

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211617Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: February 25, 2020

To: Kati Johnson
Senior Regulatory Project Manager
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPIs)

Drug Name (established name): NEXLIZET (bempedoic acid and ezetimibe)

Dosage Form and Route: tablets, for use

Application Type/Number: NDA 211617

Applicant: Esperion Therapeutics, Inc.

1 INTRODUCTION

On February 26, 2019 Esperion Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) for bempedoic acid and ezetimibe tablets, for oral use. The tradename NEXLIZET was approved on May 24, 2019 for bempedoic acid. The Applicant proposes the indication for NEXLIZET to be an adjunct to diet (b) (4)

who require additional lowering of low density lipoprotein cholesterol (LDL-C).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on June 11, 2019 for DMPP and OPDP to review the Applicant's proposed PPI for NEXLIZET (bempedoic acid and ezetimibe) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft NEXLIZET (bempedoic acid and ezetimibe) tablets, for oral use PPI received on February 26, 2019 and received by DMPP and OPDP on February 19, 2020.
- Draft NEXLIZET (bempedoic acid and ezetimibe) tablets, for oral use Prescribing Information (PI) received on February 26, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 19, 2020.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

- The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

9 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

SHARON W WILLIAMS
02/25/2020 08:53:11 AM

CHARUNI P SHAH
02/25/2020 08:56:42 AM

LASHAWN M GRIFFITHS
02/25/2020 09:24:15 AM



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: February 20, 2020

Team Leader: Yandong Qiang, MD, PhD, MPH, MHS,
Division of Epidemiology I

Division Director: Simone Pinheiro, ScD, MSc, ALM
Division of Epidemiology I

Subject: ARIA Sufficiency Assessment for Pregnancy and Lactation Safety

Drug Name(s): Bempedoic acid (Nexletol®) and Bempedoic acid/ezetimibe (Nexlizet)

Application Type/Number: NDA 211616 (Bempedoic acid)
NDA 211617 (Bempedoic acid/ezetimibe)

Applicant/sponsor: Esperion Therapeutics Inc.

OSE RCM #: 2019-448, 2019-402



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

| | |
|--|---|
| Memo type | |
| -Initial | X |
| -Interim | |
| -Final | |
| Source of safety concern | |
| -Peri-approval | X |
| -Post-approval | |
| Is ARIA sufficient to help characterize the safety concern? | |
| -Yes | |
| -No | X |
| If "No", please identify the area(s) of concern. | |
| -Surveillance or Study Population | |
| -Exposure | |
| -Outcome(s) of Interest | |
| -Covariate(s) of Interest | |
| -Surveillance Design/Analytic Tools | X |

1. BACKGROUND INFORMATION

1.1. Medical Product

In February 2019, Esperion Therapeutics Inc. submitted the following two New Drug Applications (NDA) to the Food and Drug Administration (FDA) seeking approval of these products as adjunct to diet (b) (4)

who require additional lowering of low density lipoprotein cholesterol (LDL-C):

- Nexletol, NDA 211616, bempedoic acid, administered orally once daily as 180 mg tablets, submitted on February 20, 2019
- Nexlizet, NDA 211617, bempedoic acid and ezetimibe fixed-dose combination [FDC] product, administered orally once daily as a 180 mg/10 mg tablet, submitted on February 26, 2019

Bempedoic acid is an inhibitor of adenosine triphosphate-citrate lyase (ACL), an enzyme in the cholesterol and fatty acid biosynthesis pathways. Ezetimibe is an inhibitor of intestinal cholesterol absorption.

Drugs currently approved in the United States for the treatment of primary hyperlipidemia include statin, bile acid sequestrants, and PCSK9 inhibitors.

1.2. Describe the Safety Concern – Pregnancy and lactation Risk

In the general population of the United States, medication use during pregnancy was reported in almost half of the pregnancies.^a The estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.^b

Bempedoic acid is in the cholesterol biosynthesis pathway. It may cause fetal harm when administered to pregnant women because it decreases the cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol. An embryofetal development study indicated that there were non-adverse fetal skeletal variations in rats at doses ≥ 10 mg/kg/day (below the clinical exposure at human dose of 180 mg, based on area under the concentration-time curve [AUC]) without maternal toxicity. At doses from four to 11 times the maximum clinical exposure at human dose of 180 mg, adverse outcomes such as decreased fetal body weights, numbers of viable fetuses, and increased post-implantation loss and total resorptions were observed in rats. Adverse effects on delivery including increases in stillbirth, reduction in live birth and delay in growth, learning, and memory in the presence of maternal toxicity were also observed in a pre- and post-natal development study using pregnant rats. Among pregnant rabbits exposed to doses up to 12 times the maximum clinical exposure at human dose of 180 mg during organogenesis period, the study did not observe adverse development effects. The Division of Metabolic and Endocrine Products (DMEP) considers that the low safety margins identified from

^a Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol.* 2011;205(1):51.e51-58.

^b U.S. Food and Drug Administration (FDA), Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products -- Content and Format, Guidance for Industry, available at <https://www.fda.gov/media/90160/download>, retrieved on Feb 1, 2020.

fertility, embryo-fetal and pre-and postnatal development studies conducted in rat (Appendix I) are acceptable, “because the adverse effects were only observed at materially toxic doses. Additionally, the adverse effects observed in offspring were consistent with the type and degree of maternal toxicity observed. Hence, these effects are considered unlikely to be clinically relevant.” (Integrated Review in draft form, dated January 28, 2020)

For ezetimibe, animal studies observed an increased incidence of common fetal skeletal findings in rats at doses 10 times the human exposure at 10 mg daily, based on AUC; increased incidence of extra thoracic ribs in rabbits at doses 150 times the human exposure at 10 mg daily, based on AUC; and no maternal toxicity or adverse developmental outcomes at doses up to 17 times the human exposure at 10 mg daily, based on AUC.

The animal study results for bempedoic acid/ezetimibe FDC were consistent with the above at doses four times the human exposure to bempedoic acid at 180 mg daily and 112 times the human exposure to ezetimibe at 10 mg daily, based on AUC.

However, there is currently limited published human pregnancy data (and no outcome data) and findings from the sponsor’s pharmacovigilance database of Nexletol (NDA 211616) and Nexlizet (NDA 211617) to inform the safety or exclude the risk of bempedoic acid and ezetimibe use during pregnancy.

The impact on lactation was not investigated in the animal studies. Although there is no data suggesting the presence of bempedoic acid in human or animal milk, and the effects of the drug on the milk production and breastfed infant, the potentially plausible harm of bempedoic acid to the breastfed infant cannot be ruled out.

According to the postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under Section 506B of the Federal Food, Drug, and Cosmetic Act (FDCA) and the Food and Drug Administration Amendments Act, DMEP of OND indicated in the PMR/506B PMC development templates (in draft form, as of January 23, 2020) that the “Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized” through postmarketing studies.

Section 8, USE IN SPECIFIC POPULATIONS, of the proposed labeling for both products (in draft form, as of January 31, 2020) specifies the use of both products in pregnancy and lactation as the following:

- Discontinue NEXLETOL (or NEXLIZET) when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.
- Because of the potential for serious adverse reactions in a breastfed infant, based on the mechanism of action, advise patients that breastfeeding is not recommended during treatment with NEXLETOL (or NEXLIZET).



1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)

| | |
|--|---|
| Assess a known serious risk | |
| Assess signals of serious risk | |
| Identify unexpected serious risk when available data indicate potential for serious risk | X |

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† **If checked, please complete General ARIA Sufficiency Template.**

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify: Single-arm pregnancy safety study, which prospectively enrolls pregnant women exposed to a medication before the birth outcome is known into a protocol-driven observational cohort study and collects follow-up data through medical records for outcome validation but does not come with the sample size requirements of a traditional pregnancy registry

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Analytical Tools:

(b) (4)

2.5. Please include the proposed PMR language in the approval letter.

The following language (in draft form, as of January 23, 2020) has been proposed by the OND/DMEP for PMRs related to pregnancy outcomes regarding Nexletol (NDA 211616, bempedoic acid) tablets and Nexlizet (NDA 211617, bempedoic acid and ezetimibe) tablets

Conduct a worldwide, descriptive study that collects prospective and retrospective data in women exposed to Nexletol (bempedoic acid) 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 finalized PMR language will be issued upon approval.

CC: CallowayP/ChangP/HamppC/HuaW/SandhuS/PinheiroS/DEPI-I
JohnsonK/PetrucelliM/YanoffL/HigginbothamL/SharrettsJ/RajpalaA/ThanhHaiMT/DMEP
ChenM/WeaverJ/BostonN/LaCivitaC/DRM
ChungA/CaoC/DPV
LiedtkaJ/DinataleM/SahinL/JohnsonT/YaoL/DPMH
Hamilton-StokesD/OSE



Appendix I: Bempedoic Acid Reproductive Toxicity Safety Margins (Table 47 of the Integrated Review in draft form, dated January 28, 2020)

| Study | NOAEL (mg/kg) | Nonclinical Exposure¹ (µg.h/mL) | Safety Margins² (multiples) | Basis for NOAEL |
|---------------|----------------------|---|---|--|
| Fertility rat | 10 mg/kg/day | 58.5* | <1 | Adverse female reproductive indices (increases in early embryonic deaths, lower corpora lutea, implants and litter sizes) at ≥30 mg/kg/day. |
| EFD rat | 30 mg/kg/day | 1418 | 4 | Lower fetus viability, postimplantation loss, increased postimplantation loss, increased resorption and reduced litter size at 60 mg/kg/day. |
| EFD rabbit | 80 mg/kg/day | 3906 | 11 | No adverse effect on embryo-fetal development at the highest dose (80 mg/kg/day) tested. |
| PPND rat | 5 mg/kg/day | 89.7** | <1 | Adverse effects on delivery including, increases in stillborn pup, reductions in numbers of live pups, pup survival, pup growth and slight delays in learning and memory at doses ≥10 mg/kg/day. |

Source:

¹Exposure is the sum of ETC-1002 and ESP12588

² Safety margins were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures (AUC_{0-24hr}) of 340 µg.hr/mL.

*No PK data; based on 6-month study (Day 180)

**No PK data: extrapolated from GD17 exposure rat EFD study assuming linear proportionality

Abbreviations: EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal

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/s/

YANDONG QIANG
02/21/2020 09:07:13 AM

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JUDITH W ZANDER
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MICHAEL D NGUYEN
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GERALD J DALPAN
02/21/2020 12:49:07 PM

2/19/2020



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24**

Date: February 14, 2019

Team Leader: Yandong Qiang, MD, PhD, MPH, MHS,
Division of Epidemiology I

Division Director: Simone Pinheiro, ScD, MSc, ALM
Division of Epidemiology I

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OSE RCM #: 2019-448, 2019-402

Instructions*:



EXECUTIVE SUMMARY (place "X" in appropriate boxes)

| | |
|--|---|
| Memo type | |
| -Initial | X |
| -Interim | |
| -Final | |
| Source of safety concern | |
| -Peri-approval | X |
| -Post-approval | |
| Is ARIA sufficient to help characterize the safety concern? | |
| -Yes | |
| -No | X |
| If "No", please identify the area(s) of concern. | |
| -Surveillance or Study Population | |
| -Exposure | |
| -Outcome(s) of Interest | |
| -Covariate(s) of Interest | |
| -Surveillance Design/Analytic Tools | X |

1. BACKGROUND INFORMATION

1.1. Medical Product

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(b) (4) who require additional lowering of low density lipoprotein cholesterol (LDL-C):

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¹ In appendix I of this memo.

with the type and degree of maternal toxicity observed. Hence, these effects are considered unlikely to be clinically relevant.” (Integrated Review in draft form, dated January 28, 2020)

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Purpose (place an “X” in the appropriate boxes; more than one may be chosen)

| | |
|--|-------------------------------------|
| Assess a known serious risk | <input type="checkbox"/> |
| Assess signals of serious risk | <input type="checkbox"/> |
| Identify unexpected serious risk when available data indicate potential for serious risk | <input checked="" type="checkbox"/> |

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The finalized PMR language will be issued upon approval.

CC: CallowayP/ChangP/HamppC/HuaW/SandhuS/PinheiroS/DEPI-I
JohnsonK/PetrucelliM/YanoffL/HigginbothamL/SharrettsJ/RajpalA/ThanhHaiMT/DMEP
ChenM/WeaverJ/BostonN/LaCivitaC/DRM
ChungA/CaoC/DPV
LiedtkaJ/DinataleM/SahinL/JohnsonT/YaoL/DPMH
Hamilton-StokesD/OSE

References:

1. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. *Am J Obstet Gynecol.* 2011;205(1):51.e51-58.
2. Dinatale M, U.S. Food and Drug Administration (FDA), The pregnancy and lactation labeling rule (PLLR), available at <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf>, retrieved on February 1, 2020.
3. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. *MMWR Morb Mortal Wkly Rep.* 2008;57(1):1-5.
4. U.S. Food and Drug Administration (FDA), Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products -- Content and Format, Guidance for Industry, available at <https://www.fda.gov/media/90160/download>, retrieved on Feb 1, 2020.
5. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation.* 2016;133(11):1067-1072.
6. Curtin SC, Abma JC, Ventura SJ, Henshaw SK. Pregnancy rates for U.S. women continue to drop. *NCHS Data Brief.* 2013(136):1-8.



Appendix I: Cause of Death for Patients With CV-Related Deaths in Open-Label Extension Trial 050, Bempedoic Acid Treatment Group (Integrated Review in draft form, dated January 28, 2020)

| Cause of Death | Death Day in Trial 050 | Cumulative Death Day* | Days Since IMP | Additional Relevant Details |
|--------------------------------|-------------------------------|------------------------------|-----------------------|------------------------------------|
| Myocardial infarction | 205 | 567 | 1 | |
| Myocardial ischemia (s/p CABG) | 205 | 569 | 0 | |
| Sudden death | 59 | 407 | 1 | No autopsy |
| Unknown, +CV adjudicated | 337 | 709 | 0 | |

Source:

*Trial 050 is a rollover trial from Trial 040. Death days are presented based on days of exposure for bempedoic acid in Trial 050 and cumulative days of exposure from Trial 040 + Trial 050.

Abbreviations: CABG, coronary artery bypass graft; CV, cardiovascular; IMP, investigational medicinal product; s/p, status/post

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/s/

YANDONG QIANG
02/14/2020 11:06:32 PM

WEI HUA on behalf of SIMONE P PINHEIRO
02/19/2020 09:50:07 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: February 10, 2020

To: Laura B. Higginbotham, M.D., Medical Officer
Division of Metabolism and Endocrinology Products (DMEP)

Kati Johnson, Project Manager, (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEXLETOL (bempedoic acid) tablets, for oral use

NDA: 211616

In response to DMEP's consult request dated June 11, 2019, OPDP has reviewed the proposed product labeling (PI), and Patient Package Insert (PPI) for NEXLETOL (bempedoic acid) tablets, for oral use. This application is an original NDA indicated 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

PI, PPI: OPDP's comments on the proposed PI are based on the draft materials sent by DMEP on January 31, 2020 and are provided below.

Please note that comments on the PPI will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Program (DMPP).

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
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Clinical Inspection Summary

| | |
|-----------------------------------|---|
| Date | 12/20/2019 |
| From | Cynthia F. Kleppinger, M.D., Senior Medical Officer Anthony Orencia, M.D., Ph.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI) |
| To | Laura Higginbotham, M.D., M.P.H., Clinical Reviewer John Sharretts, M.D., Clinical Team Leader Kati Johnson, Senior Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP) |
| NDA | 211617 |
| Applicant | Esperion Therapeutics, Inc. |
| Drug | Bempedoic acid + ezetimibe |
| NME | Yes |
| Therapeutic Classification | (b) (4) |
| Proposed Indication | (b) (4) |
| Consultation Request Date | 4/17/2019 |
| Summary Goal Date | 12/21/2019 |
| Action Goal Date | 2/21/2020 |
| PDUFA Date | 2/26/2020 |

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of five domestic sites in addition to the sponsor.

In general, based on the inspections of the five clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

The Esperion Therapeutics, Inc. (sponsor) site inspection included a focus on the lack of any drug product found by the sponsor after database lock in pharmacokinetic (PK) blood samples from certain subjects at certain clinical sites who had reported that they took the investigational drug product. The inspections did not reveal a definitive root cause. The clinical investigators and their staff did not appear to be aware of the PK discrepancies and each site had followed the protocol. The assumption that subjects may have been perpetuating some level of subject misconduct is likely and, therefore, data from these sites (1028, 1058, and 1068) are suspect. We agree with the sponsor's decision to do post hoc sensitivity analyses of key safety, efficacy, and PK study results with all data from Sites 1028, 1058, and 1068 removed. In general, the sponsor handled this issue appropriately, and had proper oversight of Study 1002FDC-053. Data from this sponsor inspection appear acceptable to support this submitted application.

II. BACKGROUND

Esperion Therapeutics, Inc. submitted a new drug application (NDA) for a fixed dose combination (FDC) product of bempedoic acid 180 mg + ezetimibe 10 mg tablets as an adjunct to diet (b) (4)

(b) (4) who require additional lowering of low density lipoprotein cholesterol (LDL-C). The FDC product was developed under investigational new drug (IND) 130707. Bempedoic acid is a new chemical entity and a first in class novel inhibitor of adenosine triphosphate citrate lyase (ACL), developed for the treatment of (b) (4). In the US, the development program of bempedoic acid has been carried out under IND 106654 since September 2009. Esperion Therapeutics, Inc. submitted NDA 211616 for bempedoic acid 180 mg tablets on February 20, 2019. It was agreed with the Division to review the bempedoic acid NDA concurrent with the FDC NDA. Bempedoic acid is not approved or marketed anywhere in the world.

Ezetimibe is an active ingredient approved in the US under the proprietary name Zetia® (NDA N021445, October 25, 2002) for the treatment of primary hyperlipidemia.

Inspections were requested for Study **1002FDC-053** entitled, “A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy”.

The study was conducted at 78 sites in the US. The study started October 23, 2017 and completed July 3, 2018.

This was a Phase 3, randomized, double-blind parallel-group study evaluating the efficacy and safety of bempedoic acid 180 mg + ezetimibe 10 mg fixed dose combination (FDC) compared with ezetimibe alone, bempedoic acid alone, and placebo in subjects treated with maximally tolerated statin therapy.

The target population for this study comprised subjects with documented atherosclerotic cardiovascular diseases (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH) and/or multiple cardiovascular risk factors who required additional LDL-C-lowering therapy despite already being on maximally tolerated statin background therapy.

A total of 821 subjects were screened, 382 subjects were randomized, and 363 subjects completed the study (338 subjects on study drug).

Subjects were randomized in a 2:2:2:1 ratio on Day 1/Week 0 to receive either bempedoic acid 180 mg + ezetimibe 10 mg FDC, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo for 12 weeks. Randomized subjects returned for clinic visits at Week 4, Week 8, and Week 12.

The primary endpoint was percent change from baseline to Week 12 in LDL-C.

Plasma pharmacokinetic (PK) samples were collected at Weeks 4, 8, and 12 of treatment with bempedoic acid 180 mg, ezetimibe 10 mg, and bempedoic acid 180 mg + ezetimibe 10 mg FDC. Trough plasma PK samples were collected but were not analyzed in subjects treated with placebo.

Following database lock, it became apparent that an unusual number of subjects who reported routinely ingesting study drug (as they reported to the clinical site and as was recorded in the electronic case report form) had no detectable study drug in their PK blood samples. Subsequent investigation revealed that of the 78 sites included in this study, most of these subjects (34 of 51 subjects) were from three sites located in the Miami, Florida area. This led to completion of a detailed Root Cause Analysis (RCA). Review of these findings revealed that these Miami sites and/or subjects may have been perpetuating some level of subject misconduct and, therefore, data from these sites (1028, 1058, and 1068) were suspect.

At Site 68/ Terrelonge (Miami Springs, Florida), 16 of 24 randomized subjects had no detectable study medication in blood at Week 12.

At Site 58/Bravo (Miami, Florida), 10 of 17 subjects had no detectable study medication in blood at Week 12.

At Site 28/ Rodriguez-Ables (Miami, Florida), 8 of 24 subjects had no detectable study medication in blood at Week 12.

In response, post hoc sensitivity analyses of key safety, efficacy, and PK study results were completed with all data from Sites 1028, 1058, and 1068 removed. (The plan was submitted to FDA on November 27, 2018).

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Wilfredo E. Bravo, M.D.
7200 NW Seventh Street, Suite 206
Miami, FL 33126-2941
Site: 5301058

Dates of inspection: July 9 – 15, 2019

There were 34 subjects screened and 21 subjects enrolled into the study; 21 subjects completed the study. There were 21 subject records reviewed.

The clinical trial took place at Clinical Research of Miami, Inc., a contract research organization (CRO) for phase I-III clinical trials. Subjects were screened, enrolled and treated at this site. Clinical Research of Miami, Inc. was established in 2011 and has no subsidiaries. The site is owned by (b) (6). Dr. Bravo is an interest and has been doing clinical research since 2010. He has been a paid employee of Clinical Research of Miami, Inc. since 2011. Dr. Bravo divides his time between research and a private practice group (b) (6).

The IRB used for the study was (b) (4). The informed consent was in both English and Spanish.

The source documents were legible and contemporaneous. There were records for every subject with evidence of study involvement. The source records were compared to the sponsor data line listings. There were no discrepancies noted.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable (laboratory results matched those of the data line listings; the percent change calculation was not done).

During the inspection it was noted that Dr. Bravo's subjects had 100% investigational product (IP) compliance and 100% of the subjects brought back the IP blister packs at subsequent visits. When the IP was dispensed, the Study Coordinator would annotate on the blister pack the day the subject needed to take the IP. Site staff believed this practice helped the subjects remember to take their IP every day as per protocol. There was no indication from the inspection that staff were aware that subjects were not taking IP.

The inspection revealed adequate adherence by the investigator and site staff to the regulations and the investigational plan. No Form FDA-483, Inspectional Observations, was issued.

2. Bernard Garcia, M.D.
4800 N Federal Highway, Suite 202
Fort Lauderdale, FL 33308-4611
Site: 5301056

Dates of inspection: August 13 – 15, 2019

There were 27 subjects screened and 18 subjects enrolled into the study (one withdrew consent after randomization and did not received treatment; one withdrew due to adverse event); 16 subjects completed the study. There were 18 subject records reviewed.

Dr. Garcia is the Chief Executive Officer (CEO) of Invesclinic, U.S., LLC and an investigator at the site. Invesclinic, LLC was incorporated in the State of Florida in 2008. [REDACTED] (b) (6) and became the investigator for studies conducted there. He is an internist and has had a private practice since 2006.

The IRB used for the study was [REDACTED] (b) (4) The informed consent was in both English and Spanish.

The source documents consisted of all paper records which were well organized, in good condition, legible and complete. There was adequate documentation to ensure that all subjects were alive and available for the duration of their stated participation in the study. The source records were compared to the sponsor data line listings. There were no discrepancies noted.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable (laboratory results matched those of the data line listings; the percent change calculation was not done).

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. David S. Ramstad, M.D.
1035 Champions Way, Suite 600
Suffolk, VA 23435-3763
Site: 5301024

Dates of inspection: August 12 – 13, 2019

There were 42 subjects screened and 12 subjects enrolled into the study; 11 subjects completed the study. One subject stopped investigational drug due to an adverse event and was then lost to follow-up. There were 12 subject records reviewed.

Dr. Ramstad is a licensed physician who has been doing clinical research for 18 years. Since September 2018, IACT Research Health has become the 51% majority owner of the research operation. Dr. Ramstad has the remaining 49% of the research operation. He allocates approximately 20% of his time to research and 80% to medical practice. Subjects were recruited from his private practice.

The IRB used for the study was [REDACTED] (b) (4) The informed consent was in both English and Spanish.

These study records were neat, authentic, legible, and organized. Dr. Ramstad uses a computer to record subjects' progress notes. Afterwards, he prints out these notes to insert with the subject records. There were records for every subject with evidence of study

involvement. The source records were compared to the sponsor data line listings. There was one discrepancy noted. At the onset, Dr. Ramstad stated that 12 subjects completed the study. The enrollment log shows that Subject (b) (6) did not discontinue, inferring completion. That subject is included among the 12 that were recorded as “completed”. During the review of Subject (b) (6) records, there is a note stating that this subject discontinued due to lost to follow-up. Dr. Ramstad agreed with the note dated 6/13/18 stating that the subject was lost to follow-up. It appears that only 11 subjects completed. Dr. Ramstad promised to update the records with the sponsor.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable (laboratory results matched those of the data line listings; the percent change calculation was not done).

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Lilia Rodriguez-Ables, M.D.
7270 NW 12th Street, Suite 400
Miami, FL 33126
Site: 5301028

Dates of inspection: June 12 – 28, 2019

There were 41 subjects screened and 29 subjects enrolled into the study; 29 subjects completed the study. There were 29 subject records reviewed.

Dr. Rodriguez-Ables has been conducting research since 2013 and has been practicing medicine in the United States since 1995. She works as a contractor for Finlay Medical Research, the site of the study, and has no hire/fire authority and no ownership in the company. Dr. Rodriguez-Ables maintains a private practice in Miami, Florida. The subjects were recruited through Finlay Medical Research’s database of subjects, patients at her private practice, as well as patients at her sub-investigator’s private practices.

The IRB used for the study was (b) (4). The informed consent was in both English and Spanish.

The source documents were legible and contemporaneous. There were records for every subject with evidence of study involvement. The source records were compared to the sponsor data line listings. There were no discrepancies noted.

The primary efficacy endpoint was verifiable (laboratory results matched those of the data line listings; the percent change calculation was not done).

Subject (b) (6) had two adverse events of skin rash and itching recorded on the AE log that were not reported in the eCRF. A skin rash with itching began January (b) (6) that was

mild and felt to be unrelated to the study drug. No diagnosis was given. There was no other under-reporting of adverse events observed.

The FDA inspector questioned the site staff person who had the responsibility for drawing blood for labs and pharmacokinetic samples about the process for shipping the pharmacokinetic samples. He stated that he followed the laboratory binder provided with the protocol. All blood samples for this study were shipped the same day as they were drawn, with dry ice, to the appropriate testing lab. He provided a pharmacokinetic sample shipping log, which identified the subject number, dates, and tracking information for each of the pharmacokinetic samples. No observations were uncovered. There was no indication from the inspection that staff were aware that subjects were not taking IP.

The FDA inspector was able to speak with eight subjects via telephone who were enrolled in the study. Another FDA inspector interpreted as all the subjects spoke Spanish. All subjects had been in multiple trials. Of those eight subjects, two (subjects (b) (6) and (b) (6)) stated that they could not recall whether or not they participated in the study, while one subject (b) (6) was adamant that she did not participate. When the subject was asked how she was certain that she did not participate in the study (e.g., she was out of the country or out of town, etc.) she could not articulate a definitive answer.

The subject did not provide any more information to help confirm that she did not participate in the study. The FDA inspector discussed this with the clinical investigator. There was a possibility that the subject did not want authorities to know she was receiving payment for participation. The FDA inspector was unable to conclude that Subject (b) (6) had not participated in the study.

The inspection revealed adequate adherence by the investigator and site staff to the regulations and the investigational plan. No Form FDA-483, Inspectional Observations, was issued.

5. Antonio Terrelonge, M.D.
286 Westward Drive
Miami Springs, FL 33166-5260
Site: 5301068

Dates of inspection: July 23 – 29, 2019

There were 60 subjects screened and 31 subjects enrolled into the study (two subjects withdrew consent and two subjects were lost to follow-up); 27 subjects completed the study. There were 27 subject records reviewed.

The clinical trial took place at Ocean Blue Medical Research Center, Inc. a CRO for phase I-IV clinical trials. Mrs. Yanet R. Ferrera has 100% ownership of the site which was established in Dec 2009. There are no other subsidiaries for Ocean Blue Medical Research, Inc. Subjects were screened, enrolled and treated at this site. Dr. Terrelonge is

hired as a full-time employee and divides his time with three private practice groups, 50% research and 50% private practice. He has been working at Ocean Blue Medical Research, Inc. for more than 12 years. He has been doing clinical research for 14 years.

The IRB used for the study was [REDACTED] (b) (4). The informed consent was in both English and Spanish.

The source documents were legible and contemporaneous. There were records for every subject with evidence of study involvement. The source records were compared to the sponsor data line listings. There were no discrepancies noted.

All the protocol deviations were reported properly and consisted of out of window visits; subject's not returning IP; and incorrect stratification of 6 out of 30 subjects in the study. The Study Coordinator was stratifying subjects as multiple cardiovascular (CV) risk factor even though they met ASCVD. Once the subject was stratified, this could not be changed in the electronic data capture system (EDC). This key deviation was caught during a site audit by the sponsor and a Corrective and Preventive Action (CAPA) was implemented by Dr. Terrelonge. After the CAPA was implemented, no further incorrect subject stratifications were noted.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable (laboratory results matched those of the data line listings; the percent change calculation was not done).

The IP was kept in a double locked temperature-controlled room accessible only to delegated staff and the IP was handled properly by designated staff. The IP was reconciled by the CRO. The Study Coordinator documented properly in the source when the subjects failed to return the IP with the reason why. There was no indication from the inspection that staff were aware that subjects were not taking IP.

The inspection revealed adequate adherence by the investigator and site staff to the regulations and the investigational plan. No Form FDA-483, Inspectional Observations, was issued.

6. Esperion Therapeutics, Inc. / Sponsor
3891 Rancho Drive, Suite 150
Ann Arbor, MI 48108

This sponsor inspection included all inspected trials for NDA 211616 (1002-040, 1002-047, 1002-048) and NDA 211617 (1002-FDC-053). Please refer to the Clinical Inspection Summary for issues related to NDA 211616.

Dates of inspection: July 29 – August 9, 2019

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions

taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight. There were 11 site master files reviewed.

There were no instances of non-compliances/terminations involving any clinical investigator sites.

Esperion Scientific Founder, Roger Newton, PhD, co-discovered and helped lead the development of drugs to inhibit HMG-CoA reductase, Lipitor® (atorvastatin calcium) in the 1990s. Initially, Esperion Therapeutics, Inc. operated as a different business entity. The firm re-started in April 2008 under a new business entity. From 2008 to 2014, the firm was located at 46701 Commerce Center Drive Plymouth, MI 48170 prior to relocating to its current location.

Esperion maintains employees in 20 states across the U.S. with a total of 127 employees as of June 29, 2019. There are 38 employees in the headquarters office.

(b) (4) served as the CRO for studies 1002-040 and 1002-FDC-053. (b) (4) was used for studies 1001-047 and 1002-048. Monitoring of investigational sites was conducted by the CROs. Monitoring was performed in person, by phone, and remotely (via eCRFs) (b) (4) utilized a risk-based monitoring plan for protocol 1002-040. Source data verification was performed on 100 % of subjects involved in protocol study 1002-FDC-053.

There were several delays during the inspection in receiving requested documentation from (b) (4) to the sponsor. (b) (4) was also responsible for maintenance and quality of the eTMF which was missing several documents and resulted in repeated documentation requests.

The FDA inspector investigated the issue with the PK blood samples that were found to have no detectable study drug at various investigational sites involving study 1002FDC-053. The Deviation Report/Root Cause Analysis (RCA) was fully reviewed with sponsor staff who were involved with the report. It was conducted to identify the potential causes of these incidences. The investigation included an Ishikawa/Fish Bone diagram that was created to identify potential causes involving personnel, equipment, procedures, materials methods and processes. The investigation included review of the following processes:

- GMP Batch record information was evaluated, which focused on the supply chain and chain of custody. A retrospective review was done of the carding and labeling batches associated with the investigational drug product (lot 99053-014), which was identified as the batch of bulk products used at Sites 1028, 1058, and 1068 for clinical study 1002FDC-053.
- Identity testing of returned IP was tested for identification of the active ingredient, bempedoic acid and/or ezetimibe. The investigation found that the ID tests confirm

the identify of each sample as being confirmed positive and no issues were identified with the IP.

- An evaluation of the contract packaging operation and the quality management system was performed. A for-cause audit was conduct of (b) (4) where all shipping and return activities occurred. It was noted that (b) (4) (b) (4) distribution unit used validated shippers to ship all investigations products to the clinical sites involved in this incident. There were no issues identified that would explain the reason for the incident.
- There was an evaluation of the clinical site chain-of-custody to the CRO (b) (4) facility. The investigation concluded that upon review of the PK Sample Management Handling Quality Questionnaire (QQ) for study 1002FDC-053, supporting documents, and PK biosample chain of custody was verified as accurate and that no issues were identified to support problems involving the receipt and handling or sample storage.

In addition, evaluations were conducted for various sites involving clinical investigator site control and an evaluation of the PK sample analysis. Upon review of the aforementioned operations, no root cause could be identified that would explain the incident.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to ensure proper monitoring for protocols 1002-047 and 1002-048 under NDA 211616. However, there were no observations related to NDA 211617 Study 1002FDC-053.

Esperion responded to the Form FDA 483 on August 28, 2019. The firm has taken actions to improve its oversight of its CROs and assessed the impact of the observations on the underlying studies. The response was deemed adequate.

The assumption that subjects may have been perpetuating some level of subject misconduct is likely at Sites 1028, 1058, and 1068. The sponsor handled this issue appropriately. Data from this sponsor appear acceptable.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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cc:

Central Doc. Rm./ NDA 211617
DMEP/Acting Division Director/ Lisa Yanoff
DMEP /Acting Deputy Director/William Chong
DMEP/Team Lead/John Sharretts
DMEP/Clinical Reviewer/ Laura Higginbotham
DMEP /Regulatory Project Manager/Kati Johnson
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Acting Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

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KASSA AYALEW
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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: November 26, 2019

TO: Lisa Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Srinivas R. Chennamaneni, Ph.D.
Staff Fellow
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles R. Bonapace, Pharm.D.
Director
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of Study 1002FDC-034 (NDA 211617, Bempedoic Acid and Ezetimibe) conducted at [REDACTED] (b) (4)
[REDACTED]

I observed objectionable conditions and issued Form FDA 483 at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

1.1. Recommendation

Based on my review of the objectionable conditions and the firm's response to Form FDA 483, I conclude the objectionable conditions have no impact on the data from the audited studies (see Section 3). Thus, data from the audited study are reliable to support a regulatory decision.

2. Inspected Studies

Study 1002FDC-034 (NDA 211617)

"A Pilot, Phase 1, Randomized, Open-Label, Single-Dose, Three-Period, Crossover Study to Assess the Relative Oral Bioavailability of Bempedoic Acid 180 mg and Ezetimibe 10 mg Co-administered as Individual Tablets Versus as a Fixed-Dose Combination Formulation [REDACTED] (b) (4) Tablet in Healthy Humans"

Sample Analysis Period: [REDACTED] (b) (4)

3. Scope of Inspection

OSIS scientist [REDACTED] (b) (4) audited the analytical portion of the above study at [REDACTED] (b) (4)

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, study sample analysis, and interviews with the firm's management and staff. In addition, Standard Operating Procedures (SOPs) related to bioanalytical method validation, employee training records, laboratory notebooks, study sample handling, and storage records were reviewed.

4. Inspectional Findings

At the conclusion of the inspection, I observed objectionable conditions and issued a Form FDA 483 to [REDACTED] (b) (4). The Form FDA 483 observation (**Attachment-1**), the firm's response dated [REDACTED] (b) (4) (**Attachment-2**) and my evaluation are presented below.

4.1. FDA 483 Observations

[REDACTED] (b) (4)

Firm's Response:

[REDACTED] (b) (4)

OSIS Evaluation:

[REDACTED] (b) (4)

5. Conclusion

I conclude the data from the audited study **1002FDC-034 (NDA 211617)** are reliable. In addition, data from studies using similar methods, conducted between the previous inspection [REDACTED] (b) (4) and the end of the current surveillance interval, should be considered reliable without an inspection.

Final Classification:

VAI - [REDACTED] (b) (4)

CC: [REDACTED] (b) (4)

Draft: SRC 11/12/2019

Page 4 - Surveillance inspection of [REDACTED] (b) (4)

Edit: [REDACTED] (b) (4)

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/[REDACTED] (b) (4)
[REDACTED] Post-Inspection
Folder/EIR & EIR Review

OSIS File#: [REDACTED] (b) (4) (NDA 211617)

FACTS: [REDACTED] (b) (4)

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/s/

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11/26/2019 01:07:01 PM

CHARLES R BONAPACE
11/26/2019 01:50:35 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 23, 2019

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: NDA 211616 and NDA 211617

Product Name and Strength: Nexletol (bempedoic acid) Tablets, 180 mg
Nexlizet (bempedoic acid and ezetimibe) Tablets, 180 mg/10 mg

Applicant/Sponsor Name: Esperion Therapeutics, Inc (Esperion)

OSE RCM #: 2019-403-1 and 2019-449-1

DMEPA Safety Evaluator: Valerie S. Vaughan, PharmD

DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

On September 10, 2019, Esperion submitted response to the Agency's September 3, 2019 information request (Appendix A). This memorandum provides additional recommendations for the Division's consideration based on Esperion's response and our assessment of the labels and labeling completed in our previous reviews^{ab}.

2 CONCLUSION AND RECOMMENDATIONS FOR THE DIVISION

Esperion indicates that

(b) (4)



^a Wilson, V. Label and Labeling Review for Nexletol (NDA 211616). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 06. RCM No.: 2019-403.

^b Wilson, V. Label and Labeling Review for Nexlizet (NDA 211617). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 06. RCM No.: 2019-449.

Recommendations for the Division

Based on Esperion's response we have the following recommendations for the Division:

1.  (b) (4)
2. To provide additional clarity on the storage and handling of these products, we recommend revising the storage statement to include "store and dispense in original container" on the container labels and within the prescribing information. We ask that the Division convey our container label recommendation below to the Applicant so that it can be implemented prior to the approval of these NDAs.

Recommendation for Esperion Therapeutics, Inc.

1. To provide additional clarity on the storage and handling of Nexletol and Nexlizet tablets, we recommend revising the storage statement on the container labels to include "store and dispense in original container."

APPENDIX A. RESPONSE TO INFORMATION REQUEST

Response to Agency CMC Information Request, received on September 10, 2019, available at:
<\\cdsesub1\evsprod\nda211616\0029\m1\us\111-information-amendment\rtq-cmc-info-request-20190910.pdf>

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/s/

VALERIE S VAUGHAN
09/23/2019 12:55:31 PM

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09/23/2019 01:22:08 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

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|---------------------------------------|--|
| Date of This Review: | September 6, 2019 |
| Requesting Office or Division: | Division of Metabolism and Endocrinology Products (DMEP) |
| Application Type and Number: | NDA 211617 |
| Product Name and Strength: | Nexlizet (bempedoic acid and ezetimibe) Tablets, 180 mg/10 mg |
| Product Type: | Multi-Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Esperion Therapeutics, Inc. (Esperion) |
| FDA Received Date: | February 26, 2019 and June 7, 2019 |
| OSE RCM #: | 2019-449 |
| DMEPA Safety Evaluator: | Valerie S. Wilson, PharmD |
| DMEPA Team Leader: | Sevan Kolejian, PharmD, MBA |

1 REASON FOR REVIEW

As part of the approval process for Nexlizet (bempedoic acid and ezetimibe) tablets, 180 mg/10 mg, the Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed Prescribing Information, Patient Package Insert, and container labels for areas that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B (N/A) |
| Human Factors Study | C (N/A) |
| ISMP Newsletters* | D (N/A) |
| FDA Adverse Event Reporting System (FAERS)* | E (N/A) |
| Other | F (N/A) |
| Labels and Labeling | G |

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted label and labeling, DMEPA’s rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Metabolism and Endocrinology Products

| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
|--|---|---|---|
| Prescribing Information and Container Label | | | |
| 1. | The HOW SUPPLIED/ STORAGE AND HANDLING section of the Prescribing Information (PI) indicates that Nexlizet tablets are to be stored in the original container with the desiccant. It is unclear whether it is appropriate for the pharmacy to dispense tablets outside of the original container. | We are concerned that dispensing tablets for home use outside the original container could lead to deteriorated drug medication errors. | <p>We communicated our concern to the Office of Pharmaceutical Quality (OPQ). We defer to OPQ and DMEP to determine the appropriateness of the storage statement, “Store in the original package.”</p> <p>If it is determined that dispensing tablets for home use outside the original container is not appropriate, we recommend the storage statement be revised to include, “Store and dispense in the original package” within the PI and on the container labels.</p> <p>Based on OPQ and DMEP’s final determination, we may have additional recommendations.</p> |
| Patient Package Insert (PPI) | | | |
| 2. | The Patient Package Insert (PPI) does not include storage instructions. | Omission of storage instructions could lead to deteriorated drug product errors. | Ensure storage instructions are included in the PPI. We defer to the Division of Medical Policy Programs Patient Labeling Team to determine the appropriate storage statement to place in the PPI. |

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| 3. | The PPI states in the <i>How should I take Nexlizet</i> section to take binding bile acids at least 2 hours before or 4 hours after Nexlizet which is stated slightly different in the prescribing information (PI) (i.e. administer Nexlizet 2 hours before or at least 4 hours after bile acid). | Discrepancy between the order of drug administration within the dosage instructions in the PI and PPI could lead to confusion or administration error for patients receiving Nexlizet while on concomitant therapy with bile acid sequestrants. | Ensure the administration instructions are aligned between the PI and PPI. |
|----|--|---|--|

Table 3: Identified Issues and Recommendations for Esperion Therapeutics, Inc (entire table to be conveyed to Applicant)

| Container Labels and Carton Labeling | | | |
|---|---|---|---|
| | IDENTIFIED ISSUE | RATIONALE FOR CONCERN | RECOMMENDATION |
| Container Labels | | | |
| 1. | On the side panel, there is no space between the numerical strength and unit of measurement for the active ingredient in the “Each tablet contains...” statement. | Including space between the numerical strength and unit of measurement improves readability of the product strength. | Ensure adequate space is present between the numerical strength and unit of measure for the active ingredient. For example, list the strength as “180 mg bempedoic acid and 10 mg ezetimibe” instead of “180mg bempedoic acid and 10mg ezetimibe.” |
| 2. | The format of the expiration date is not defined. | We are unable to evaluate whether the proposed format of the expiration date reduces the risk of deteriorated drug medication errors. | Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if |

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| | | | <p>alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY- MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.</p> <p>See <i>Draft Guidance: Product Identifiers Under the Drug Supply Chain Security Act- Questions and Answers, September 2018</i> for further insight into FDA’s current thinking (Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf).</p> |
| Professional Sample Blister Package | | | |
| 1. | The strength listed on the blister card is not expressed as milligrams per single unit. | The current presentation of the strength could lead to wrong dose errors as it is unclear that each tablet contains 180 mg/10 mg of bempedoic acid and ezetimibe, respectively. | <p>Revise the blister label to express the strength as:</p> <p style="text-align: center;"><i>180 mg/10 mg per tablet</i></p> <p>See <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013</i> for further insight into FDA’s current thinking (Available at:</p> |

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|--|--|--|---|
| | | | https://www.fda.gov/media/85879/download |
|--|--|--|---|

4 CONCLUSION

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nexlizet received on February 26, 2019 from Esperion Therapeutics, Inc..

| Table 2. Relevant Product Information for Nexlizet | |
|---|--|
| Initial Approval Date | N/A |
| Active Ingredient | bempedoic acid and ezetimibe |
| Indication | Indicated as an adjunct to diet (b) (4) who require additional lowering of LDL-C. |
| Route of Administration | Oral |
| Dosage Form | Tablets |
| Strength | 180 mg/10 mg |
| Dose and Frequency | One tablet once daily |
| How Supplied | Bottles of 30 tablets (NDC 72426-818-03) Bottles of 90 tablets (NDC 72426-818-09) (b) (4) Professional Sample: Carton containing 1 blister card of 7 tablets (NDC 72426-818-99) |
| Storage | Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original packet protected from extreme heat and humidity. Do not discard desiccant. |
| Container Closure | For patient use: <ul style="list-style-type: none"> • 30-count bottles: 60 cc, HDPE bottles sealed with (b) (4) child-resistant closure with induction seal and silica gel desiccant canister • 90-count bottles: 100 cc, HDPE bottles sealed with (b) (4) child-resistant closure with induction seal and silica gel desiccant canister (b) (4) Professional Sample: <ul style="list-style-type: none"> • (b) (4) aluminum unit dose blisters |

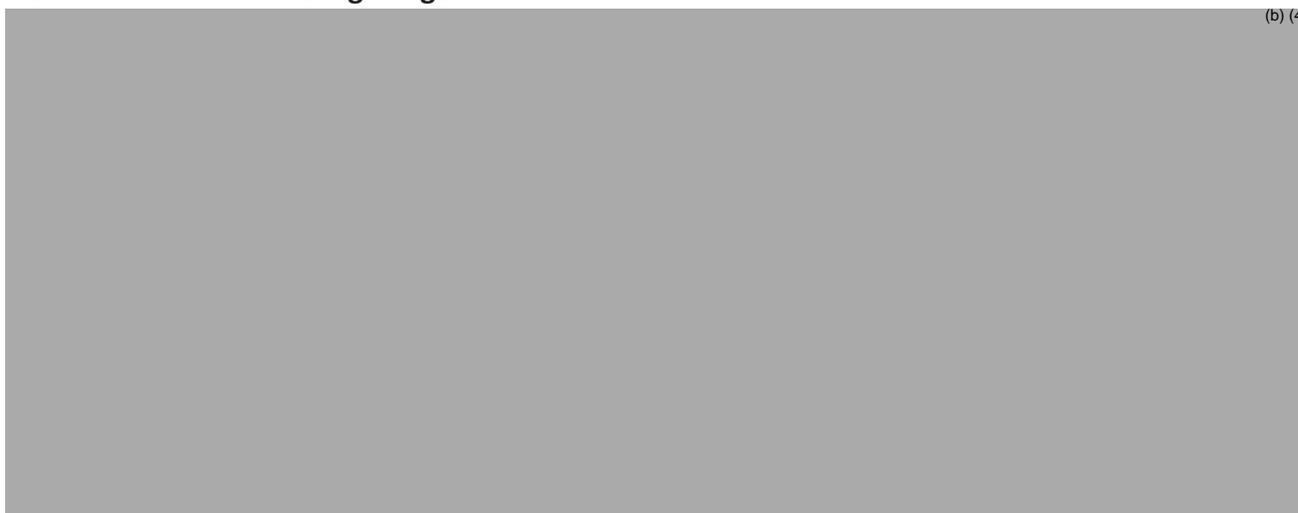
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Nexlizet labels and labeling submitted by Esperion Therapeutics, Inc..

- Container label received on February 26, 2019
- Professional Sample Blister card received on February 26, 2019
- Professional Sample Carton Labeling received on February 26, 2019
- Prescribing Information (Image not shown) received on February 26, 2019 available at: <\\cdsesub1\evsprod\nda211617\0001\m1\us\114-labeling\draft\labeling\11413-uspi-nexlizet.pdf>
- Patient Package Insert (Image not shown) received on June 7, 2019, available at: <\\cdsesub1\evsprod\nda211617\0018\m1\us\114-labeling\draft\labeling\proposed-pi-nexlizet.pdf>

G.2 Label and Labeling Images



3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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09/06/2019 04:35:39 PM

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