FDA/CDC

# FDA panel recommends CBD for pediatric seizure disorders

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REPORTING FROM AN FDA ADVISORY COMMITTEE MEETING

Advisors to the Food and Drug Administration have found a generally favorable benefit-risk profile for cannabidiol oil solution in the treatment of two forms of severe pediatric seizure disorders. The drug is under expedited review by the agency.

In a unanimous vote, the 13 members of the FDA's Peripheral and Central Nervous System Drugs Advisory Committee found that the benefit-risk profile of cannabidiol is favorable for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older.

If the FDA supports this recommendation, cannabidiol oral solution would be the first cannabis-based medication approved in the United States.

"At this point, this is a spectacular advance," said committee member John Mendelson, MD, chief medical officer of Ria Health, San Francisco.

Fellow committee member Mark Green, MD, concurred. "It is clearly an honor to be making a decision based on science and public interest, rather than political discussion," said Dr. Green, professor of neurology, anesthesiology, and rehabilitation medicine at Icahn School of Medicine, Mt Sinai, New York.

Patients with LGS taking cannabidiol oral solution at 20 mg/kg/day in two clinical trials saw a 42%-44% reduction in drop seizure frequency over a 14-week treatment period ($P$ = .0047 and $P$ = .0135, compared to placebo). A 50% reduction of drop seizure frequency was seen in 40% and 44% of LGS patients in the two clinical trials.

For patients with DS, 20 mg/kg/day of cannabidiol oral solution resulted in a 39% decrease in convulsive seizure frequency during a 14-week treatment period ($P$ less than .05). There was a numeric, but not statistically significant, increase in the number of DS patients who saw a 50% reduction in convulsive seizure frequency on this dose.

Sustained efficacy for both seizure disorders has been seen during an extended open-label follow-on study.

The potential for abuse of the non-psychoactive substance derived from cannabis plants was judged very low. Though animal studies didn't yield a significant signal for abuse

potential with cannabidiol oral solution, the fact that cannabis is currently a schedule I drug prompted the FDA to recommend a human abuse potential study.
From the totality of the studies, "We see little evidence that cannabidiol has meaningful abuse potential, even at supratherapeutic doses in adults," said Katherine Bonson, PhD, a pharmacologist with the FDA's Controlled Substance Staff, in the Office of the Center Director of the Center for Drug Evaluation and Research (CDER).

The committee also agreed with the FDA staff that the mild to moderate elevations in liver enzymes seen with cannabidiol oral solution administration can be managed with package labeling and patient monitoring.

Both the FDA and GW Pharmaceuticals, which seeks to market cannabidiol oral solution as Epidiolex, acknowledged that the cannabidiol oral solution was associated with a significant elevation in liver transaminases in some patients. In pooled data, 16.3% of patients taking the drug at the higher dose of 20 mg/kg/day experienced transaminase elevation greater than three times the upper limit of normal, compared with 0.9% of those taking placebo.

Concomitant use of valproic acid was associated with greater likelihood of transaminase elevation. In patients taking both valproic acid and cannabidiol oral solution at the higher dose, 13% experienced transaminase elevations over five times the upper limit of normal.

However, many patients had mild transaminase elevations at baseline, and most cases of transaminase elevation did not require discontinuation of cannabidiol oral solution. Both the sponsor and the FDA agreed that no cases of severe liver injury meeting Hy's law criteria were seen during the clinical trials; the two cases of "hepatic failure" reported were not associated with elevated bilirubin or international normalized ratio (INR) levels.

The FDA staff clinical reviewer who presented the agency's overview of liver safety did note one still-unknown factor.

"There are not enough patients exposed to this drug to know whether some might have a smoldering inflammatory response that might potentially – and I can only say potentially – cause a problem down the line," said Lara Dimick-Santos, MD, of the Division of Gastroenterology and Inborn Errors Products of the Office of Drug Evaluation III, Office of New Drugs.

Advisory committee member Dr. Mendelson asked for long-term monitoring, noting that "we need to watch for long-term safety data because this is a novel drug."

The FDA's re-analysis of data from 3 randomized, double-blind, placebo-controlled trials agreed with the efficacy findings reported by GW Pharmaceuticals. Cannabidiol oral solution met its primary endpoint of a reduction in frequency of seizures in LGS and DS patients in all 3 pivotal clinical trials, showing a significant improvement in seizure control when added to standard of care antiepileptic drug therapy for patients with drug-resistant LGS and DS.

The safety evaluation was based on a total of 1,756 patients who were exposed to cannabidiol oral solution, "adequate exposure to allow for assessment of safety," said Natalie Getzoff, MD, a clinical review in the CDER's Division of Neurology Products. Though 20 deaths were seen in the study population, "overall, the causes of death were varied and not unexpected for the patient population, and not clearly linked to the drug," she said. "At this point in our review, we have not identified any obstacles to approval."

To be included in the clinical trials, LGS patients had to be 2-55 years old, using at least one antiepileptic drug and still having at least 8 drop seizures every 4 weeks and at least two drop seizures weekly. DS patients were aged 2-18 years old, also using at least one antiepileptic drug at baseline and having at least 4 convulsive seizures in a 4 week period.

A total of 235 patients with LGS and 88 patients with DS were enrolled in the clinical trials, and an additional 157 patients with LGS and 209 patients with DS were enrolled in the open-label extension study.

An expanded access program for individuals with refractory epilepsy is ongoing, and 684 patients have been enrolled to date, including 97 LGS patients and 64 DS patients.

The proposed indications for cannabidiol oral solution are for the adjunctive treatment of seizures associated with LGS and DS in patients 2 years of age and older. Initial dosing recommendations are to titrate to a dose of 10 mg/kg/day, with dose adjustments permissible up to 20 mg/kg/day depending on clinical response and tolerability. Cannabidiol received fast track designation in 2014, and rare pediatric designation for LGS and DS in 2017.

The FDA is not obligated to support the recommendations of its advisory committees, though it often does. The agency is slated to take action on cannabidiol oral solution by June.