RXADVANCE
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NEW DRUG APPROVAL

Brand Name	Nexletol™
Generic Name	bempedoic acid
Drug Manufacturer	Esperion Therapeutics, Inc.

New Drug Approval

FDA Approval Date: February 21, 2020
Review Designation: New Chemical Entity
Type of Review: New Drug Application 211616

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Familial hypercholesterolaemia (FH) is the genetic disorder most commonly associated with elevated LDL cholesterol (LDL-C) levels from birth and with premature atherosclerotic cardiovascular disease (ASCVD). It is caused by mutations in genes related to the clearance of LDLs such as LDL receptor (*LDLR*), apolipoprotein B-100 (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*). The prognosis for patients with FH has improved in the past 30 years, with statins improving clinical outcomes and reducing total mortality.

Familial hypercholesterolemia (FH) is a common yet underdiagnosed autosomal dominant disorder that affects ≈1 in 220 individuals globally. FH is characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) and if untreated leads to early-onset atherosclerosis and increased risk of cardiovascular events. Affected men and women who are untreated have a 30% to 50% risk of a fatal or nonfatal cardiac event by ages 50 and 60 years, respectively.

Efficacy

The efficacy of NEXLETOL was investigated in two multi-center, randomized, double-blind, placebo-controlled trials that enrolled 3009 adult patients with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who were on maximally tolerated statin therapy. Demographics and baseline disease characteristics were balanced between the treatment arms in all trials. In both trials, the maximum LDL-C lowering effects occurred at Week 4. These results were consistent across all subgroups studied in any of the trials, including age, gender, race, ethnicity, region, history of diabetes, baseline LDL-C, body mass index (BMI), HeFH status, and background therapies.

Study 1 (NCT02666664)

Study 1 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. Efficacy of NEXLETOL was evaluated at Week 12. The trial included 2230 patients randomized 2:1 to receive either NEXLETOL (n = 1488) or placebo (n = 742) as add-on to a maximally tolerated lipid lowering therapy. Maximally tolerated lipid lowering therapy was defined as a maximally tolerated statin dose alone or in combination with other lipid-lowering therapies. Patients were stratified by presence of HeFH and by baseline statin intensity. Patients on simvastatin 40 mg per day or higher and patients taking PCSK9 inhibitors were excluded from the trial.

Overall, the mean age at baseline was 66 years (range: 24 to 88 years), 61% were ≥ 65 years old, 27% women, 2% Hispanic, 96% White, 3% were Black, and 1% Asian. Ninety-five percent (95%) of patients had established atherosclerotic cardiovascular disease, and 5% of patients had HeFH. Twenty-nine percent (29%) of patients had

diabetes at baseline. The mean baseline LDL-C was 103.2 mg/dL. At the time of randomization, all patients were receiving statin therapy and 50% were receiving high-intensity statin therapy.

The primary efficacy outcome measure of the study was the percent change from baseline to Week 12 in LDL-C. The difference between NEXLETOL and placebo in mean percent change in LDL-C from baseline to Week 12 was -18% (95% CI: -20%, -16%; $p < 0.001$). High-density lipoprotein (HDL) and triglycerides (TG) were examined as exploratory endpoints and were not included in the statistical hierarchy. The difference between NEXLETOL and placebo in mean percent change from baseline to Week 12 was -6% for HDL and median percent change from baseline to Week 12 was +3% for TG.

Study 2 (NCT02991118)

Study 2 was a multi-center, randomized, double-blind, placebo-controlled, 52-week trial in patients with HeFH and/or ASCVD. Efficacy of NEXLETOL was evaluated at Week 12. The trial included 779 patients randomized 2:1 to receive either NEXLETOL (n = 522) or placebo (n = 257) as add-on to a maximally tolerated lipid lowering therapy. Maximally tolerated lipid lowering therapy was defined as a maximally tolerated statin dose alone or in combination with other lipid-lowering therapies. Patients were stratified by presence of HeFH and baseline statin intensity. Patients on simvastatin 40 mg/day or higher were excluded from the trial.

Overall, the mean age at baseline was 64 years (range: 28 to 91 years), 51% were ≥ 65 years old, 36% women, 8% Hispanic, 94% White, 5% were Black, and 1% Asian. Ninety-five percent (95%) of patients had established atherosclerotic cardiovascular disease, and 5% of patients had HeFH. Thirty percent (30%) of patients had diabetes at baseline. The mean baseline LDL-C was 120.4 mg/dL. At the time of randomization, 90% of patients were receiving statin therapy, 53% were receiving high-intensity statin therapy, and 0.3% were receiving PCSK9 inhibitors.

The primary efficacy outcome measure of the study was the percent change from baseline to Week 12 in LDL-C. The difference between NEXLETOL and placebo in mean percent change in LDL-C from baseline to Week 12 was -17 % (95% CI: -21%, -14%; $p < 0.001$). HDL and TG were exploratory endpoints and not included in the statistical hierarchy. The difference between NEXLETOL and placebo in mean percent change from baseline to Week 12 was -6% for HDL and the median percent change from baseline was -2% for TG.

Safety

ADVERSE EVENTS

Most common (incidence ≥ 2% and greater than placebo) adverse reactions are upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes.

WARNINGS & PRECAUTIONS

Hyperuricemia: Elevations in serum uric acid have occurred. 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: Tendon rupture has occurred. Discontinue NEXLETOL at the first sign of tendon rupture. Avoid NEXLETOL in patients who have a history of tendon disorders or tendon rupture.

CONTRAINDICATIONS

None

NEW DRUG APPROVAL

Clinical Pharmacology

MECHANISMS OF ACTION

Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. Bempedoic acid and its active metabolite, ESP15228, require coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver. Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of low-density lipoprotein receptors.

Dose & Administration

ADULTS

Administer 180 mg orally once daily with or without food.

PEDIATRICS

The safety and effectiveness of NEXLETOL have not been established in pediatric patients.

GERIATRICS

Of the 3009 patients in clinical trials of NEXLETOL, 1753 (58%) were 65 years and older, while 478 (16%) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

RENAL IMPAIRMENT

No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is limited experience with NEXLETOL in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m2), and NEXLETOL has not been studied in patients with end-stage renal disease (ESRD) receiving dialysis.

HEPATIC IMPAIRMENT

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B). Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 180 mg