for the treatment period of the trial, patients had to have experienced 4 or more convulsive seizures (tonic, clonic, tonic-clonic, or atonic) during the 4-week baseline period. The primary endpoint studied was the percentage change from baseline during the treatment period (including titration and maintenance) of the study in convulsive seizure frequency. The secondary endpoint studied was the number of patients who experienced at least a 50% reduction from baseline in convulsive seizure frequency. With regard to the primary endpoint, cannabidiol patients experienced a median 38.94% reduction in seizure frequency, and placebo patients experienced a median 13.29% reduction in seizure frequency, with a median difference of 22.79 between the two percentage changes

(p-value = 0.0123). The secondary endpoint was also met, with 42.6% of cannabidiol patients meeting the criteria, versus 27.1% of placebo patients (p=0.0784).

GWEP1414 (n=225) and GWEP1423 (n=171) enrolled male and female LGS patients, between the ages of 2 and 55 years. Patients who experienced at least 2 drop seizures each week during the baseline period qualified for enrollment in the trials. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic–clonic) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface. The primary endpoint studied was the percentage change from baseline in drop seizure frequency. The key secondary endpoints in both studies were the proportion of patients who achieved at least a 50% reduction from baseline in drop seizure frequency, and the percent change across all seizure frequencies. GWEP1414 demonstrated a median percentage reduction in seizure frequencies of 37.16% in the 10mg/kg cannabidiol group, 41.86% in the 20mg/kg cannabidiol group, and 17.17% in the placebo group. The differences between treatment and placebo were -19.19 (10 mg/kg cannabidiol; p-value = 0.0016) and -21.57 (20 mg/kg cannabidiol; p-value = 0.0047). The secondary endpoint in GWEP1414 also was met, with cannabidiol 20mg/kg subjects responding at a rate of 39.5% and 10 mg/kg at 35.6%, compared to placebo at 14.5% (p=0.0006 and p=0.0030 respectively). In GWEP1423, the primary endpoint showed a median 43.29% reduction in seizure frequency in cannabidiol patients, versus 21.80% reduction in placebo (difference of -17.21%; p-value = 0.0135). The secondary endpoint also was met, with cannabidiol patients responding at a rate of 44.2% versus placebo at 23.5% (p=0.0043).

Overall, the clinical reviewer has concluded that the significant and clinically meaningful results from these three studies provide substantial evidence of the effectiveness of cannabidiol for the treatment of seizures associated with DS and LGS.[12]

# 5 Risk Assessment & Safe-Use Conditions

In addition to the safety data collected in the three pivotal trials, the safety database for cannabidiol includes results from an ongoing open-label extension study (GWEP1415 [NCT02224573]), as well as data collected via the Agency's expanded access program (EAP). At the time of the original NDA submission, 1756 subjects had been exposed to cannabidiol oral solution in the applicant's development program; 1391 of these subjects had been treated for epilepsy. Approximately half of the subjects with epilepsy (684) were exposed in the uncontrolled EAP for drug-resistant epilepsy.

For both cannabidiol and placebo groups, most of the AEs were mild to moderate in intensity. The most common adverse events that occurred in 10% or more of patients are somnolence, decreased appetite, diarrhea, pyrexia, and fatigue.[13] Thirty subjects in the cannabidiol groups (9.3%) reported an adverse event leading to discontinuation, compared to 3 subjects (1.3%) in the placebo group.

## 5.1 Serious Adverse Events

The incidence of serious adverse events[e] (SAEs) across the DS and LGS cannabidiol subjects was 5%, versus 3.1% in the placebo group. The most common serious adverse events in the cannabidiol subjects were status epilepticus (SE) (5%), pneumonia (2.8%), convulsion (2.2%), and increased aspartate aminotransferase (AST) (2.2%). The clinical reviewer has concluded that these SAEs, with the exception of increased hepatic transaminases, are considered to be typical for these patient populations.[f,14]

**DEATHS**

At the time of original submission of the NDA, there had been 20 deaths in the development program. In the controlled trials, there was 1 death in a patient in the cannabidiol 20 mg/kg group and no deaths in the placebo group. Seven deaths were reported in the open-label extension trial, with 12 deaths in the EAP. Causes of death were related to SUDEP, and other various causes that are typical for this patient population and include (but are not limited to), asphyxia, hypoxemia, respiratory failure, and complications related to pneumonia. These patients were generally quite ill, with complex, chronic multisystem diseases and complicated courses. The clinical reviewer has concluded that it is not possible to attribute the deaths to cannabidiol, nor is it possible to rule out the possibility that the drug was in some way contributory. Moreover, the numbers of deaths did not seem to differ importantly from the numbers that would be expected in the DS or LGS patient populations.[13]

## 5.2 TRANSAMINASE ELEVATIONS

Transaminase elevations were observed in 14% of cannabidiol patients versus 3% in placebo. In the clinical development program for cannabidiol, the incidence of elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3X the upper limit of normal (ULN) was 2/219 (0.9%) in placebo, 2/67 (3.0%) in CBD 10 mg/kg/day, and 18/228 (18.1%) in CBD 20 mg/kg/day. Elevations in ALT were more pronounced than AST, suggesting that the liver was the source of the transaminase elevations. There also was a clear dose association, 8% elevations overall in the 10 mg/kg group and 16% in the 20 mg/kg group. However, none of the cannabidiol subjects experienced liver failure, as hyperbilirubinemia or INR elevation were not seen in conjunction with the enzyme elevations. Although small increases in total bilirubin were seen in a few cases, the bilirubin levels generally remained within normal limits and there were no cases that met Hy's law criteria (ALT ≥ 3X ULN and bilirubin > 2X ULN). Some events of transaminase elevation were serious or severe; however, there were no events of liver

[e] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

failure or death related to liver injury. Identified risk factors for transaminase elevation included concomitant valproic acid use, elevated baseline liver function tests, and higher doses of cannabidiol. Most events of transaminase elevation occurred within 30 to 90 days after initiation of cannabidiol treatment; however, rare cases were observed up to 200 days after initiation of treatment, particularly in patients taking concomitant valproic acid. Events of transaminase elevation generally resolved with discontinuation of cannabidiol or dose decreases in cannabidiol or valproic acid; however, some events resolved during continued treatment with cannabidiol at the same dose.[12]

## 5.3 ABUSE POTENTIAL

Under the Controlled Substances Act (CSA), cannabidiol is a Schedule I substance based on its derivation from the plant, Cannabis sativa, also known as marijuana or cannabis. Given that cannabidiol is proposed for the treatment of a central nervous system (CNS) condition, epilepsy, it was necessary to evaluate the abuse potential of cannabidiol through various studies, including receptor binding, animal behavioral studies, and human abuse potential studies. In particular, dronabinol ((-)-trans-delta-9-tetrahydrocannabinol [THC]), a synthetic form of the major psychoactive cannabinoid present in the cannabis plant, and currently marketed as a schedule III drug, was used as a positive control drug for the abuse potential studies.

A human abuse potential study (GWEP1431) was conducted, with a primary objective to evaluate the abuse potential of single doses of cannabidiol compared with alprazolam at a dose of 2 mg, dronabinol at doses of 10 mg and 30 mg, and placebo in healthy recreational polydrug users. Cannabidiol was used at the proposed therapeutic dose of 750 mg (10 mg/kg in a 75 kg adult), and at high therapeutic and supratherapeutic doses of 1500 mg and 4500 mg. Forty-three patients were randomized into the trial, with 35 completing the planned treatments and included in the analysis. For the primary endpoint of drug liking maximum effect (Emax), no cannabidiol dose was more than 15 points (clinically meaningful threshold) greater than placebo while the active comparators were each more than 15 points greater than placebo. All doses of cannabidiol produced a drug liking visual analogue scale (VAS) Emax that was statistically significantly lower compared with the single dose of alprazolam and both doses of dronabinol ($p =< 0.0033$ or less in each case). When compared with alprazolam and dronabinol, cannabidiol was significantly less likely to be associated with drug liking, or with the desire to take the drug again.[15]

Other studies completed to characterize the abuse potential of cannabidiol found the following:

- It does not bind to cannabinoid receptors or any other receptor associated with drugs of abuse, such as dronabinol
- It does not produce overt behaviors similar to those produced by drugs of abuse such as dronabinol
- It does not produce a cannabinoid agonist response in the tetrad test that is similar to that produced by dronabinol

- It does not generalize to dronabinol or to the depressant, midazolam, in separate drug discrimination studies, showing it does not produce effects similar to a cannabinoid agonist or to a benzodiazepine

- It does not produce self-administration, suggesting it does not have rewarding properties like many known drugs of abuse

There were no euphoria-related AEs in other Phase 1 clinical studies conducted with cannabidiol that would be indicative of abuse potential. Drugs that have abuse potential typically produce euphoria-related AEs in clinical studies. Phase 2 and 3 clinical studies with cannabidiol were not assessed for euphoria-related AEs because the antiepileptic medications patients were also taking can have known abuse potential that would confound the evaluation. Therefore, an overall assessment of the abuse-related data from preclinical and clinical studies leads to the finding that CBD has negligible abuse potential.

# 6 Expected Postmarket Use

The proposed indication for cannabidiol is for adjunctive treatment of patients with Dravet Syndrome or Lennox Gastaut Syndrome. This combination of a pharmacoresistant epilepsy and the need for adjunctive treatment should result in most of these patients being diagnosed, receiving care, and being prescribed cannabidiol in comprehensive epilepsy centers. These centers with neurologists, pediatric neurologists and epileptologists should have the experience with anticonvulsants and the risks associated with them both generally and specifically for cannabidiol and the adjunctive therapies that are required when using cannabidiol. The risk of liver toxicity associated with cannabidiol is also a risk associated with other anticonvulsants used for the treatment of DS and LGS, and the healthcare providers prescribing cannabidiol should be familiar with appropriate laboratory monitoring. The dispensing of cannabidiol will likely occur in outpatient and inpatient pharmacies.

# 7 Risk Management Activities Proposed by the Sponsor

No further risk management activities for cannabidiol have been proposed beyond routine pharmacovigilance and labeling.

# 8 Discussion of Need for a REMS

The Division of Neurology Products recommends approval of cannabidiol on the basis of the efficacy and safety information currently available.[12]

Dravet Syndrome and Lennox Gastaut Syndrome are both severe forms of refractory epilepsy syndromes which currently have no cure and limited treatment options. Cannabidiol presents an adjunctive therapy option which has demonstrated clinically significant seizure reduction in both these populations. Additionally, the adverse events associated with cannabidiol were mild to moderate in

severity. The risk of liver injury has the potential to be serious, however it can be communicated via labeling, and monitored via periodic laboratory testing, as is the standard of care with other antiepileptic drugs that have demonstrated potential hepatotoxicity. Current standard of care for patients receiving valproic acid for epilepsy management includes baseline liver function tests and continued periodic testing. At the time of this review, the proposed label for cannabidiol includes a statement in Section 5 (Warnings and Precautions) of the Prescribing Information regarding the risk of transaminase elevations and the need for periodic laboratory monitoring.to mitigate this risk.[13]

Further, cannabidiol did not demonstrate drug liking in any abuse liability studies.

# 9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for cannabidiol to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should DNP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

# 10 Appendices

## 10.1 References


[1] Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791-802.

[2] Selassie AW, Wilson DA, Malek AM, Wagner JL, Smith G, Martz G, Edwards J, Wannamaker B, Zack MM, Kobau R. Premature deaths among children with epilepsy - South Carolina, 2000-2011. MMWR Morb Mortal Wkly Rep. 2014 Nov;63(44):989-94.

[3] Hancock E, Cross J. Treatment of Lennox–Gastaut syndrome. Cochrane Database Syst Rev, 2 (2013), Article CD003277.

[4] Allen AS, et al. De novo mutations in epileptic encephalopathies. Nature 2013. 501:217.

[5]Hughes JR. A review of sudden unexpected death in epilepsy: prediction of patients at risk. Epilepsy Behav 2009; 14:280.

[6] Chiron C. Current therapeutic procedures in Dravet syndrome. Developmental Medicine and Child Neurology. 2011;53:16-18.

[7] Wirrell EC. Treatment of Dravet Syndrome. Canadian Journal of Neurological Sciences. 2016;43:S13-S18.

[8] Freeman JM. The ketogenic diet: additional information from a crossover study. J Child Neurol 2009; 24:509.

[9] Kostov K, et al. Long-term vagus nerve stimulation in the treatment of Lennox-Gastaut syndrome. Epilepsy Behav 2009; 16:321.

[10] Cukiert A, et al. Extended, one-stage callosal section for treatment of refractory secondarily generalized epilepsy in patients with Lennox-Gastaut and Lennox-like syndromes. Epilepsia 2006; 47:371.

[11] Shmuely S, et al. Mortality in Dravet syndrome: A review. *Epilepsy Behav.* 2016;64(Pt A):69-74.

[12] Division of Neurology Products. FDA Briefing Document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting. NDA 210365 cannabidiol. April 19, 2018.

[13] Greenwich Biosciences Research Ltd. Proposed Prescribing Information for Epidiolex. October 26, 2017.

[14] Raspall-Chaure M, et al. The epidemiology of convulsive status epilepticus in children: a critical review. Epilepsia 2007; 48:1652.

[15] Greenwich Biosciences Research Ltd. Eight Factor Analysis, Schedules of Controlled Substances: Recommended Placement of Cannabidiol in a Drug Product (Cannabidiol Oral Solution) into Schedule V. October 26, 2017.

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05/10/2018

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