

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211616Orig1s000

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 10, 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): NEXLETOL (bempedoic acid)

Dosage Form and Route: tablets, for use

Application Type/Number: NDA 211616

Applicant: Esperion Therapeutics, Inc.

1 INTRODUCTION

On February 19, 2019 Esperion Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) for bempedoic acid tablets, for oral use. The tradename NEXLETOL was approved on May 24, 2019 for bempedoic acid. The Applicant proposes the indication for NEXLETOL to be an adjunct to diet

(b) (4)
[REDACTED] 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 10, 2019 for DMPP and OPDP to review the Applicant's proposed PPI for NEXLETOL (bempedoic acid) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft NEXLETOL (bempedoic acid) tablets, for oral use PPI received on June 7, 2019 and received by DMPP and OPDP on January 31, 2020.
- Draft NEXLETOL (bempedoic acid) tablets, for oral use Prescribing Information (PI) received on February 19, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 31, 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.

12 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
02/10/2020 01:51:23 PM

CHARUNI P SHAH
02/10/2020 01:59:14 PM

LASHAWN M GRIFFITHS
02/10/2020 02:09:03 PM

Clinical Inspection Summary

Date	12/19/2019
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	211616
Applicant	Esperion Therapeutics, Inc.
Drug	Bempedoic acid
NME	Yes
Therapeutic Classification	(b) (4)
Proposed Indication	
Consultation Request Date	4/17/2019
Summary Goal Date	12/21/2019
Action Goal Date	2/21/2020
PDUFA Date	2/21/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) covering three clinical trials consisted of five domestic and three foreign clinical sites representing ten study sites, in addition to the sponsor.

The inspection of two clinical investigators listed below and the sponsor revealed regulatory deficiencies which are unlikely to have a significant impact on overall results. The inspection of the remaining clinical investigators revealed no regulatory violations. Based on the inspections, the study data generated are considered acceptable and may be used in support of this NDA.

II. BACKGROUND

Esperion Therapeutics Inc. submitted an original new drug application for bempedoic acid tablets as an adjunct to diet (b) (4)

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

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). The development program for bempedoic acid was carried out under investigational new drug (IND) 106654.

Inspections were requested for three studies:

1002-040 A Randomized, Double-Blind, Placebo-Controlled, Multicenter Long-Term Safety and Tolerability Study of ETC-1002 in Subjects with Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of bempedoic acid 180 mg once daily (QD) added onto current, stable lipid-modifying therapy (LMT) in subjects with hyperlipidemia who were at high risk for cardiovascular (CV) events.

Subjects were screened at 116 clinical sites in Canada, Germany, Netherlands, Poland, the United Kingdom, and the United States, of which 114 sites randomized subjects. A total of 3395 subjects were screened, 2230 subjects were randomized and 2110 completed the study (1742 on study medication). The study began January 21, 2016 and completed February 21, 2018.

During the double-blind treatment period, subjects were randomized 2:1 to receive either bempedoic acid 180 mg or matching placebo orally QD for 52 weeks. Subjects were also required to be receiving stable LMT(s), including a maximally tolerated statin, for at least 4 weeks prior to screening. Starting with Amendment 5 of the protocol, simvastatin at doses ≥ 40 mg/day was not allowed in this study.

The primary safety endpoint for this study was general safety, which included adverse events (including pre-specified adverse events of special interest as well as adjudicated CV and fatal clinical endpoints), clinical safety laboratories, physical examinations, vital signs, and electrocardiogram (ECGs).

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

1002-047 A Long-Term, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Subjects with Hyperlipidemia at High Cardiovascular Risk not Adequately Controlled by Their Lipid-Modifying Therapy

This was a Phase 3, long-term, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and long-term safety of bempedoic acid 180 mg in subjects with hyperlipidemia who are at high risk for CV events with prior history of atherosclerotic cardiovascular disease (ASCVD) and/or confirmed heterozygous familial hypercholesterolemia (HeFH) and who are receiving stable background LMT. Simvastatin at doses ≥ 40 mg/day was not allowed in this study.

Subjects were screened at 91 clinical sites in Canada, Germany, Poland, Ukraine, the United Kingdom, and the United States, of which 86 sites randomized subjects. A total of 2300 subjects were screened, 779 subjects were randomized, and 740 subjects completed the study (629 subjects on drug). The study began November 18, 2016 and completed September 22, 2018.

The study consisted of an approximate 1-week screening period, a 4-week single-blind placebo run-in period, and a 52-week double-blind, randomized treatment period.

The primary efficacy endpoint for this study was the percent change from baseline to Week 12 in LDL-C.

1002-048 A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Subjects with Elevated LDL-C on Low Dose or Less Than Low Dose Statins

This was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of bempedoic acid as an add-on therapy to ezetimibe in subjects with elevated LDL-C who are unable to tolerate a statin at no more than its lowest dose.

The study was conducted at 90 sites in North America and Europe. There were 616 subjects who entered screening, 269 subjects enrolled, and 257 subjects completed the study (243 subjects on study drug). The study began November 29, 2016 and completed January 11, 2018.

The study consisted of an approximate 1-week screening period, a 4-week single-blind placebo and ezetimibe run-in period, and a 12-week treatment period.

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

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.

Summary of General Central Laboratory Programming Issues at All Sites

It was discovered with the inspection of the initial site that there were issues with the central laboratory (b) (4) for Study 1002-047. This was not reported in the clinical study report (CSR).

In summary, per the protocol, beginning at Week 24 (Visit T5) and for the duration of the study, the central laboratory was to notify the investigator when the subject's blinded LDL-C value was >170 mg/dL (4.4 mmol/L) or $\geq 25\%$ from the subject's baseline value at Week 0 (Visit T1). After confirming that the blinded LDL-C value met the threshold criteria, the investigator adjusted the patient's lipid-lowering treatment regimen per standard-of-care and local practice, with the exception of simvastatin at daily doses greater than 40 mg and the fibrate, gemfibrozil. The initiation of any new or dose changes of any existing lipid-lowering treatment should have been documented on the eCRF as a concomitant medication with the associated start date.

The central lab for the study, (b) (4) had a programming issue that was triggering false high LDL-C levels above protocol threshold. This issue was not identified until the study coordinator at one site contacted the monitor and complained about getting blank lab reports for unscheduled study visits for lab repeats due to the blinded LDL-C showing that the threshold was met. This communication was done via e-mail on 1/23/2018 (The study completed 9/22/2018). On 2/2/2018, a memo was received at the sites from (b) (4) stating that they had programming errors and the sites were told to ignore the flags. The study medical monitors were to ensure that critical alerts were reported to the sites and instructed the investigators to disregard messages on laboratory reports. (b) (4) said that they would notify the sites when the programming error would be fixed and send updated labs. The sites had no memo from (b) (4) that the error was fixed; however, the sites did have updated repeat labs for the majority of the subjects in question.

As the primary efficacy endpoint for this study was the percent change from baseline to Week 12 in LDL-C, this programming error should not have affected the primary endpoint. However, subjects with falsely high LDL-C levels could have been dosed with LDL lowering therapy they did not need. Once this issue was discovered at the first inspected site, the FDA inspectors inspecting the other sites were made aware and were asked to report any similar findings.

In addition, high sensitivity C-Reactive Protein (HsCRP) and Apolipoprotein-B (Apo-B) were added to the Week 24 visit with protocol amendment 3 for Study 1002-047. The central laboratory (b) (4) did not update the laboratory programming to add these tests to the panel for the visit. Once this was discovered, sites were instructed to collect blood samples at unscheduled visits.

Normal glucose levels were also being flagged as being Level 2 High (H2) in error. The false flags did not result in improper treatment of subjects as glucose results were not blinded and it was clear to the investigators that the results were within normal range.

For Study 1002-048, (b) (4) laboratory requisition forms were not updated to reflect Amendment 2 protocol changes. Laboratory requisition forms for Treatment 1 (Week 0) continued to indicate collection of pharmacokinetic (PK) samples. The laboratory continued to ship collection kits for plasma PK to the sites after implementation of Amendment 2 and the testing was erroneously done by sites.

1. Imrozia Arif, M.D.
1 Venture Building
Kelvin Campus
West of Scotland Science Park
Glasgow, Lanarkshire G20 0SP
Great Britain

Site: 605 in Study 1002-040

Site: 14004 in Study 1002-047

Dates of inspection: July 2 – 12, 2019

For Study 1002-040, there were 79 subjects screened and 54 subjects enrolled into the study. There were 25 subject records reviewed.

For Study 1002-047, there were 78 subjects screened and 23 subjects enrolled into the study. There were 23 subject records reviewed.

Dr. Arif is a clinical investigator

(b) (4)

For Study 1002-040, Dr. Arif was a sub-investigator from the start of the study until Oct 14, 2016 when she became investigator for the study. On Oct 10, 2017, she became a sub-investigator again and Holly Ross, M.D. became study investigator. Dr. Ross was involved with the study from the start as a sub-investigator. Dr. Arif was investigator for Study 1002-047 from the start of the study and remained so.

The sponsor considered the studies to be performed under IND at this site and collected signed Form FDA 1572s.

The lead ethics committee (EC) for Study 1002-040 was

(b) (4)

from the start of the study until this EC closed and the lead EC was changed to

(b) (4)

EC for Study 1002-047 was

(b) (4)

Source records were legible, organized and available. All subjects met inclusion/exclusion criteria except for Subject (b) (6) in Study 1002-040. This subject met exclusion criteria for systolic blood pressure ≥ 160 mmHg at screening. The subject had not taken normal anti-hypertensives prior to screening and did not meet this exclusion criteria at randomization (blood pressure recorded as 119/55). This was reported to the sponsor as a deviation and included in the data listings provided to FDA.

Two subjects were randomized with incorrect screening numbers. Subject (b) (6) in Study 1002-040 was randomized in the Interactive Web Response System (IWRS) under (b) (6) in error. This was discovered when Subject (b) (6) came to the clinic for randomization. The clinical site contacted the monitor, who instructed them to randomize Subject (b) (6) under number (b) (6). The monitor stated he was taking care of submitting data change requests (DCR) to the (IWRS) vendor. It appears the monitor submitted a DCR to correct demographic information instead of the randomization numbers and the subjects were dispensed under different randomization numbers at later visits. The stratification for both subjects was the same (Atherosclerotic Cardiovascular Disease and High Intensity Statins). While both subjects received kits based on different randomization numbers at randomization and later follow-up visits, neither subject received incorrect kit assignments as they were both randomized to the same arm (bempedoic acid 180 mg).

Review of laboratory reporting indicated numerous problems at (b) (4) (the central laboratory) for Study 1002-047. As reported to the review team, elevated LDL-C alerts were erroneously reported to investigator sites beginning at Week 24. The medical monitors were to ensure that critical alerts were reported to the sites and instructed the investigators to disregard messages on laboratory reports. A total of 14 subjects had a message for elevated LDL-C on their laboratory reports at this site. Of the 14 reports, only one subject (Subject (b) (6)) had a true elevated LDL-C. An email alert was not sent immediately for this subject. The sample date was January 5, 2018 and the laboratory report was dated January 11, 2018; however, the email alert was not sent until February 22, 2018. This subject returned for repeat testing on March 28, 2018. An email alert was sent by the medical monitor on March 30, 2018.

Normal glucose levels were also being flagged as being Level 2 High (H2) in error. The false flags did not result in improper treatment of subjects as glucose results were not blinded and Dr. Arif stated that it was clear the results were within normal range.

Due to central laboratory error, High sensitivity C-Reactive Protein (HsCRP) and Apolipoprotein-B (Apo-B) were not performed for five subjects at Week 24: Subjects (b) (6). The site was instructed to collect blood samples at unscheduled visits for the five subjects. Subject (b) (6) returned on January 18, 2018 for an unscheduled visit; however, the HsCRP results were not included on the sponsor data listings. The source report says “pending”.

Review of laboratory reporting did not observe any problems of reporting from (b) (4) for Study 1002-040. For Study 1002-040, LDL-C at screening was reported to the site in mmol/L and in the data listings submitted to FDA as mg/dL; therefore, they could not be confirmed. The FDA inspector did confirm that the laboratory testing was done.

For Study 1002-047, the FDA inspector confirmed that the LDL-C laboratory results from the screening and T1 visits matched the average reported in the data listings for the baseline. Also, it was confirmed that samples were collected on the dates reported in the data listings for Week 12 and Week 24 LDL-C results.

There were no unreported adverse events found for the selected subjects reviewed in both studies and all possible clinical events were submitted for adjudication. All events submitted to the Clinical Events Committee (CEC) were reported in the data listings provided to FDA.

Of note, for Subject (b) (6) in Study 1002-040, an incorrect date was entered for discontinuation of investigational product (IP), which resulted in a clinical MACE endpoint being considered “not treatment emergent.” The last date of IP was entered as Aug 3, 2017 on the Drug Accountability-Study Medication/Compliance page and End of Treatment – Study Completion page of the eCRF. The reason for stopping treatment was entered as “adverse event”. However, the AE page for proteinuria documents no action was taken with IP. The investigator’s notes for follow-up visits do not document discontinuation of IP prior to death on (b) (6). The data listing for Adjudicated MACE reports none of the adjudicated events on (b) (6) were considered treatment emergent. This is incorrect as there is no information to indicate the subject discontinued IP prior to death on (b) (6). Dr. Ross and Dr. Arif stated they would contact the sponsor regarding data change requests for the locked data.

OSI Reviewer Comment: It is recommended that the clinical team review the adjudication package for Subject (b) (6) in Study 1002-040 with this additional information in mind.

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.

2. Jose F. Cardona, M.D.
3700 West 12th Avenue
Hialeah, FL 33012-4170

Site: 1025 in Study 1002047

Dates of inspection: June 24 – 27, 2019

There were 36 subjects screened and 14 subjects enrolled into the study; 14 subjects completed the study. There were 14 subject records reviewed.

The clinical trial took place at (b) (4) a CRO for phase I-IV clinical trials owned by (b) (4)

Dr. Cardona is one of two clinical investigators at the site. He is hired as a full-time employee and has a private practice which is open by appointment only on the weekends. He has been in clinical research for seven years.

The IRB of record was (b) (4) IRB.

The source documents were legible and contemporaneous with detailed progress notes. 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.

Dr. Cardona's site was the first site inspected where the central laboratory programming error that was triggering false high LDL-C levels above protocol threshold became known. There were 8 out of 14 subjects affected by the programming error (2 out of the 8 affected were dosed due to lab error and did not need it).

SUMMARY OF EIGHT SUBJECTS WITH LAB ERRORS

SUBJECT	ISSUE	CONCLUSION
Subject (b) (6) (placebo)	Visit T5 labs (b) (6) flagged as elevated LDL-C and updated lab received (b) (6) still shows elevation.	Not a false positive. Subject dosed and needed it.
Subject (b) (6) (BA)	Visit T5 labs (b) (6) flagged as elevated LDL-C and updated lab received on (b) (6) show LDL-C not flagged (WNL).	False positive. Subject dosed and did not need it.
Subject (b) (6) (placebo)	Visit T5 labs (b) (6) flagged as elevated and updated lab received on (b) (6) show LDL-C not flagged (WNL).	False positive. Subject dosed and did not need it.
Subject (b) (6) (BA)	Visit T5 labs (b) (6) hemolyzed so repeat labs done (b) (6) flagged as elevated LDL-C and updated labs received on (b) (6) show LDL-C not flagged (WNL). Subject was never given LDL lowering therapy because Dr. Cardona failed to do a 1-week retest; however, due to lab error subject did not need the lowering therapy.	False positive. Subject not dosed and did not need it.
Subject (b) (6) (placebo)	Visit T5 labs (b) (6) flagged high LDL-C and updated lab report received during the inspection on (b) (6) shows LDL-C not	False positive. Subject not dosed and did not need it.

	flagged (WNL). Subject was never given LDL lowering therapy because Dr. Cardona failed to do a 1-week retest; however, due to lab error subject did not need the lowering therapy.	
Subject (b) (6) (BA)	Visit T5 labs (b) (6) flagged LDL-C high. Subject was never given LDL lowering therapy because the repeat labs done (b) (6) was blank. Dr. Cardona never confirmed with (b) (4) why a blank lab report was received and never requested a confirmatory report. Per updated labs sent during the inspection on (b) (6), LDL-C not flagged high (WNL). Due to lab error the subject did not need the lowering therapy.	False positive. Subject not dosed and did not need it.
Subject (b) (6) (BA)	Visit T5 labs (b) (6) flagged as high per the updated labs (missing in source record but referenced in an email from (b) (4) dated 3/6/2018) stated that the LDL-C for the repeat lab was still high and needed LDL lowering therapy. Subject's dose of Pravastatin was increased from 40 mg to 80 mg per day.	Not a false positive. Subject dosed and needed it.
Subject (b) (6) (placebo)	Visit T5 labs (b) (6) flagged as high; per updated labs received on (b) (6) not flagged. Subject was not given LDL lowering therapy.	False positive. Subject not dosed and did not need it.

(b) (4) was supposed to send a communication to the site when the programming error was fixed and was also supposed to send updated T5 visit/week 24 labs for those 8 affected subjects. The updated communication from (b) (4) was never received. Updated labs were received for 6 out of the 8 affected subjects. The updated labs for visit T5/week 24 for

Subject (b) (6) and Subject (b) (6) were requested while the FDA inspector was at the site and came back as LDL-C not flagged.

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. The central laboratory programming errors found at this site were previously reported to the review team.

3. Carl J. Gessler, Jr., M.D.
105 Rands Avenue
Huntsville, AL 35801-4317

Site: 1092 in Study 1002-047

Site: 105 in Study 1002-040

Dates of inspection: August 14 – 23, 2019

For Study 1002-047, there were 18 subjects screened and 8 subjects enrolled into the study; 8 subjects completed the study. There were 8 subject records reviewed.

For Study 1002-040, there were 52 subjects screened and 38 subjects enrolled into the study; 34 subjects completed the study. There were 13 subject records reviewed.

Dr. Gessler is (b) (4).
(b) (4). Dr. Gessler has been in practice for thirty-two years and has participated in 35-40 clinical research studies since 1987.

Participation in clinical trials is governed by seven voting board members of (b) (4) who review and approve studies, and allocates the studies to cardiologists according to their expertise. Dr. Gessler's patients are recruited and enrolled for participation in clinical studies if protocol criteria are met.

(b) (4) was the IRB of record for Study 1002-040. (b) (4)
(b) (4) was the IRB of record for Study 1002-047.

Source documentation was captured manually and in electronic format. Source records were attributable, legible, contemporaneous, organized and accurate. For both studies, source was 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.

Prior to formal notification by the central laboratory regarding the programming error, the site Study Coordinator (SC) had previously notified the laboratory on 01/24/18 regarding

four LDL-C alerts received in one week for Subjects (b) (6) (with additional confusing results the following week for Subjects (b) (6). Prior to contacting subjects for laboratory redraws, the SC requested that the laboratory confirm the alerts had not been generated in error. The site was told not to redraw labs. No subjects were treated based on the erroneous laboratory results. On 02/02/18, a formal notification was sent to participating sites regarding the programming error.

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. Alan Miller, M.D.
4553 North Shallowford Road
Suite 50B
Dunwoody, GA 30338-6400

Site: 1038 in Study 1002-048

Dates of inspection: June 10 – 14, 2019

There were 16 subjects screened and 10 subjects enrolled into the study; 10 subjects completed the study. There were 16 subject records reviewed.

Dr. Miller (b) (4)
He has been in practice for more than 20 years and has participated in over two hundred clinical research studies since 1992.

(b) (4) was the IRB of record.

Source documentation was captured in electronic data format. Source was readily available for review and attributable, legible, contemporaneous, organized and accurate. Source was compared to the sponsor data line listings; there were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

5. Chris Recknor, M.D.
2350 Limestone Parkway
Gainesville, GA 30501-2013

Site: 1021 in Study 1002048

Dates of inspection: July 15 – 18, 2019

There were 80 subjects screened and 43 subjects enrolled into the study; 43 subjects completed the study. There were 27 subject records reviewed.

Dr Recknor began his research practice in 2002 and has been at the same location since 2003.

(b) (4) was the IRB of record.

Source records were legible and available. Source was compared to the sponsor data line listings; there were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

6. Małgorzata Stefania Sipińska-Surzyńska, M.D.
ul. Konckiego 3
Katowice, Slaskie
40-040 Poland

Site: 5012 in Study 1002047

Dates of inspection: July 29 – August 2, 2019

There were 119 subjects screened and 40 subjects enrolled into the study. There were 15 subject records reviewed.

Dr. Sipińska-Surzyńska has been a practicing physician for 35 years specializing in internal medicine. She has been working for (b) (4)

Subjects were recruited by from the firm's databases, referrals from doctor offices, and via word-of-mouth. The site also advertised on the radio and in the local newspaper.

The EC of record was (b) (4)

Records were observed to be well organized, legible and in good condition. Source records were compared to the sponsor data line listings; there were two discrepancies:

- Source documentation indicates Subject (b) (6) was taking Euphyllin (theophylline) 300 mg tablet every day since 2010 for treatment of Chronic Obstructive Pulmonary Disease. The use of this concomitant medication was not reported to the sponsor.
- The dosing amount of rosuvastatin (Atoris) taking by Subject (b) (6) listed on the source document did not match the amount listed in the eCRF and data line listing. The source lists 20 mg and the eCRF and data listing lists 40 mg.

There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The site received alerts for elevated LDL-C values drawn at Week 24 (Visit T5) for 15 subjects. The memorandum from (b) (4) dated 02 February 2018, explaining the programming error was present at the site. An email from the CRO (b) (4) instructed the site to disregard the messages on the laboratory reports. Review of the 15 subjects' laboratory reports revealed there was no increase in lipid medication per standards of care due to the inaccurate LDL-C results that were reported at Week 24 (Visit T5).

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.

7. Josefina Tur, M.D.
7270 NW 12th Street, Suite 400
Miami, FL 33126

Site: 1027 in Study 1002048

Dates of inspection: July 24 – 29, 2019

There were 29 subjects screened and 19 subjects enrolled into the study; 18 subjects completed the study. There were 19 subject records reviewed.

Dr. Tur has been (b) (4)
(b) (4) She also has been practicing medicine as a
General Practitioner in the United States for 25 years and maintains a private practice. (b) (4)
(b) (4)

The IRB of record was (b) (4) The informed consents were written in English and Spanish.

The site created source documentation templates for site visits based on the protocol requirements. Source records were organized and available. 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.

8. Lucyna Woznicka-Leskiewicz, M.D.
ul. Glogowska 31/33
Poznan, Wielkopolskie
60-702 Poland

Site: 505 in Study 1002040

Dates of inspection: July 22 – 26, 2019

There were 85 subjects screened and 59 subjects enrolled into the study. There were 19 subject records reviewed.

The site supplied their own translations. Some of the documents requested during the inspection that were in Polish language were translated to English by site staff and are uncertified translated documents.

Dr. Woznicka-Leskiewicz has been a practicing physician for 11 years specializing in internal medicine and cardiology. She has been working (b) (4)

The ethics committee of record was (b) (4)

Records were observed to be well organized, legible and in good condition. Original source documents were compared to the eCRF and data line listings. For Subject (b) (6) (bempedoic acid 180 mg), the 12-Week LDL-C primary efficacy endpoint unblinded laboratory result of 39 mg/dL, dated 16 March 2017, did not match the data line listing result of 54 mg/dL submitted by the sponsor. All other primary endpoint data was verifiable.

One adverse event of increased intraocular pressure was not reported to the sponsor for Subject (b) (6) (bempedoic acid 180 mg). There was no other under-reporting of adverse events.

Of note, the site reported an adverse event of three-systems cytopenia for Subject (b) (6) (bempedoic acid 180 mg), which was reported on 17 January 2018; however, this adverse event was not observed on the data line listing submitted by the sponsor to FDA.

- The T2 Visit (Week 4) Clinical Note, dated 9 February 2017, documented a consultation to the hematologist for prolonged bleeding.
- Clinical Note from hematologist, dated 16 February 2017, mentions “suspected thrombophiles”.
- T6 Visit (Week 36) Clinical Note, dated 16 October 2017, documented no coagulation disorder being present.

- Laboratory Report for T7 Visit (End-of-Study) collected on 12 January 2018 for hematology was observed to be below the laboratory reference ranges and was documented as clinically significant by the Grzegorz Konieczny, M.D., Sub-Investigator
- Clinical Note, dated 16 January 2018, documented the AE of cytopenia
- eCRF Adverse Event Form was generated 09 January 2019 for “Three-System Cytopenia”

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for not following the protocol and investigational plan. Specifically, Subject (b) (6) was not on a stable dose of statin for 4 weeks prior to screening and did not meet inclusion criterion #5, as specified in the protocol.

OSI Reviewer Note: This issue was also found when the site was preparing for this inspection in June 2019 and a CAPA was opened. The site had already begun conducting a double check to ensure subjects met inclusion/exclusion criteria in September 2018 as part of quality improvement identified by the site director.

Dr. Woznicka-Leskiewicz responded to the Form FDA 483 on August 8, 2019. Her response was deemed acceptable.

9. Esperion Therapeutics, Inc./ Sponsor
c/o Timothy M. Mayleben, President & Chief Executive Officer
3891 Ranchero 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).

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 central laboratory programming error discovered in Study 1002-047 was investigated. On 1/30/18, the sponsor/ (b) (4) were initially made aware of the programming error issuing false positive alerts to have subjects take LDL-lowering therapy. All affected sites are accounted for, and a (b) (4) alert review summary was completed. This error was corrected immediately upon sponsor notification. An internal CAPA was issued by (b) (4) and not reported to FDA as the understanding was this oversight did not affect safety of subjects. Since no safety consequences arose, these are noted as minor protocol deviations within the clinical study report. The sponsor also conducted an audit of (b) (4) that resulted in change control that was found to be adequate with issues identified as corrected. Confirmed at the sponsor inspection with review of the site files, the (b) (4) programming error affected two subjects (b) (6) at Site#1025 with three false positive reports. Per the sponsor, there are no subjects with false positives that received LDL lowering therapy at this site.

The FDA inspectors were instructed to evaluate an incidence where two members of the study team inadvertently received an ad hoc data listing, involving Study 1002-040, with a limited amount of LDL-C data during the study, as reported in the CSR. The investigation found that two individuals opened excel documents and discovered that LDL-C data for post randomization visits for patients in the laboratory database were included; no treatment codes were included. A Declaration was completed by employee #1 which indicates the sequence of events surrounding this incidence. The FDA inspector verified that the investigation found that no potential unblinding occurred, no treatment codes were included and that there was no information that could have potentially unblinded the staff.

At Site 1027/Dr. Tur, a duplicate subject was identified. Randomized subject (b) (6) withdrew from the study, and therefore the subject was discontinued per sponsor decision. A second subject (b) (6) had screened and consented onto the study, but had not yet randomized, and was therefore screen failed from the study. This issue was escalated and brought to the sponsor's attention by (b) (4) verified study demographics to alert the sponsor of this concern. Subject (b) (6) was listed within this site's data line listings as discontinued at the firm's discretion, but screen fail subject (b) (6) is not mentioned within the clinical study report.

For Study 1002-048, a shortage of investigational product (IP) available for dispensing resulted in a CAPA completed by the firm. This sponsor oversight affected 10 sites, with 15 subjects across those sites. Subjects were off study drug for an allowable period without medical monitor intervention of between 2 and 19 days. In the interim, subjects had to return to their site to collect IP; sites were notified by the CRO when IP would be available for dispensing. The root cause assessment was that the IWRS system was not accurately reflecting what was on site. The sponsor was able to dispense to subjects with what was on hand as a manual override. The CAPA included a list of manual dispensations that identified treatment arm assigned and given. Manual dispensations were given either 35 or 100 ct. bottles. The CAPA included only those subjects that were delayed or missed IP. Review of manual dispensing efforts also indicated that all subjects received and were remained on their appropriate treatment.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to ensure proper monitoring of the study. Specifically, for protocols 1002-047 and 1002-048 under NDA 211616:
 - a. The monitor assigned to Site 1021 under Protocol 1002-048 did not provide a comprehensive protocol deviation log to the site investigator for signature and review at the close-out visit held 3/15/18. A complete deviation log, including 22 additional protocol deviations that occurred during the study, was revealed and provided to the site investigator on 7/12/19 in anticipation of the upcoming inspection.

OSI Reviewer Comment: The study monitor failed to ensure that the investigator site file was complete. The monitor went to the site 7/11-12/19 to prepare them for their upcoming FDA inspection. The site had only page 1 of the deviation log, which had been signed at close-out. While on site, the monitor had pages 1-4 of the deviation log and presented it to the site investigator for signature. All deviations were reported to the sponsor. Esperion did a root cause analysis and determined that its oversight procedures did not include routine checks of site close-out visits. This has been corrected.

In addition, following the inspection, Esperion conducted a retrospective review to assess whether this issue was limited to Site 1021 and found that

there were a few gaps in site documentation for Study 1002-047 and 1002-048. Specifically, a comprehensive final, signed Protocol Deviations (PD) log was missing from one Investigator Site File and a few filed PD logs contained missing PDs as follows:

Description of Final PD Log Analysis	1002-047 # of sites (%)	1002-048 # of sites (%)
Final site signed PD log is not filed in the TMF	1 (1%)	0
Final site signed PD log is filed in the TMF but does not include all PDs for the site	13 (14%)	8 (9%)

The missing PD log was sent to the site investigator. Updated incomplete PD logs were sent to all the affected sites.

- b. Training documents under Protocol 1002-047 for Amendment 3 - version date 5/9/17 at Site 1025 for a sub-investigator is absent from the trial master file. The FDA 1572 lists this sub-investigator on 4/11/18. The delegation log denotes that the sub-investigator was delegated from 4/11/18-10/23/18.

OSI Reviewer Comment: The site investigator stated that he trained the sub-investigator, although there was no documentation. Esperion did a root cause analysis and determined that its oversight procedures did not include a study-specific oversight plan. This deficiency has been corrected.

- c. The screening and enrollment log maintained during the study duration for Site 1025 under Protocol 1002-047 was not verifiable during the inspection as this document was absent from the trial master file.

OSI Reviewer Comment: Correspondence provided by the site to the sponsor during the inspection provided a separate screening log as a subject visit log and an enrollment log. They had effective dates of 2/8/19 and 8/6/19, respectively, that were after the study close out visit (10/23/18). Esperion did a root cause analysis and determined that its oversight procedures did not include routine checks of site close-out visits. This has been corrected. In addition, signed informed consent forms and randomization documents confirm enrollment numbers.

- d. At Site 1021 under Protocol 1002-048, the tiering tracker for risk-based monitoring was not documented throughout the study duration. Therefore, adjustments in monitoring were not made for increase in enrollment.

OSI Reviewer Comment: Additional correspondence from the CRO (b) (4) provided 8/9/19 just prior to inspection close-out states that the tier tracker was updated manually by the study team during the study. The audit trail for the tier tracker to verify tier tracking updates was requested by the sponsor to (b) (4) and not provided during the current inspection. However, post-

inspection it was determined that the incorrect documentation was given to the FDA inspector and that there were sufficient monitoring visits. A retrospective review confirmed that only one site (Site 1012) for Study 1002-048 had a tier change requiring increased monitoring frequency.

- e. Neither version of the Clinical Operations Plan under Protocol 1002-048 specifies a definitive plan of monitoring frequency and issuance of site triggers allowing for early identification of risks and mitigating negative impact to data integrity.

OSI Reviewer Comment: *Esperion did a root cause analysis. They relied upon the CRO's expertise and their proprietary systems and processes (to which Esperion was not permitted access). This limited Esperion's ability to conduct independent quality control over certain areas. Additional resources have been added to the Clinical Operations and Clinical Quality Assurance teams to support the enhancements made to monitoring and oversight. An independent audit of the CRO (b) (4) is also scheduled to be performed.*

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.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this sponsor appear acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Central Doc. Rm./ NDA 211616
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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
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OSI/DCCE/GCPAB/ActingTeam Leader/Anthony Orendia
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OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of
Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Telephone 301-796-2200
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PLLR Labeling Memorandum

Date: December 12, 2019 **Date consulted:** April 17, 2019

From: Jane Liedtka, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Kati Johnson, Regulatory Project Manager (RPM)
Division of Metabolic and Endocrine Products (DMEP)

Drug: NEXLETOL (Bempedoic acid), NEXLIZET [(Bempedoic acid/ezetimibe fixed drug combination (FDC))]

NDA: 211616, 211617

Applicant: Esperian

Subject: Pregnancy and Lactation Labeling Rule (PLLR) language (New NDAs)

Indication:

NEXLETOL is an adenosine triphosphate-citrate lyase (ACL) inhibitor indicated as an adjunct to diet (b) (4)

who require additional lowering of LDL-C.

NEXLIZET, which contains an adenosine triphosphate-citrate lyase (ACL) inhibitor and a cholesterol absorption inhibitor, is indicated as an adjunct to diet (b) (4)

who require additional lowering of LDL-C.

Materials Reviewed:

- Sponsor's submitted background package for NDAs 211616 dated 2/20/2019 and 211617, dated 2/26/19.
- Sponsor's response to IR received May 7, 2019 which included PLLR supporting information for both submissions.
- DPMH review of Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) NDAs 19766 S-099/21445 S-042/21687 S-061. Jane Liedtka, M.D. 02/27/2019. DARRTS Reference ID# 4396340.^{1,2}

Consult Question: We are requesting review of the PI for compliance with PLLR

INTRODUCTION AND BACKGROUND

On 2/20/19, Esperian submitted a new NDA for bempedoic acid (BA), # 211616. On 2/26/19, Esperian submitted a new NDA for a BA/ezetimibe (BA/E) FDC, # 211617. BA and BA/E have a proposed indication of the following: "treatment of adults (b) (4) who require additional lowering of LDL-C." On 4/17/19, DMEP consulted DPMH to provide input for appropriate labeling of the pregnancy and lactation sections of BA and BA/E to comply with the PLLR format.

Pregnancy

Hypercholesterolemia and Pregnancy³

During pregnancy, it is normal for total cholesterol, high density lipoprotein (HDL-C) and low-density lipoprotein (LDL) to increase by 25-50%, while triglycerides increase two to four times. The increase in cholesterol during pregnancy does not lead to endothelial dysfunction. Current recommendation is that women who are planning pregnancy or who become pregnant should stop HMG-CoA reductase inhibitor therapy. Discontinuation of lipid-lowering medication for a short period of time during pregnancy is thought to have little impact on long-term therapy for hyperlipidemia and is unlikely to affect outcomes for cardiovascular disease.

¹DPMH review of Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) NDAs 19766 S-099/21445 S-042/21687 S-061. Jane Liedtka, M.D. 02/27/2019. DARRTS Reference ID# 4396340.

² The previous DPMH review for Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) was a part of the materials reviewed but was not a source relied upon for the labeling recommendations below. Although there is overlap in the labeling proposed for this previous review and that being proposed here, the labeling recommendations in this review are based on DPMH's independent analysis of the underlying data.

³Dukic A, et al. Hyperlipidemia and Pregnancy. Med Pregl. 2009; 62 Suppl 3: 80-84.

Bempedoic Acid

Nonclinical Experience

In animal reproduction studies, bempedoic acid was not teratogenic in rats and rabbits when administered at doses up to 11-and 12-fold MRHD, based on AUC. However, there were increases in the incidence of non-adverse fetal skeletal variations (bent long bones and bent scapula and incomplete ossification) at clinical exposures in the absence of maternal toxicity .

For further details, the reader is directed to the Nonclinical Review by, Lydia Haile, PhD.

Applicant's Review of the Literature

The Applicant stated that “no human data are available from bempedoic acid clinical trials on the use of the drug in pregnant or lactating women. Bempedoic acid is a new molecular entity that is not currently approved or marketed anywhere in the world.” In addition, the applicant performed a literature search regarding ezetimibe, on page 35 of that report the applicant states “No clinical data are available on the use of ezetimibe during pregnancy or lactation”.

Applicant's Review-Pharmacovigilance Database (PVDB) Summary

The current safety database was searched for cases reporting events relating to pregnancy and/or lactation. The applicant noted that

- One subject in study 1002-022 became pregnant on BA 240 mg per day for 9 days but was lost to follow-up on day 13.
- One subject in study 1002-037 became pregnant while receiving atorvastatin but never “made it through screening” so never received BA.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and EMBASE on 11/5/19 using the search terms “bempedoic acid and pregnancy” “bempedoic acid and pregnant women,” “bempedoic acid and pregnancy and birth defects,” “bempedoic acid and pregnancy and congenital malformations,” “bempedoic acid and pregnancy and stillbirth,” “bempedoic acid and spontaneous abortion”, “bempedoic acid and pregnancy and prematurity”, “bempedoic acid and pregnancy and low birth weight” and “bempedoic acid and pregnancy and miscarriage”. No publications were identified.

Bempedoic acid is not referenced in Briggs⁴ *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Bempedoic acid is not referenced in MicroMedex⁵.

⁴ Briggs, GG, Freeman, RK. & Yaffe, SJ. (2015). *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

⁵Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 9/5/19.

Ezetimibe

DPMH has performed a previous review of the moiety ezetimibe, see DPMH review of Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) NDAs 19766 S-099/21445 S-042/21687 S-061¹ for details of literature search. See **DPMH Proposed NEXLETOL (Bempedoic acid), NEXLIZET [(Bempedoic acid/ezetimibe FDC] Pregnancy and Lactation Labeling** at the end of this review for details of recommended labeling.

Lactation

Bempedoic acid

Nonclinical Experience

There are no data regarding the presence of bempedoic acid in animal milk.

Applicant's Review of the Literature

The Applicant did not identify any relevant publications.

Applicant's Review of Pharmacovigilance Database

The safety database was searched for bempedoic acid cases reporting events relating to lactation; none were identified.

DPMH's Review of the Literature

DPMH conducted a search of published literature in PubMed and EMBASE using the search terms "bempedoic acid and lactation" and "bempedoic acid and breastfeeding". No relevant publications were identified.

According to the proposed labeling¹, bempedoic acid has a molecular weight of ≈345 Daltons. Plasma protein binding of bempedoic acid, its glucuronide and its active metabolite, ESP15228, were 99.3%, 98.8% and 99.2%, respectively. The mean terminal half-life is about 19 hours.

Bempedoic acid is not referenced in Hale's *Medication and Mother's Milk*,⁶ or in the LactMed database.

Ezetimibe

Nonclinical Experience

In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed in maternal plasma.

DPMH has performed a previous review of the moiety ezetimibe, see DPMH review of Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) NDAs 19766 S-099/21445 S-042/21687 S-061¹ for details of literature search. See **DPMH Proposed NEXLIZET [(Bempedoic acid/ezetimibe**

⁶ Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

FDC] Pregnancy and Lactation Labeling at the end of this review for details of recommended labeling.

Females and Males of Reproductive Potential

Nonclinical Experience

In fertility and early embryofetal development study in rats, bempedoic acid was orally administered to male and female rats at 10, 30 and 60 mg/kg/day. Males were dosed for 28 days prior to mating, and females were dosed 14 days prior to mating and continued through mating period to Gestation day 7. In females, there were decreases in numbers of corpora lutea and implants and viable embryos at $\geq$ 30 mg/kg/day (4-fold MRHD). No effect was observed in male and female fertility despite changes in estrus cyclicity and decreases in sperm count at 60 mg/kg/day (9-fold MRHD).

For further details, the reader is directed to the Nonclinical Review by Lydia Haile, PhD.

DPMH's Review of the Literature

DPMH reviewed bempedoic acid and effects on fertility in published literature in PubMed and Embase using the search terms "bempedoic acid and fertility"; there were no publications identified.

Ezetimibe

DPMH has performed a previous review of the moiety ezetimibe, see DPMH review of Zocor (simvastatin)/Zetia (ezetimibe)/Vytorin (ezetimibe and simvastatin) NDAs 19766 S-099/21445 S-042/21687 S-061¹ for details of literature search. See **DPMH Proposed NEXLETOL (Bempedoic acid), NEXLIZET [(Bempedoic acid)/ezetimibe FDC] Pregnancy and Lactation Labeling** at the end of this review for details of recommended labeling.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are minimal human pregnancy data (and no outcome data) for bempedoic acid in the published literature and in the applicant's PVDB. The findings in animal studies with minor skeletal variations at doses below the clinical exposure were not worrisome. The Applicant recommended (b) (4) DPMH recommends (b) (4) a notice of the possibility of fetal harm based on mechanism of action in section 8.

DPMH concludes there are insufficient human data available to inform the safety of bempedoic acid use during pregnancy. The limited available human pregnancy data from clinical trial experience and the applicant's pharmacovigilance database are insufficient to exclude pregnancy risk. Considering bempedoic acid is a systemically absorbed new molecular entity with a potential for use amongst

females of reproductive potential, gathering additional pregnancy exposure data is important to assess the safety of bempedoic acid use during pregnancy. Therefore, DPMH recommends that a post-marketing requirement (PMR) for a pregnancy exposure registry and a postmarketing pregnancy study of a different design is issued to the applicant for both bempedoic acid alone and for the bempedoic acid and ezetimibe combination product.

Lactation

Based on the high protein binding (99%), it is unlikely that significant amounts of bempedoic acid would be present in human milk. However, because of theoretical concerns about the mechanism of action of anti-lipid agents and the presence of hyperlipidemia being relatively common in the population of females of reproductive potential, DPMH proposes a PMR for a milk-only lactation study to confirm a low level being present in human milk. Should a significant amount of bempedoic acid be found in the milk-only lactation study, a milk-plasma study should be considered.

DPMH proposes the following for the “Risk Summary” labeling in Section 8.2:

(b) (4)

(b) (4)

RECOMMENDATIONS

DPMH revised the HPI and sections 4, 5.X, 8.1, 8.2, 8.3 and 17 in NEXLETOL (Bempedoic acid) and NEXLIZET [(Bempedoic acid/ezetimibe FDC)] labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

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

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/s/

JANE E LIEDTKA
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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
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SEVAN H KOLEJIAN
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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*****

Date of This Review:	September 6, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 211616
Product Name and Strength:	Nexletol (bempedoic acid) Tablets, 180 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Esperion Therapeutics, Inc.
FDA Received Date:	February 21, 2019 and June 7, 2019
OSE RCM #:	2019-403
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 Nexletol (bempedoic acid) tablets, 180 mg, the Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed prescribing information, patient package insert, container labels, and carton labeling 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
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS 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 labels 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

Prescribing Information			
	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 bempedoic acid is 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.	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." 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. Based on OPQ and DMEP's final determination, we may have additional recommendations.
Patient Package Insert			
1.	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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Table 3: Identified Issues and Recommendations for Esperion (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels (30, 90, (b) (4))			
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” instead of “180mg.”
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 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. 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).
Professional Sample Blister Card			
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 of bempedoic acid.	Revise the blister label to express the strength as: <i>180 mg per tablet</i> 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: https://www.fda.gov/media/85879/download

4 CONCLUSION

Our evaluation of the proposed prescribing information, container labels, and carton 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 MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nexletol received on February 21, 2019 from Esperion Therapeutics, Inc.

Table 2. Relevant Product Information for Nexletol	
Initial Approval Date	N/A
Active Ingredient	bempedoic acid
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
Dose and Frequency	One tablet once daily
How Supplied	Bottles of 30 tablets (NDC 72426-118-03) Bottles of 90 tablets (NDC 72426-118-09) (b) (4) Professional Sample: Carton containing 1 blister card of 7 tablets (NDC 72426-118-99)
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 package. Do not discard desiccant.
Container Closure	(b) (4) 30- & 90-count: 60-cc HDPE bottles with child-resistant caps, induction seals, and silica gel desiccant canister (for patient use) (b) (4) Professional sample: (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 Nexletol labels and labeling submitted by Esperion Therapeutics, Inc.

- Container label received on February 21, 2019
- Professional Sample Blister cards received on February 21, 2019
- Professional Sample Carton Labeling received on February 21, 2019
- Prescribing Information (Image not shown) received on February 21, 2019 available at: <\\cdsesub1\evsprod\nda211616\0001\m1\us\114-labeling\draft\labeling\11413-pi-nexletol.pdf>
- Patient Package Insert (Image not shown) received on June 7, 2019 available at: <\\cdsesub1\evsprod\nda211616\0019\m1\us\114-labeling\draft\labeling\proposed-pi-nexletol.pdf>

G.2 Label and Labeling Images

- Container Labels



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

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/

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