FDA Approves Expanded Indications for NEXLIZET® & NEXLETOL®

NEXLIZET & NEXLETOL are the only non-statins FDA approved to lower LDL-C and reduce the risk of MI and coronary revascularization in primary prevention and secondary prevention patients[1,2].

ANN ARBOR, MICH., March 22nd 2024-- The FDA approval is based on data from the CLEAR Outcomes trial, a 13,970 patient cardiovascular outcomes trial, which assessed the impact of bempedoic acid, a component of NEXLIZET and NEXLETOL, on CV outcomes in patients with either established cardiovascular disease or who were at high-risk for their first cardiovascular disease event[3]. The results were published in the *New England Journal of Medicine* in March of 2023[3].

"We are excited to receive FDA approval for our highly anticipated label expansions for NEXLETOL and NEXLIZET in the U.S. With these revised labels, the accessibility of our highly effective medicines is now expanded to include primary prevention and secondary prevention patients," said Sheldon Koenig, President and CEO.

The bempedoic acid component of NEXLIZET and NEXLETOL significantly reduced the risk of CV events in primary prevention and secondary prevention patients who were unable to take recommended doses of statin therapy (including no statin). Bempedoic acid's impact on the individual components of the primary endpoint included:

- **27% reduction in risk of nonfatal MI**[2] and
- **19% reduction in risk of coronary revascularization**[2].

INDICATION

NEXLIZET and NEXLETOL are indicated:

- The bempedoic acid component of NEXLIZET and NEXLETOL is indicated to reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with:
  - established cardiovascular disease (CVD), or
  - at high risk for a CVD event but without established CVD.

- As an adjunct to diet:
  - NEXLIZET, alone or in combination with other LDL-C lowering therapies, to reduce LDL-C in adults with primary hyperlipidemia, including HeFH.
  - NEXLETOL, in combination with other LDL-C lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including HeFH.

IMPORTANT SAFETY INFORMATION

NEXLIZET and NEXLETOL are contraindicated in patients with a prior hypersensitivity to bempedoic acid or ezetimibe or any of the excipients. Serious hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria have been reported.

See additional Important Safety Information below.

In a prespecified, exploratory analysis of primary prevention patients that made up 30% of the study population, bempedoic acid has a **32% and 39% reduction in risk of MACE-4 and MACE-3**[4,5] respectively[*^].

[*]Methods[4]

Although prespecified, this study reports on outcomes in a subgroup within a larger clinical trial. Therefore, the results should be interpreted as hypothesis-generating rather than definitive evidence of benefits.

This exploratory subgroup analysis of primary prevention patients enrolled 2100 patients to bempedoic acid and 2106 patients to placebo. Criteria for primary prevention were based on meeting at least one of the following: presence of either type 1 or 2 diabetes in women older than 65 years or men older than 60 years, Reynolds risk score >30% or SCORE risk score >7.5% over 10 years, or coronary artery calcium score >400 Agatston units at any time in the past. Enrollment of primary prevention patients was capped at 30% of the total population (which included a mixed population of primary and secondary prevention patients).

^Study Limitations[4]

This is a secondary analysis of a subpopulation in a larger randomized trial. Such analyses can result in false-positive findings due to the testing of multiple subgroups and may represent the play of chance

• The sample size represented a fraction of the total enrolled population, and the number of events was smaller, resulting in wider confidence intervals

• The inclusion of patients who reported inability to tolerate statins resulted in a high mean baseline LDL-C level. The effects of cholesterol lowering on cardiovascular events in populations with lower pretreatment LDL-C levels was not studied

• The trial selected patients using specific criteria for a high level of risk of a first cardiac event. Whether outcomes would be similar in patients identified using other criteria for an increased risk remains uncertain.

Additionally, NEXLIZET provides the proven primary & secondary CV risk reduction of NEXLETOL with even more LDL-C lowering. At week 12, NEXLIZET provides an **additional 38% mean placebo-corrected reduction from baseline on top of statins**[1,+].

[+]Study Design[1]

053 Trial: A 12-week, randomized, double-blind, Phase 3 trial in 301 patients with HeFH, established CVD, or multiple risk factors for CVD taking a maximally tolerated statin and randomized 2:2:2:1 to receive NEXLIZET (n=86), NEXLETOL (n=88), ezetimibe (n=86), or placebo (n=41). The primary endpoint was percent change from baseline to Week 12 in LDL-C. Results shown are based on a mean 38% placebo-corrected LDL-C reduction (-36% NEXLIZET vs +2% placebo).

IMPORTANT SAFETY INFORMATION

Hyperuricemia: Bempedoic acid, a component of NEXLIZET and NEXLETOL, may increase blood uric acid levels, which may lead to gout. Hyperuricemia may occur early in treatment and persist throughout treatment, returning to baseline following discontinuation of treatment. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.

Tendon Rupture: Bempedoic acid, a component of NEXLIZET and NEXLETOL, is associated with an increased risk of tendon rupture or injury. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders. Discontinue NEXLIZET or NEXLETOL at the first sign of tendon rupture. Consider alternative therapy in patients who have a history of tendon disorders or tendon rupture.

Please see additional Important Safety Information below.

IMPORTANT SAFETY INFORMATION CONTINUED

The most common adverse reactions in the primary hyperlipidemia trials of bempedoic acid, a component of NEXLIZET and NEXLETOL, in ≥2% of patients and greater than placebo, were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes.

Adverse reactions reported in ≥2% of patients treated with ezetimibe (a component of NEXLIZET) and at an incidence greater than placebo in clinical trials were upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza.

In the primary hyperlipidemia trials of NEXLIZET, the most commonly reported adverse reactions (incidence ≥3% and greater than placebo) observed with NEXLIZET, but not observed in clinical trials of bempedoic acid or ezetimibe, were urinary tract infection, nasopharyngitis, and constipation.

The most common adverse reactions in the cardiovascular outcomes trial for bempedoic acid, a component of NEXLIZET and NEXLETOL, at an incidence of ≥2% and 0.5% greater than placebo were hyperuricemia, renal impairment, anemia, elevated liver enzymes, muscle spasms, gout, and cholelithiasis.

Concomitant use of NEXLIZET or NEXLETOL with greater than 20 mg of simvastatin or 40 mg of pravastatin should be avoided due to the potential for increased risk of simvastatin or pravastatin-related myopathy.

Discontinue NEXLIZET or NEXLETOL when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. Because of the potential for serious adverse reactions in a breast-fed infant, breastfeeding is not recommended during treatment with NEXLIZET or NEXLETOL.

Report pregnancies to Esperion Therapeutics, Inc. Adverse Event reporting line at 1-833-377-7633.

Please see full Prescribing Information for ***NEXLIZET*** and ***NEXLETOL***.

HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; PCSK9=proprotein convertase subtilisin/kexin type 9; CVD=cardiovascular disease

References:
1. NEXLIZET. Prescribing information. Esperion Therapeutics, Inc.; 2024. 2. NEXLETOL. Prescribing information. Esperion Therapeutics, Inc.; 2024. 3. Nissen SE, Lincoff DB, Ray KK, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med. 2023;388:1353-1364. Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. 4. JAMA. 2023;330(suppl 2):131-140.

Esperion Therapeutics, Inc | 3891 Ranchero Drive, Suite 150, Ann Arbor, MI 48108