

Brand Name: Nexletol

Generic Name: bempedoic acid

Manufacturer¹: Esperion Therapeutics

Drug Class^{1,2,3,4,5}: adenosine triphosphate-citrate lyase (ACL) inhibitor, antilipemic agent

Uses:

Labeled Uses^{1,2,3,4,5}: Adjunct to diet and maximally tolerated statin therapy for treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease to reduce low-density lipoprotein cholesterol (LDL-C)

Unlabeled Uses^{1,2,3,4,5}: None at this time

Mechanism of Action^{1,2,3,4,5}:

Bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme located upstream from HMG-CoA reductase that links carbohydrate metabolism to the pathways for cholesterol and fatty synthesis within the liver. Bempedoic acid, an inactive prodrug, and its active metabolite, ESP15228, require coenzyme A (CoA) activation in the liver by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA. Inhibition of ACL by ETC-1002-CoA decreases cholesterol and fatty acid synthesis in the liver resulting in upregulation of low-density lipoprotein receptors and reduced LDL-C in blood.

Pharmacokinetics^{1,2,3,4,5}:

Absorption:

T _{max}	3.5 hours
V _d	18 L
T _{1/2}	21 ± 11 hours
Clearance	11.2 mL/min
Protein Binding	99.3% to plasma proteins
Bioavailability	Not reported

Metabolism: Bempedoic acid is primarily metabolized through acyl glucuronidation. Bempedoic acid is reversibly converted by aldo-keto reductase to its metabolite ESP15228. Both are converted to inactive glucuronide conjugates in vitro by UGT2B7.

Elimination: Primary elimination is through acyl glucuronidation. 70% of the dose was recovered in urine mainly in the form of the acyl glucuronide conjugate with less than 5% unchanged. 30% of the dose was recovered in feces with less than 5% unchanged.

Efficacy:

Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis*. 2018;277:195-203.

Study Design: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: *Methods:* After a 4-week ezetimibe 10 mg/day run-in period, 269 patients with a history of statin intolerance and an LDL-C >100 mg/dL while on stable lipid-modifying therapy were randomized 2:1 to treatment with bempedoic acid 180 mg or placebo once daily added to ezetimibe 10 mg/day for 12 weeks. Efficacy measures consisted of fasting lipid levels, apolipoprotein B, and hsCRP. Safety assessments included continuous monitoring of treatment-emergent AEs (TEAEs), clinical safety laboratory results physical examination findings, vital sign measurements, electrocardiograph readings, and weight measurements. *Outcome Results:* Bempedoic acid 180 mg once daily resulted in a placebo-corrected LS mean change in LDL-C of 28.5% (95% CI: 34.4%, 22.5%; $p < 0.001$) from baseline to week 12 ($n=181$) while placebo group ($n=81$) increased from 123.0 mg/dL at baseline to 128.8 mg/dL at week 12. Least-squares mean non-HDL-C, total cholesterol, and apoB decreased significantly from baseline to week 12 in the bempedoic acid treatment group but increased slightly among those who received placebo ($p < 0.001$).

Limitations: Multiple authors have received funding or are current or past employees of Esperion Therapeutics, the manufacturer of the study drug introducing a potential conflict of interest. Pill counts were the only method of tracking adherence, and at least 3 sites had issues with adherence and were excluded from results, affecting the power of the study. Patients included were on no more than a low dose statin, predominately white, and female making results difficult to extract to all patients on maximally tolerated statins.

Conclusion: The study showed that bempedoic acid as an adjunct to ezetimibe in patients with a history of statin intolerance who were on no more than low-dose statin therapy significantly lowered LDL-C compared to placebo. This supports the effectiveness of using bempedoic acid as an adjunct therapy to lower LDL. However, more studies need to be conducted with more patients with less stringent inclusion criteria and a longer duration to assess effectiveness for the treatment population.

Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N Engl J Med*. 2019;380(11):1022-1032.

Study Design: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: *Methods:* 2230 patients with a history of atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia with an LDL >70 mg/dL on a maximally tolerated statin were randomized 2:1 to receive bempedoic acid 180 mg daily or placebo for 52 weeks. Follow-up visits were conducted at weeks 4, 8, 12, 24, 36, and 52 and included the obtaining of fasting blood samples for biomarker measurements including LDL-C. Safety was assessed according to the incidence of adverse events and changes in safety laboratory variables. Levels of non-high-density lipoprotein (non-HDL) cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein were measured at baseline and week 12. *Outcome Results:* Treatment with bempedoic acid resulted in greater lowering of the LDL cholesterol level than was observed in the placebo group both at week 12 (difference, -18.1 percentage points; 95% confidence interval [CI], -20.0 to -16.1; $P < 0.001$) and at week 24 (difference, -16.1 percentage points; 95% CI, -18.2 to -14.0; $P < 0.001$). The differences in the changes from baseline, as compared with placebo, in the levels of non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein at week 12 were all significantly improved. Adverse events that occurred during the intervention period, regardless of causality, were reported in 1167 patients (78.5%) receiving bempedoic acid and in 584 (78.7%) receiving placebo, with the majority of events (in 982 of 1167 patients [84.1%] and 514 of 584 [88.0%], respectively) being graded as mild to moderate. The incidence of reported serious adverse events was generally small and similar in the two groups (216 patients [14.5%] in the bempedoic acid group and 104 [14.0%] in the placebo group). The percentage of patients who discontinued the blinded trial regimen owing to a reported adverse event was higher in the bempedoic acid group than in the placebo group (162 patients [10.9%] vs. 53 [7.1%]; $p = 0.005$).

Limitations: This study was sponsored by Esperion Therapeutics, the manufacturer of bempedoic acid. Multiple authors have received grants or personal fees from Esperion, introducing a potential conflict of interest. The study sample included more males than females and a large majority reported white race. This could make extrapolation of results more difficult for patients outside of this demographic. Maximally tolerated statin was determined by an investigator and includes the absence of a statin which could have resulted in a lack of uniformity.

Conclusion: The study provides substantial evidence that long-term bempedoic acid therapy as an adjunct to ACC/AHA and ESC/EAS guideline-based statin regimens appeared to have an acceptable safety profile. When added to mostly moderate-intensity or high-intensity statin therapy in this predominantly white trial population, treatment with bempedoic acid reduced the levels of LDL cholesterol, non-HDL cholesterol, total cholesterol, apolipoprotein B, and high-sensitivity C-reactive protein significantly, as compared with placebo, from baseline to week 12.

Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial [published correction appears in JAMA. 2020 Jan 21;323(3):282]. JAMA. 2019;322(18):1780-1788.

Study Design: Multicenter, multinational, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: *Methods:* 779 patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both with LDL-C level 70 mg/dL or greater while receiving maximally tolerated lipid-lowering therapy were randomized 2:1 to treatment with bempedoic acid 180 mg (n=522) or placebo (n=257) once daily for 52 weeks. Assessment of fasting lipids, including levels of LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, and triglycerides were collected at baseline and at weeks 4, 12, 24, and 52. apolipoprotein B (apoB) and high-sensitivity C-reactive protein (hsCRP) were measured at baseline and at weeks 12, 24, and 52. Safety and tolerability were assessed by treatment-emergent adverse events, laboratory findings, physical examination findings, vital sign measurements, and electrocardiogram readings. *Outcome Results:* At week 12, bempedoic acid lowered LDL-C levels significantly more than placebo (−15.1% vs 2.4%, respectively; $P < .001$). At week 24, change in LDL-C level from baseline was −12.1% in the bempedoic acid group and 2.7% in the placebo group (difference, −14.8% [95% CI, −19.5% to −10.0%]; $P < .001$). Significant reductions at week 12 with bempedoic acid vs placebo were observed for levels of non-HDL-C, total cholesterol, apoB, and hsCRP ($P < .05$). Changes from baseline in triglyceride levels were comparable between treatment groups, and statistically significant reductions in HDL-C levels were observed in the bempedoic acid group ($P < .001$). Treatment-emergent adverse events occurred in 70.1% of patients in the bempedoic acid group and 70.8% of patients in the placebo group. Serious adverse events occurred in 19.8% of patients (154/779). Three serious adverse events were considered to be at least possibly related to study treatment: ulcerative colitis and ischemic stroke in the bempedoic acid group and upper abdominal pain in the placebo group. Gout and increased blood uric acid level were experienced, respectively, by 2.1% and 2.7% of patients in the bempedoic acid group and 0.8% and 0.4% of patients in the placebo group. Overall, mean uric acid levels increased by 0.6 (SD, 1.2) mg/dL at week 52 in the bempedoic acid group compared with 0.1 (SD, 1.1) mg/dL in the placebo group (Table 3). Rates of aminotransferase level elevations greater than 3 times the upper limit of normal were 1.1% in the bempedoic acid group and 0.8% in the placebo group. Mean creatinine concentration increased by 0.05 (SD, 0.16) mg/dL and estimated glomerular filtration rate (calculated based on creatinine concentration) decreased by 3.8 (SD, 10.2) mL/min/1.73 m² from baseline to week 52 among patients who received bempedoic acid.

Limitations: This study was sponsored by Esperion Therapeutics, the manufacturer of bempedoic acid. Multiple authors have received grants or personal fees from Esperion,

introducing a potential conflict of interest. The study sample included more males than females and a large majority reported white race. This could make extrapolation of results more difficult for patients outside of this demographic. Differences in adverse events between groups were not statistically analyzed. This study was still only 52 weeks in duration and not powered to evaluate cardiovascular outcomes. Maximally tolerated lipid-lowering therapy was determined by the investigator and included a maximally tolerated statin dose alone or in combination with other approved lipid-lowering therapies which could have resulted in a lack of uniformity.

Conclusion: The study showed that the addition of bempedoic acid compared with placebo in patients taking maximally tolerated statins resulted in a significant lowering of LDL-C level over 12 weeks. The drug appeared to be fairly well tolerated by patients over the 52 weeks. More studies need to be conducted to assess the durability of clinical effects and long-term safety.

Contraindications^{1,2,3,4,5}: Specific contraindications have not been determined.

Precautions^{1,2,3,4,5}:

Hyperuricemia: Bempedoic acid inhibits OAT2 within the renal tubule and may lead to an increase in blood uric acid levels and the development of gout. Increases in serum uric acid have occurred within 4 weeks of treatment and persisted throughout treatment. Individuals with a history of gout have increased risk. Assess uric acid levels periodically as clinically indicated. Monitor patients for signs and symptoms and treat with urate-lowering drugs when deemed appropriate.

Tendon Rupture: Bempedoic acid is associated with an increased risk of tendon rupture and injury. In trials, tendon ruptures occurred in weeks to months of treatment initiation. Patients >60 years of age, those taking corticosteroid or fluoroquinolone drugs, and patients with renal failure were at increased risk. Consider alternative therapy in patients with a history of tendon disorders or rupture. Consider discontinuing therapy if joint pain, swelling, or inflammation occurs. Discontinue immediately if tendon rupture occurs.

Pregnancy: Discontinue bempedoic acid when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There is no available data on use in human pregnancy to determine drug-associated risk of major defects, miscarriage, or adverse maternal or fetal outcomes. Because cholesterol and products of the cholesterol synthesis pathway are essential for fetal development, the mechanism of action of bempedoic acid suggests in utero exposure may cause fetal harm and therefore cannot be ruled out.

Lactation: There is no information regarding the presence of bempedoic acid in human milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended.

Pediatric Use: Safety and effectiveness not established in pediatric patients.

Geriatric Use: Studies suggest bempedoic acid is safe and effective for geriatric use with no dosage adjustment necessary. Greater sensitivity of some older individuals cannot be ruled out.

Hepatic Disease: No dosage adjustment necessary in mild to moderate impairment (Child-Pugh class A and B). Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

Kidney Disease: No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is limited experience with bempedoic acid in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²).

Dialysis: Has not been studied in patients with end-stage renal disease (ESRD) receiving dialysis.

Adverse Effects^{1,2,3,4,5:}

Occurring in >10% of patients

Endocrine & metabolic

Gout (2% [placebo: 0.4%]; with prior gout history: 11% [placebo: 2%])

Hyperuricemia (4% to 26% [placebo: 1% to 10%])

Occurring in 1% to 10% of patients

Cardiovascular

Atrial fibrillation (2%)

Increased serum creatine kinase (1%)

Gastrointestinal

Abdominal distress (≤3%)

Abdominal pain (≤3%)

Genitourinary

Benign prostatic hyperplasia (1%)

Hematologic & oncologic

Anemia (3%)

Leukopenia (9%)

Thrombocytopenia (10%)

Hepatic

Increased liver enzymes (2%)

Increased serum aspartate aminotransferase (1%)

Neuromuscular & skeletal

Back pain (3%)
Limb pain (3%)
Muscle spasm (4%)

Renal

Increased blood urea nitrogen (4%)
Increased serum creatinine (2%)

Respiratory

Upper respiratory tract infection (5%)
Bronchitis (3%)

Occurring in <1% of patients

Neuromuscular & skeletal

Rupture of tendon 0.5% (placebo: 0%)

Drug Interactions^{1,2,3,4,5:}

Asunaprevir

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Asunaprevir.

Atorvastatin

Pharmacokinetic interactions between bempedoic acid and atorvastatin 10 mg were evaluated in clinical trials showing AUC elevations but were generally within the individual statin exposures and do not impact dosing recommendations.

Elagolix

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Elagolix.

Eluxadoline

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Eluxadoline. Management: Decrease the eluxadoline dose to 75 mg twice daily if combined with OATP1B1/1B3 inhibitors and monitor patients for increased eluxadoline effects/toxicities.

Grazoprevir

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Grazoprevir.

Probenecid

Administration of bempedoic acid 180 mg with steady-state probenecid resulted in a 1.7- and a 1.2-fold increase in bempedoic acid AUC and C_{max}, respectively. AUC and C_{max} for bempedoic acid active metabolite (ESP15228) were increased 1.9- and 1.5-fold, respectively.

Pravastatin

Bempedoic Acid may increase the serum concentration of Pravastatin. Management: Avoid coadministration of bempedoic acid with pravastatin doses greater than 40 mg due to the potential for increased pravastatin concentrations and pravastatin-related myopathy.

Revefenacin

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase serum concentrations of the active metabolite(s) of Revefenacin.

Rosuvastatin

Pharmacokinetic interactions between bempedoic acid and rosuvastatin 10 mg were evaluated in clinical trials showing AUC elevations but were generally within the individual statin exposures and do not impact dosing recommendations.

Simvastatin

Bempedoic Acid may increase the serum concentration of Simvastatin.
Management: Avoid coadministration of bempedoic acid with simvastatin doses greater than 20 mg due to the potential for increased simvastatin concentrations and simvastatin-related myopathy.

Voxilaprevir

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Voxilaprevir.

Dosing/Administration^{1,2,3,4,5:}

Adult Dosing

180 mg orally once daily in combination with maximally tolerated statin therapy; avoid concomitant use with simvastatin greater than 20 mg/day or pravastatin greater than 40 mg/day

Pediatrics

Safety and effectiveness not established in pediatric patients.

Elderly

No dosage adjustment necessary.

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. There is limited experience with bempedoic acid in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²).

Hepatic Impairment

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

Use in special circumstances:

Overdosage^{1:} There is no clinical experience with NEXLETOL overdose. In the event of an overdose, contact Poison Control (1-800-222-1222) for latest recommendations.

Conclusion:

Bempedoic Acid is an effective adjunct therapy for patients receiving maximally tolerated statins, including no statin, who have not met LDL-C goals. Bempedoic acid also has an additive

effect when combined with ezetimibe for lipid lowering therapy. The side effects and adverse effects of the drug appear to be minimal, but more studies are needed to look at adverse effects of special concern and long-term safety. More studies are also needed to look at the durability of clinical effect and use in special patient populations. A longer study is needed to assess the cardiovascular outcomes of this drug. With its tolerability and effectiveness, bempedoic acid will be useful as an adjunct to statins for lipid-lowering therapy. At this time, however, the price/month of roughly \$300 may not make this drug cost effective if trials of other alternative lipid lowering therapies have not been maximized.

Recommended References:

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5. Bempedoic Acid. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: <http://online.factsandcomparisons.com>. Accessed May 27, 2020.
6. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. *Atherosclerosis*. 2018;277:195-203.
7. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. *N Engl J Med*. 2019;380(11):1022-1032.
8. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial [published correction appears in JAMA. 2020 Jan 21;323(3):282]. *JAMA*. 2019;322(18):1780-1788.

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