

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211617Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

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

Application Type	NDA
Application Number	211616 and 211617
PDUFA Goal Date	February 21, 2020
OSE RCM #	2019-402 and 404
Reviewer Name	Mei-Yean Chen, Pharm.D.
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Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 14, 2020
Subject	Evaluation of Need for a REMS
Established Name	Bempedoic acid and bempedoic acid/ezetimibe fixed dose combination (FDC)
Trade Name	Nexletol and Nexlizet
Name of Applicant	Esperion Therapeutics, Inc.
Therapeutic Class	An adenosine triphosphate-citrate lyase inhibitor
Formulation(s)	Nexletol 180 mg tablet and Nexlizet (bempedoic acid 180 mg and ezetimibe 10 mg)
Dosing Regimen	Oral tablet once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Nexletol/Nexlizet (bempedoic acid and bempedoic acid/ezetimibe) is necessary to ensure the benefits outweigh its risks. Esperion Therapeutics, Inc. submitted a New Drug Application (NDA 211616 and 211617) for bempedoic acid and bempedoic acid/ezetimibe with the proposed indication as an adjunct to diet and maximally tolerated statins therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of low-density lipoprotein cholesterol (LDL-C), with Limitations of Use: the effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined. The risks associated with bempedoic acid include hyperuricemia and tendon rupture. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of bempedoic acid outweigh its risks. Statin therapy sometimes is not enough to achieve appropriate lowering of LDL-C. There remains a clear need to develop a new therapy that is both effective and safe in lowering LDL-C. Although bempedoic acid effect in reducing LDL-C is modest, with its safety profile, it provides an additional therapeutic option in patients who are not able to meet goals with current available therapies. If the product is approved, the recommendations for monitoring signs and symptoms of hyperuricemia and tendon rupture will be communicated in the Warnings and Precautions section of the labeling.

1. INTRODUCTION

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) bempedoic acid is necessary to ensure the benefits outweigh its risks. Esperion Therapeutics, Inc. (Esperion) submitted a New Drug Application (NDA) 211616 and 211617 for Nexletol and Nexlizet (bempedoic acid and bempedoic acid/ezetimibe) with the proposed indication as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFM) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C), with Limitations of Use: the effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined. Nexlizet is a fixed dose combination (FDC), which contains bempedoic acid and ezetimibe (a cholesterol absorption inhibitor). This application is under review in the Division of Metabolism and Endocrinology Products (DMEP). The applicant did not submit a proposed REMS or risk management plan with this application.

2. BACKGROUND

2.1 PRODUCT INFORMATION

Bempedoic Acid, a new molecular entity, is an adenosine triphosphate (ATP)-citrate lyase (ACL) inhibitor with the proposed indication as an adjunct to diet and maximally tolerated statins therapy for the treatment of adults with HeFM or established ASCVD who require additional lowering of LDL-C. As an

ACL inhibitor, bempedoic acid acts upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase to inhibit cholesterol biosynthesis in the liver and lower LDL-C in blood via upregulation of LDL receptors. Bempedoic acid is available as a 180 mg tablet with the proposed dosing as one tablet orally once daily. Bempedoic Acid is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211616 and NDA 211617 relevant to this review:

- October 2009: Investigation New Drug (IND 106654) opened
- August 2015: End of phase 2 (EOP2) meeting
- September 2018: pre-NDA meeting
- 02/20/2019: NDA 211616 submission received
- 02/26/2019: NDA 211617 submission received
- 08/15/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for bempedoic acid.

3 THERAPEUTIC CONTEXT AND TREATMENT OPTIONS

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Familial hypercholesterolemia (FH) is the most common autosomal dominant genetic disease. The clinical syndrome is characterized by extremely elevated levels of LDL-C and a propensity to early onset of ASCVD. The American Heart Association criteria for clinical diagnosis of FH is LDL-C > 190 mg/dL and either a first degree relative with LDL-C > 190 mg/dL or with known premature coronary heart disease (<55 years men; <60 years women)¹. The prevalence of FH varies on definition used and the population studied. Few patients in a general medicine practice have FH using a definition that includes genetic testing. FH is an autosomal dominant disorder inherited with a gene dosing effect, in which homozygotes are more adversely affected than heterozygotes. Homozygous FH patients are rare and have an estimated prevalence of about 1:300,000 to 1:400,000. LDL-C level in patients with homozygous FH usually is higher than 500 mg/dL, while LDL-C level in patients with heterozygous FH (HeFH) is around 200-550 mg/dL. HeFH is estimated to occur in about 1 in 300 individuals in Europe and 1 in 200-250 individuals in the United States (US).² HeFH patients have high LDL-C levels from birth and a higher risk of premature coronary heart disease. Individuals with HeFH often demonstrate tendon xanthomata if untreated and have a family history of hypercholesterolemia. The prevalence of xanthomata increases with age, eventually occurring in 75% of patients with HeFH.

Cardiovascular disease (CVD) is the leading cause of death in the United States (US)^a affecting over one third of Americans^{b,3}. Heart attack and stroke are usually caused by ASCVD. ASCVD develops because of a buildup of sticky cholesterol-rich plaque. The plaque can harden and narrow the arteries as patients age. Elevated levels of LDL-C are associated with an increased risk of CVD events and lowering of LDL-C is associated with a reduction in these events. LDL-C level is an important modifiable risk factor for ASCVD. A meta-analysis of data from 14 randomized trials of statins demonstrated that lower LDL-C can significantly reduce the incidence of CVD in a wide range of patients⁴.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The following is 2018 American Heart Association (AHA)/American Chest Association (ACA) treatment guideline for LDL-C reduction, in addition to adhere a healthy lifestyle⁵,

- Primary prevention: for adults who are free from ASCVD, use moderate-intensity statin
- Secondary prevention: for patients with ASCVD
 - Not very high risk for recurrence: use high intensity statin +/- ezetimibe
 - Very high risk for recurrence: use high intensity statin +/- ezetimibe +/- Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor

Table 1: Summary of Treatment Options and relevant to proposed indication and their adverse events

Drug name	Route	Warnings & Precautions
Statins: atorvastatin ⁶ , rosuvastatin ⁷ , simvastatin ⁸ , pravastatin ⁹ , lovastatin ¹⁰ , Fluvastatin ¹¹ , pitavastatin ¹²	Oral	Myopathy, rhabdomyolysis, liver enzyme abnormalities
Ezetimibe (ZETIA) ¹³	Oral	Myopathy, rhabdomyolysis (co-administered with statins), liver enzyme abnormalities

^a Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Alirocumab (PRALUENT) (a PCSK9 inhibitor) ¹⁴ Evolocumab (REPATHA) (a PCSK9 inhibitor) ¹⁵	Subcutaneous injection	Allergic reactions
Bile acid sequestrant Cholestyramine ¹⁶ Colestipol (COLESTID) ¹⁷ Colesevelam (WELCHOL) ¹⁸	Oral	None, not absorbed and do not cause systemic side events, but associated with gastrointestinal complaints such as constipation or obstruction, hypertriglyceridemia and pancreatitis, vit K or fat-soluble vitamin deficiency

4 BENEFIT ASSESSMENT

There were 3,009 adult patients with HeFH or established ASCVD enrolled in two multi-center, randomized, double-blind, placebo-controlled trials to evaluate the efficacy of bempedoic acid. In both trials, the maximum LDL-C lowering effects occurred at week 4.²⁰

Study 1 (NCT 02666664) was a multi-center, randomized, double-blind, placebo-controlled 52-week trial that evaluated safety and efficacy of bempedoic acid in patients with HeFH and/or ASCVD. At week 12, efficacy of bempedoic acid was evaluated. The trial included 2,230 patients randomized 2:1 to receive either bempedoic acid (n=1488) or placebo (n=742) as add-on to a maximally tolerated lipid lowering therapy. Patients were stratified by presence of HeFH and by baseline statin intensity. The mean age at baseline was 66 years (24-88 years), 61% were ≥ 65 years old, 27% women, 2% Hispanic, 96% White, 3% Black, and 1% Asian. Ninety-five percent of patients had established ASCVD, and 5% of patients had HeFH. Twenty-nine percent of patients had diabetes at baseline. The mean baseline LDL-C was 103.2 mg/dL. All patients were receiving statin therapy and 50% were receiving high-intensity statin therapy. The primary efficacy outcome measure was the percent change of LDL-C from baseline to week 12. The difference between bempedoic acid and placebo of LDL-C was -18.1% (95% confidence interval: -20.0%, -16.1%; p<0.001).

Study 2 (NCT 02991118) was a multi-center, randomized, double-blind, placebo-controlled, 52-week trial in patients with HeFH and/or ASCVD. The efficacy of bempedoic acid was evaluated at week 12. The trial included 779 patients randomized 2:1 to receive either bempedoic acid (n=522) or placebo (n=257) as add-on to maximally tolerated lipid lowering therapy. The mean age at baseline was 64 years (28-91 years), 51% were ≥ 65 years old, 36% women, 8% Hispanic, 94% white, 5% Black, and 1% Asian. Ninety-five percent of patients had established ASCVD, and 5% of patients had HeFH. The mean baseline LDL-C was 120.4 mg/dL. Ninety percent of patients were receiving statin therapy and 53% were receiving high-intensity statin therapy, and 0.3% were receiving PCSK9 inhibitors. The primary efficacy outcome measure was the percent change of LDL-C from baseline to week 12. The difference between bempedoic acid and placebo in mean percent change in LDL-C from baseline to week 12 was -17.4% (confidence interval -21%, -13.9%; p<0.001).

The medical officer communicated at the midcycle meeting that there was a 17-18% additional LDL-C reduction at 12 weeks when bempedoic acid was added to maximally-tolerated statins and effects were sustained throughout treatment. Thirty percent of patients treated with bempedoic acid were able to achieve LDL-C <70 mg/dL. The medical reviewers conclude that even though the effect of bempedoic acid on LDL-C reduction is modest, the effect is clinically meaningful. Bempedoic acid provides an additional option to lower LDL-C in patients who are not able to meet goals with currently available therapy , such as maximally tolerated statins, ezetimibe or a PCSK9 inhibitor).¹⁹

5 RISK ASSESSMENT & SAFE-USE CONDITIONS

The safety of bempedoic acid was evaluated in 2 placebo-controlled trials that included 2009 patients treated with bempedoic acid for 52 weeks. The mean age for bempedoic acid treated patients was 65 years, 34% were women, 94% were White, 4% Black, 1% Asian, and 1% other races. All patients received bempedoic acid 180 mg orally once daily plus maximally tolerated statin therapy alone or in combination with other lipid-lowering therapies. Ninety-seven percent of patients had clinical ASCVD and about 4% had a diagnosis of HeFH.

Study 1 and Study 2 randomized patients 2:1 to receive either bempedoic acid or placebo. There were 25 deaths (1.2%) reported in bempedoic acid arm compared to 8 deaths (0.8%) in placebo arm. Table 2 lists the causes of deaths. The medical officer concluded that “the overall imbalance in all-cause deaths between arms was primarily driven by malignancy-associated deaths that occurred > 30 days after drug discontinuation. Observed imbalances in deaths were most likely due to chance. Review of the safety database did not support an association between bempedoic acid exposure and mortality, CV harm, or malignancy risk.”¹⁹

Table 2 Deaths in safety population (studies 1 and 2), 52 weeks

deaths	Bempedoic acid N=2009, n (%)	Placebo N=999, n(%)
Total deaths	25 (1.2%)	8 (0.8%)
cardiovascular	12 (0.6%)	5 (0.5%)
Malignancy	9 (0.4%)	1 (0.1%)
Other	4 (0.2%)	2 (0.2%)
Within 30 days of last dose	14 (0.7%)	4 (0.4%)
Cardiovascular	11 (0.5%)	4 (0.4%)

Malignancy	1 (0.0%)	1 (0.1%)
Other	3 (0.1%)	1 (0.1%)
Beyond 30 days of last dose	11 (0.5%)	4 (0.4%)
Cardiovascular	1 (0.0%)	2 (0.2%)
Malignancy	8 (0.4%)	0 (0.0%)
Other	1 (0.0%)	1 (0.1%)

The followings are the risks^b associated with the use of bempedoic acid that will be included in warnings and precautions of the label.

5.1 HYPERURICEMIA

Bempedoic acid inhibits renal tubular Organic Anion Transporter 2 (OAT2) and may increase blood uric acid levels. In clinical trials, hyperuricemia usually occurred within the first 4 weeks and persisted throughout therapy. Twenty-six percent of bempedoic acid treated patients with normal baseline uric acid (versus 9.5% placebo) reported hyperuricemia one or more times and 3.5% of patients experienced significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). The mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients in bempedoic acid arm after 12 weeks of therapy.

Gout may occur due to hyperuricemia. Gout was reported in 1.5% of patients in bempedoic acid arm compared to 0.4% of patients in placebo arm. The risk of developing gout was higher in patients with a history of gout, 11.2% in bempedoic acid arm versus 1.7% in placebo arm. Gout also occurred more frequently in patients treated with bempedoic acid (1.0%) than placebo (0.3%) who had no prior gout history.²⁰

HCPs are advised to assess serum uric acid if clinically indicated. Signs and symptoms of hyperuricemia are to be monitored and start therapy with urate-lowering drugs as appropriate.

5.2 TENDON RUPTURE

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

Increased risk of tendon rupture or injury associated with bempedoic acid was reported in clinical trials, 0.45% versus 0% of placebo arm. The most frequently involved were the bicep's tendon, rotator cuff, and the Achilles tendon.⁵ Tendon rupture occurred within weeks to months of starting bempedoic acid. Patients who were over 60 years old, take corticosteroid or fluoroquinolone drugs, with renal failure, or with previous tendon disorders were to have increased risk of tendon rupture.²⁰

If approved, Healthcare Providers (HCPs) are advised to discontinue bempedoic acid immediately if the patient experiences rupture of a tendon. If patients experience joint pain, swelling, or inflammation, consider discontinuing bempedoic acid. HCPs also need to advise patients to rest at the first sign of tendinitis or tendon rupture and to contact HCPs. If patients have a history of tendon disorders or tendon rupture, HCPs are advised to consider an alternative therapy.

6 EXPECTED POSTMARKET USE

If approved, bempedoic acid will be used in both outpatient and inpatient settings. The likely prescribers will be primary care practitioners, internal medicine practitioners, and cardiologists.

7 RISK MANAGEMENT ACTIVITIES PROPOSED BY THE APPLICANT

The Applicant did not propose any risk management activities for bempedoic acid beyond routine pharmacovigilance and labeling.

8 DISCUSSION OF NEED FOR A REMS

The Clinical Reviewer recommends approval of bempedoic acid based on the efficacy and safety information currently available. DRM and DMEP agree that a REMS is not necessary to ensure the benefits of bempedoic acid outweigh its risks. When evaluating factors of a REMS is necessary to ensure that the benefits outweigh the risks for bempedoic acid, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and prescribing population.

HeFH is estimated to occur in about 1 in 200-250 individuals in US. Cardiovascular disease (CVD) is the leading cause of death in US and affects over one third of American. Elevated levels of LDL-C are associated with an increased risk of CVD events and lowering of LDL-C is associated with a reduction in CVD events. In the clinical trials of bempedoic acid, there was a 17% additional LDL-C reduction which occurred at 12 weeks when added to maximally-tolerated statins, and the effect was sustained throughout treatment. Thirty percent of patients treated with bempedoic acid was able to achieve LDL-C <70 mg/dL.

The serious risks associated with bempedoic acid during clinical trials were tendon rupture and hyperuricemia. The recommendations for monitoring signs and symptoms of tendon rupture and hyperuricemia will be communicated in the Warnings and Precautions section of the labeling if the product is approved. Bempedoic acid will likely be prescribed by primary care practitioners, internal medicine practitioners, and cardiologists who are familiar with these risks and how to manage them.

LDL-C reduction is generally considered a surrogate for lowering CVD risk. Use of LDL-C lowering as a surrogate is based on data from several large trials demonstrated CVD risk reduction with statins in primary and secondary prevention.²¹ However, statin therapy alone sometimes is not enough to achieve appropriate lowering of LDL-C. Therefore, many patients have LDL-C levels that are not at goal for their level of perceived risk. There remains a clear medical need to develop a new therapy that is both effective and safe in lowering LDL-C. Although bempedoic acid effect in reducing LDL-C is modest, with its safety profile, it provides an additional therapeutic option in high-risk patients who are not able to meet goals with current available therapies.

9 CONCLUSION & RECOMMENDATIONS

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for bempedoic acid to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 APPENDICES

10.1 REFERENCES

¹ American College of Cardiology/American Heart Association: Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults, 2013

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⁴ Baigent C, Keech A, et al; Cholesterol treatment trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. *Lancet*. 2005; 366: 1267-1278.

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⁶ Atorvastatin (Lipitor) prescribing information, Drugs@FDA, accessed 02/03/2020.

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- ¹⁶ Cholestyramine prescribing information, Drugs@FDA, accessed 02/11/2020
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- ¹⁸ Colesevelam (Welchol) prescribing information, Drugs@FDA, accessed 02/03/2020
- ¹⁹ Higginbotham L., Kettermann A. et al Draft Integrated Review of Nexletol (bempedoic acid) NDA 211616 on 02/04/2020
- ²⁰ Bempedoic acid NDA 211616 draft prescribing information 02/05/2020

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