CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s000

APPROVAL LETTER

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210365Orig1s000

Trade Name:	Epidiolex (cannabidiol) 100 mg/mL oral solution
Generic or Proper Name:	Cannabidiol
Sponsor:	GW Research, Ltd.
Approval Date:	June 25, 2018
Indication:	For the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210365

NDA APPROVAL

GW Research, Ltd.
Attention: Catherine Maher, Ph.D., RAC
Head of U.S. Regulatory Affairs
68 T.W. Alexander Drive, P.O. Box 13628
Research Triangle Park, NC 27709

Dear Dr. Maher:

Please refer to your New Drug Application (NDA), dated and received October 27, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Epidiolex (cannabidiol) 100 mg/mL oral solution.

This new drug application provides for the use of Epidiolex (cannabidiol) 100 mg/mL oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients two years of age and older.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTROLLED SUBSTANCE SCHEDULING

The drug substance, cannabidiol, is currently controlled in Schedule I under the Controlled Substances Act (CSA). A scheduling recommendation has been transmitted to the Drug Enforcement Administration (DEA) but your drug product, Epidiolex, remains a Schedule I controlled substance and may not be marketed until the DEA has made a final scheduling decision in accordance with the CSA (21 U.S.C. 811). We further note that, when a final scheduling decision has been published in the Federal Register, you will need to make appropriate revisions to the package insert, Medication Guide, and the carton and container labels through supplementation of your NDA. For changes to the prescribing information, Medication Guide, and carton and immediate-container labels of Epidiolex, you may submit a Changes Being Effected supplement described in 21 CFR 314.70(c)(6). Permission to use a Changes Being Effected supplement for this purpose reflects a waiver by the Agency, pursuant to 21 CFR 314.90, of the requirement to submit a Prior Approval Supplement for changes to reflect the scheduling to the Highlights section of the prescribing information for Epidiolex described in 21 CFR 314.70(b)(2)(v)(C) and changes to the Medication Guide described in 21 CFR 314.70(b)(2)(v)(B).

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 20, 2018, except with the revisions listed below, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210365**." Approval of this submission by FDA is not required before the labeling is used.

- The product carton and container labels should not have the same NDC numbers. The carton label should state NDC 70127-100-10. The bottle label should state NDC 70127-100-01. The package insert should include both NDC numbers.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 210365. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher:

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098, which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of liver injury, to assess a signal of a serious risk of increased serum creatinine, or to identify the following unexpected serious risks: adverse maternal, fetal, or infant outcomes resulting from the use of Epidiolex; adverse effects of the 7-COOH metabolite on embryofetal development or pre- and postnatal growth and development; or the carcinogenic potential of cannabidiol or its 7-COOH metabolite.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3429-1 An embryofetal development study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-2 A pre- and postnatal development study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-3 A juvenile animal toxicology study of 7-COOH-cannabidiol in rat.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	02/2019
Final protocol submission:	04/2019
Study completion:	12/2019
Final report submission:	04/2020

3429-4 A 2-year carcinogenicity study of cannabidiol in mouse.

The timetable you submitted on June 18, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	09/2017
Final protocol submission:	07/2018
Study completion:	04/2020
Final report submission:	08/2020

3429-5 A 2-year carcinogenicity study of cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat.

The timetable you submitted on June 19, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	06/2019
Final protocol submission:	08/2019
Study completion:	08/2022
Final report submission:	02/2023

3429-6 Assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.

The timetable you submitted on June 8, 2018, states that you will conduct this study according to the following schedule:

Draft protocol submission:	09/2018
Final protocol submission:	03/2019
Study completion:	09/2019
Final report submission:	03/2020

3429-7 Assess the potential for chronic liver injury with Epidiolex, with evaluation including physical exam, serum/blood biomarkers, and other noninvasive measures of liver fibrosis, such as MRI or ultrasound-based elastography. Patients should be evaluated yearly for five years.

The timetable you submitted on June 8, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019

Study/Trial Completion:	05/2027
Final Report Submission:	11/2027

3429-8 Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case-control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex (cannabidiol) during pregnancy compared to an unexposed control population.

The timetable you submitted on June 13, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2019
Final Protocol Submission:	01/2020
Study/Trial Completion:	03/2027
Final Report Submission:	03/2028

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug-drug interactions or QT interval prolongation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3429-9 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of caffeine in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	08/2018
Final Protocol Submission:	01/2019
Trial Completion:	06/2019
Final Report Submission:	12/2019

3429-10 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2B6 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-11 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2C9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	04/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-12 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP2C19 inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	09/2018
Final Report Submission:	02/2019

3429-13 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP3A inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	09/2018
Final Report Submission:	02/2019

3429-14 Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers.

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Trial Completion:	08/2018
Final Report Submission:	04/2019

3429-15 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGT1A9 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-16 A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGTB7 substrate in healthy volunteers. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	05/2019
Trial Completion:	09/2019
Final Report Submission:	03/2020

3429-17 A thorough QT trial at the maximum tolerable dose of Epidiolex that is feasible (e.g., dosing in the fed state), with appropriate controls (i.e., placebo and positive control).

The timetable you submitted on June 8, 2018, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission	08/2018

Final Protocol Submission:	01/2019
Trial Completion:	07/2019
Final Report Submission:	01/2020

Submit clinical protocol(s) to your IND with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for liver toxicity after exposure to Epidiolex. Submit 15-day expedited reports to the Division of Neurology Products and to the NDA with sufficient data to assess causality including duration of Epidiolex administration, symptoms, whether the patient was hospitalized, or had organ dysfunction, failure, transplant, or death. Include comprehensive summaries and analyses of these events, including incidence, quarterly as part of your required postmarketing safety reports (e.g., periodic safety update reports [PSURs]). In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the

causality, along with duration of Epidiolex therapy, concomitant therapies, treatment given for the event, range of severity, and outcome of each event.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER on behalf of ROBERT TEMPLE
06/25/2018