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Review

Cannabidiol: FDA approved new drug for the Lennox-Gastaut syndrome and Dravet Syndrome: Pharmacotherapeutics review

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ABSTRACT

Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures (febrile seizures). Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5. The U.S. Food and Drug Administration in June 2018 approved Epidiolex (cannabidiol) [CBD] oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome, and Dravet syndrome, in patients two years of age and older. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.

INTRODUCTION

Dravet syndrome (previously known as 'severe myoclonic epilepsy of infancy') was first described by Dr. Charlotte Dravet in 1978. Dravet syndrome" (DS) previously named severe myoclonic epilepsy of infancy (SMEI), or epilepsy with polymorphic seizures, is a rare disorder characterized by an early, severe, generalized, epileptic encephalopathy. DS is characterized by febrile and afebrile seizures beginning in the 1st year of life followed by different types of seizures (either focal or generalized), which are typically resistant to antiepileptic drugs. A developmental delay from the 2nd to 3rd year of life becomes evident, together with motor disturbances and personality disorders.[1,2]

Lennox-Gastaut syndrome begins in childhood. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability.[1,3]

Cannabidiol (Epidiolex)

[Oral Solution] The FDA granted approval of Epidiolex to GW Research Ltd.

Indication and Uses:

Cannabidiol is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.[3]

Dosage information:

Cannabidiol is to be administered orally. The starting dosage is 2.5 mg/kg 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). Patients who are tolerating Cannabidiol at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day.[3]

Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.[3]

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Dosage forms and strengths:

Cannabidiol oral solution: 100 mg/mL for oral administration. Each bottle contains 100 mL of a clear, colorless to yellow solution.[3]

Warnings and Precautions

a. Hepatocellular injury:

Cannabidiol causes dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). In controlled studies for LGS and DS, the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% in Cannabidiol-treated patients compared with 1% in patients on placebo. Less than 1% of Cannabidiol-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking Cannabidiol. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. Resolution of transaminase elevations occurred with discontinuation of Cannabidiol or reduction of Cannabidiol and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with Cannabidiol, without dose reduction.[3]

Monitoring:

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, accompanied by elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of Cannabidiol treatment.[3]

Prior to starting treatment with Cannabidiol, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with Cannabidiol, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in Cannabidiol dosage and addition of or changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.[3]

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with Cannabidiol, as appropriate. Discontinue Cannabidiol in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Consider dosage adjustment of any co-administered medication that is known to affect the liver (e.g., valproate and clobazam).[3]

b. Somnolence and Sedation:

Cannabidiol can cause somnolence and sedation. In controlled studies for LGS and DS, the incidence of somnolence and sedation (including lethargy) was 32% in Cannabidiol-treated patients, compared with 11% in patients on placebo and was dose-related (34% of patients taking Cannabidiol 20 mg/kg/day, compared with 27% in patients taking Cannabidiol 10 mg/kg/day). The rate was higher in patients on concomitant clobazam (46% in Cannabidiol-treated patients taking clobazam compared with 16% in Cannabidiol-treated patients not on clobazam). In general, these effects were more common early in

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treatment and may diminish with continued treatment. Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of Cannabidiol. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on Cannabidiol to gauge whether it adversely affects their ability to drive or operate machinery.[3]

c. Suicidal Behavior and Ideation:

Antiepileptic drugs (AEDs), including Cannabidiol, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.[3]

d. Hypersensitivity Reactions:

Cannabidiol can cause hypersensitivity reactions. One subject in the Cannabidiol clinical trials had pruritus, erythema, and angioedema requiring treatment with antihistamines. Patients with known or suspected hypersensitivity to any ingredients of Cannabidiol were excluded from the clinical trials. If a patient develops hypersensitivity reactions after treatment with Cannabidiol, the drug should be discontinued. Cannabidiol is contraindicated in patients with a prior hypersensitivity reaction to Cannabidiol or any of the ingredients in the product, which includes sesame seed oil.[3]

e. Withdrawal of Antiepileptic Drugs (AEDs)

As with most antiepileptic drugs, Cannabidiol should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus but if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.[3]

Drug interactions

a. Effect of Other Drugs on Cannabidiol

Moderate or Strong Inhibitors of CYP3A4 or CYP2C19

Cannabidiol is metabolized by CYP3A4 and CYP2C19. Therefore, coadministration with a moderate or strong inhibitor of CYP3A4 or CYP2C19 will increase Cannabidiol plasma concentrations, which may result in a greater risk of adverse reactions. Consider a reduction in Cannabidiol dosage when coadministered with a moderate or strong inhibitor of CYP3A4 or CYP2C19.[3]

b. Strong CYP3A4 or CYP2C19 Inducers: Coadministration with a strong CYP3A4 or CYP2C19 inducer will decrease Cannabidiol plasma concentrations, which may lower the efficacy of Cannabidiol. Consider an increase in Cannabidiol dosage (based on clinical response and tolerability) when coadministered with a strong CYP3A4 or CYP2C19 inducer.[3]

c. Effect on Clobazam:

Coadministration of Cannabidiol produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19). This may increase the risk of clobazam-related adverse reactions. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when co-administered with Cannabidiol.[3]

d. Concomitant Use of Cannabidiol and Valproate:

Concomitant use of Cannabidiol and valproate increases the incidence of liver enzyme elevations. Discontinuation or reduction of Cannabidiol and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and Cannabidiol.[3]

Use in specific populations

a. Pregnancy:

There are no adequate data on the developmental risks associated with the use of Cannabidiol in pregnant women. Administration of Cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and

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adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown.[3]

b. Lactation:

There are no data on the presence of Cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cannabidiol and any potential adverse effects on the breastfed infant from Cannabidiol or from the underlying maternal condition.[3]

c. Pediatric Use:

Safety and effectiveness of Cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome have been established in patients 2 years of age and older.

Safety and effectiveness of Cannabidiol in pediatric patients below 2 years of age have not been established.[3]

d. Geriatric Use:

Clinical trials of Cannabidiol in the treatment of LGS and DS did not include any patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.[3]

e. Hepatic Impairment

Because of an increase in exposure to Cannabidiol, dosage adjustments are necessary in patients with moderate or severe hepatic impairment. Cannabidiol does not require dosage adjustments in patients with mild hepatic impairment.[3]

Drug abuse and dependence

a. Controlled Substance:

Cannabidiol is controlled in Schedule V of the Controlled Substances Act.

b. Abuse:

In other Phase 1 clinical studies conducted with Cannabidiol, there were no reports of abuse-related adverse events.

c. Dependence:

In a human physical dependence study, administration of Cannabidiol 1500 mg/day (750 mg twice daily) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning three days after drug discontinuation. This suggests that Cannabidiol likely does not produce physical dependence.[3]

Clinical Pharmacology

a. Mechanism of Action:

The precise mechanisms by which Cannabidiol exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.[3]

b. Pharmacodynamics:

There are no relevant data on the pharmacodynamic effects of Cannabidiol.

c. Pharmacokinetics:

Cannabidiol demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 20 mg/kg/day in patients.

Absorption:

Cannabidiol has a time to maximum plasma concentration (Tmax) of 2.5 to 5 hours at steady state (Css).

Effect of Food:

Coadministration of Cannabidiol with a high-fat/high-calorie meal increased Cmax by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers.[3]

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Distribution:

The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the Cannabidiol and its metabolites was >94% in vitro.

Elimination:

The half-life of Cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. The plasma clearance of Cannabidiol following a single Cannabidiol 1500 mg dose (1.1 times the maximum recommended daily dosage) is 1111 L/h.

Metabolism:

Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

Excretion:

Cannabidiol is excreted in feces, with minor renal clearance.[3]

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