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Editorial

FDA-approves the first therapy in 2018 for the seizures associated with Dravet syndrome

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ABSTRACT

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. This is the first FDA-approved drug that contains a purified drug substance derived from Cannabis sativa. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome. Previously there had been no FDA-approved therapy for use in Dravet syndrome. FDA Officials also approved stiripentol (Diacomit) for the treatment of seizures associated with Dravet syndrome.

INTRODUCTION

Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.[1,2] Dravet syndrome (previously known as 'severe myoclonic epilepsy of infancy') was first described by Dr. Charlotte Dravet in 1978. Dravet syndrome is one of the most severe epilepsy syndromes of early childhood, and it comes with very high morbidity and mortality. The typical presentation is characterized by hemiclonic or generalized clonic seizures triggered by fever during the first year of life, followed by myoclonic, absence, focal and generalized tonic-clonic seizures. Non-convulsive status epilepticus and epileptic encephalopathy are common. Development is normal in the first year of life, but most individuals suffer from intellectual impairment. Dravet syndrome is associated with mutations in the sodium channel alpha1 subunit gene (SCN1A) in 70-80% of individuals.[3,4]

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. 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. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.[1]

Epidiolex (Cannabidiol):

[Oral Solution]

The FDA granted approval of Epidiolex to GW Research Ltd.

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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). Based on individual clinical response and tolerability, CBD can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day). CBD is a chemical component of the Cannabis sativa plant. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC). It is THC (and not CBD) that is the primary psychoactive component of Cannabis sativa.[1]

"This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in Cannabis sativa can lead to important medical therapies. And, the FDA is committed to this kind of careful scientific research and drug development," said FDA Commissioner Scott Gottlieb, M.D. Controlled clinical trials testing the safety and efficacy of a drug, along with careful review through the FDA's drug approval process, is the most appropriate way to bring Cannabis sativa-derived treatments to patients. Because of the adequate and well-controlled clinical studies that supported this approval, prescribers can have confidence in the drug's uniform strength and consistent delivery that support appropriate dosing needed for treating patients with these complex and serious epilepsy syndromes. FDA will continue to support rigorous scientific research on the potential medical uses of Cannabis sativa-derived products and work with product developers who are interested in bringing patients safe and effective, high-quality products. But, at the same time, the FDA is prepared to take action when the FDA see the illegal marketing of CBD-containing products with serious, unproven medical claims. Marketing unapproved products, with uncertain dosages and formulations, can keep patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases.[1]

CBD's effectiveness was studied in three randomized, double-blind, placebo-controlled clinical trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. CBD, taken along with other medications, was shown to be effective in reducing the frequency of seizures when compared with placebo.[1]

The most common side effects that occurred in CBD-treated patients in the clinical trials were: sleepiness, sedation and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise, and weakness; insomnia, sleep disorder and poor quality sleep; and infections.[1]

CBD must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks. As is true for all drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression and panic attacks. CBD also caused liver injury, generally mild, but raising the possibility of rare, but more severe injury. More severe liver injury can cause nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice and/or dark urine.[1]

Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant. In support of this application, the company conducted nonclinical and clinical studies to assess the abuse potential of CBD.[1]

The FDA prepares and transmits, through the U.S. Department of Health and Human Services, a medical and scientific analysis of substances subject to scheduling, like CBD, and provides recommendations to the Drug Enforcement Administration (DEA) regarding controls under the CSA. DEA is required to make a scheduling determination.[1]

In this double-blind, placebo-controlled trial, randomly assigned 120 children and young adults with the Dravet syndrome and drug-resistant seizures to receive either CBD oral solution at a dose of 20 mg per kilogram of body weight per day or

placebo, in addition to standard antiepileptic treatment. The primary end point was the change in convulsive-seizure frequency over a 14-week treatment period, as compared with a 4-week baseline period. Among patients with the Dravet syndrome, CBD resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. (Funded by GW Pharmaceuticals; ClinicalTrials.gov number, NCT02091375.)[5]

Diacomit (Stiripentol):

[Capsule for oral use, powder for oral suspension]

In 2018 the FDA granted approval of Diacomit to Biocodex, the company marketing the medication.

The FDA has approved stiripentol (Diacomit), as capsules and powder, for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.[1]

The approval was backed by the effectiveness established in two, 12-week multicenter placebo-controlled, double-blind studies in patients with Dravet syndrome (Study 1 and Study 2), and open-label long-term studies. Participants enrolled in the study were required to be 2 to 18 years of age, to have Dravet syndrome that was inadequately controlled on clobazam and valproate with at least 4 generalized clonic or tonic-clonic seizures per month, despite optimized therapy. Approximately 53% of study participants were female and the mean age was 9.2 years. In both studies, the demographic and baseline clinical characteristics were similar between treatment groups.[1]

In Study 1 and Study 2, participants were randomly allocated to receive either a fixed dose of 50 mg/kg/day in divided doses with no dose titration of stiripentol or placebo, added to participants' treatment with clobazam and valproate. Stiripentol was administered to 21 participants in Study 1 and 12 participants in Study 2, while 20 participants were randomized to placebo in Study 1 and 11 in Study 2, for a treatment duration of 8 weeks.[1]

The primary endpoint for both studies was the responder rate, which researchers defined as participants who experienced greater than a 50% decrease in the frequency (per 30 days) of generalized clonic or tonic-clonic seizures throughout the double-blind treatment period compared to the 4-week baseline period. Researchers also evaluated the mean change from baseline in frequency of generalized clonic or tonic-clonic seizures.[1]

In both studies, the primary efficacy endpoint was significantly greater for stiripentol than placebo. The results also demonstrated that stiripentol was superior to placebo in the reduction in mean frequency of generalized clonic or tonic-clonic seizures. There were no reports of generalized clonic or tonic-clonic seizure for the duration of the study in 43% and 25% of participants in Study 1 and Study 2, respectively.[1]

Adverse reactions that occurred in at least 10% of stiripentol-treated patients include somnolence (67%), decreased appetite (45%), agitation (27%), ataxia (27%), weight loss (27%), hypotonia (24%), nausea (15%), tremor (15%), dysarthria (12%) and insomnia (12%).[1]

Reported adverse reactions that occurred in 5% or more of stiripentol-treated patients and at a rate greater than in patients on placebo included nausea (15%), vomiting (9%), salivary hypersecretion (6%), fatigue (9%), pyrexia (6%), bronchitis (6%), nasopharyngitis (6%), weight decreased (27%), weight increased (6%), decreased appetite (46%), somnolence (67%), ataxia (27%), hypotonia (18%), tremor (15%), dysarthria (12%), agitation (27%), insomnia (12%) and aggression (9%).[1]

Two patients were reported to discontinue stiripentol treatment because of adverse reactions: 1 patient had an adverse reaction of status epilepticus; the second patient had drowsiness, balance impairment, and sialorrhea.[1]

The recommended oral dosage of stiripentol is 50 mg/kg/day, administered in 2 or 3 divided doses. If

the exact dosage is not achievable in the available strengths, the prescribing information advises rounding to the nearest possible dosage, which is usually within 50 mg to 150 mg of the recommended 50 mg/kg/day. The maximum recommended total dosage is 3000 mg/day.[1]

If stiripentol is discontinued, the drug should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. The safety and efficacy of stiripentol is unknown in children under 2 years of age, and there is also limited information on safety in patients 6 months and older in non-pivotal trials.[1]

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