NDA 211617

NDA APPROVAL

Esperion Therapeutics, Inc.
Attention: Ashley Hall
Chief Development Officer
3891 Ranchero Drive, Suite 150
Ann Arbor, MI 48108

Dear Ms. Hall:

Please refer to your new drug application (NDA) dated and received February 26, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nexlizet (bempedoic acid/ezetimibe) tablets, 180 mg/10 mg.

This new drug application provides for the use of Nexlizet (bempedoic acid/ezetimibe) tablets as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.

APPROVAL & LABELING

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

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211617**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Nexlizet was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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.

We are waiving the pediatric studies requirement for ages less than ten years because necessary studies are impossible or highly impracticable. This is because the patient population appropriate for this medication is exceedingly small.

We are deferring submission of your pediatric studies for ages ten to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3798-1 Conduct a pharmacokinetic/pharmacodynamic study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 2 study will be a randomized, open-label, 6-week, dose-finding study of bempedoic acid in 36 patients aged 10 years to less than

18 years with HeFH on stable background lipid-modifying therapy with LDL-C ≥130 mg/dL.

Draft Protocol Submission:	March 2020
Final Protocol Submission:	August 2020
Study Completion:	March 2022
Final Report Submission:	August 2022

3798-2 Conduct an efficacy and safety study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 6-month, multicenter efficacy and safety study in 200 patients (randomized 1:1 to bempedoic acid and placebo), followed by a 6-month open-label extension in at least 100 patients assigned to bempedoic acid in pediatric patients aged 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C ≥130 mg/dL.

Draft Protocol Submission:	August 2022
Final Protocol Submission:	March 2023
Study Completion:	February 2026
Final Report Submission:	August 2026

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 130707, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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 identify an unexpected serious risk of pregnancy and maternal complications or adverse effects on the developing fetus, neonate, or infant, or of the presence of Nexlizet in human milk and the effects on the breastfed infant.

Furthermore, the active postmarket risk identification and analysis system as available 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:

3798-3 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Nexlizet (bempedoic acid and ezetimibe) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

The timetable you submitted on February 6, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	September 2020
Final Protocol Submission:	May 2021
Interim Report Submissions:	April 2022
	April 2023
	April 2024
	April 2025
	April 2026
	April 2027
	April 2028
	April 2029
	April 2030
	April 2031
Study Completion:	May 2032
Final Report Submission:	January 2033

3798-4 Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Nexlizet (bempedoic acid and ezetimibe)

using a validated assay to assess concentrations of bempedoic acid and ezetimibe in breast milk and the effects on the breastfed infant.

The timetable you submitted on February 6, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	September 2020
Final Protocol Submission:	April 2021
Study Completion:	April 2024
Final Report Submission:	December 2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of tendinopathy, tendon rupture, atrial fibrillation, and renal impairment.

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

3798-5 Complete the ongoing randomized, double-blind, placebo-controlled, parallel group, multi-center trial in approximately 14,000 patients (randomized 1:1 to bempedoic acid and placebo) designed to assess the effects of bempedoic acid on the occurrence of major cardiovascular events. The trial will include evaluation of the effects of bempedoic acid on occurrence of tendinopathy, tendon rupture, atrial fibrillation, and renal impairment as adverse events of special interest.

The timetable you submitted on February 11, 2020 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	June 2020
Final Protocol Submission:	September 2020
Trial Completion:	March 2023
Final Report Submission:	February 2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Submit clinical protocol(s) to your IND 130707 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports 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.

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 Package Insert (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 *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

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 FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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 FDA.gov.[9]

[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[8] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

[9] http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at 301-796-1234.

Sincerely,

{See appended electronic signature page}

John Sharretts, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling
  - 7-count sample carton
  - 7-count sample blister
  - 30-count bottle label
  - 90-count bottle label

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN M SHARRETTS
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