PDL DRUG REVIEW

Proprietary Name: Nexletol®
Common Name: bempedoic acid
PDL Category: Antihyperlipidemics

Comparable Products	Preferred Drug List Status
Praluent	Non-Preferred with Conditions
Repatha	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Bempedoic acid, the active ingredient of Nexletol®, is an adenosine triphosphate-citrate lyase (ACL) inhibitor that lowers 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 mainly 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.

Indication: As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. The effect of Nexletol® on cardiovascular morbidity and mortality has not been determined.

There is no pregnancy category for this medication; however, the risk summary indicates to discontinue Nexletol® when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus. There are no available data on use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Nexletol® may cause fetal harm when given to a pregnant woman based on the mechanism of action. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 180mg

Recommended Dosage: In combination with maximally tolerated statin therapy, take 180mg PO QD, with or without food. After initiation of Nexletol®, analyze lipid levels within 8 to 12 weeks.

Dose adjustments are not required with mild or moderate renal impairment. There is limited experience with use in patients with severe renal impairment and use has not been studied in patients with end-stage renal disease (ESRD) receiving dialysis. Dose adjustments are not required with mild or moderate hepatic impairment. Patients with severe hepatic impairment have not been studied.

Drug Interactions: Concomitant use of Nexletol® with simvastatin causes an increase in simvastatin concentration and may increase the risk of simvastatin-related myopathy. Avoid concomitant use of Nexletol® with simvastatin greater than 20mg. Concomitant use of Nexletol® with pravastatin causes an increase in pravastatin concentration and may increase the risk of pravastatin-related myopathy. Avoid concomitant use of Nexletol® with pravastatin greater than 40mg.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Nexletol® plus statin ± other lipid lowering therapies) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included upper respiratory tract infection (0.5%), muscle spasms (1.3%), hyperuricemia (2.4%), back pain (1.1%), abdominal pain or discomfort (0.9%), bronchitis (0.5%), pain in extremity (1.3%), anemia (0.9%), and elevated liver enzymes (1.3%). Others included increased risk of tendon rupture (0.5%), increased risk of gout (1.1%), increased risk of BPH or prostatomegaly in men with no reported history of BPH (1.2%), and atrial fibrillation (0.6%).

Nexletol® inhibits renal tubular OAT2 and may increase blood uric acid levels. Elevated blood uric acid may lead to the development of gout. The risk for gout events was higher in patients with a prior history of gout (11.2% Nexletol® vs 1.7% placebo), although gout also occurred more often with Nexletol® than placebo in patients who had no prior gout history (1% Nexletol® vs 0.3% placebo). Advise patients to contact their healthcare provider if symptoms of hyperuricemia occur. Assess serum uric acid when clinically indicated. Monitor patients for signs and symptoms of hyperuricemia and start treatment with urate-lowering drugs as appropriate.

Nexletol® is associated with an increased risk of tendon rupture or injury. Tendon rupture occurred within weeks to months of starting Nexletol®, and it 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 treatment immediately if rupture of a tendon occurs. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Esperion Therapeutics, Inc

Analysis: The safety and efficacy of Nexletol® were assessed in two multicenter, randomized, double-blind, placebo-controlled studies (N=3009) that included adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who were on maximally tolerated statin therapy. In both studies, the maximum LDL-C lowering effects occurred at week 4.

Study 1 was a 52-week trial that assessed the safety and efficacy of bempedoic acid in patients with HeFH and/or ASCVD; however, efficacy was evaluated at week 12. The study included 2230 patients randomized to 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 on simvastatin ≥40mg/day (see comment in drug interaction section) and patients taking PCSK9 inhibitors were excluded from the trial. The mean age of included patients at baseline was 66 years, while 61% were ≥65 years of age. In addition, 27% were women, 95% had established ASCVD, 5% had HeFH, 29% had diabetes, and the mean baseline LDL-C was 103.2mg/dl. At the time of randomization, all patients were receiving statin therapy and 50% were receiving high-intensity statin therapy.

The primary outcome of this study was the percent change from baseline to week 12 in LDL-C. Results suggested that the difference between Nexletol® and placebo in mean percent change in LDL-C from baseline to week 12 was -18%, which was significantly different ($p<0.001$). HDL and triglycerides (TG) were examined as exploratory endpoints and were not included 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 to week 12 was +3% for TG. Results can be seen in the table below, which was adapted from the prescribing information.

	LDL-C	Non-HDL-C	Apo B	Total cholesterol
Nexletol® ± Statins ± Other lipid lowering therapies (N=1488)	-17	-12	-9	-10
Placebo (N=742)	2	2	3	1
Mean difference from placebo	-18	-13	-12	-11

Study 2 was a 52-week study that included patients with HeFH and/or ASCVD; however, efficacy was assessed at week 12. The study included 779 patients randomized 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 on simvastatin ≥40mg/day (see comment in drug interactions section) were excluded from the trial. The mean age of included patients at baseline was 64 years, with 51% being ≥65 years of age. In addition, 36% were women, 95% had established ASCVD, 5% had HeFH, 30% had diabetes at baseline, and the mean baseline LDL-C was 120.4mg/dl. At the time of randomization, 90% were receiving statin therapy, 53% were receiving high-intensity statin therapy, and 0.3% were receiving PCSK9 inhibitors.

The primary outcome was the percent change from baseline to week 12 in LDL-C. Results suggested that the difference between Nexletol® and placebo in mean percent change in LDL-C from baseline to week 12 was -17%, which was significantly different ($p<0.001$). 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. Results can be seen in the table below, which was adapted from the prescribing information.

	LDL-C	Non-HDL-C	Apo B	Total cholesterol
Nexletol® ± Statins ± Other lipid lowering therapies (N=522)	-15	-11	-9	-10
Placebo (N=257)	2	2	4	1
Difference from placebo	-17	-13	-13	-11

Place in Therapy: Nexletol® is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LCL-D. The effect of Nexletol® on cardiovascular morbidity and mortality has not been determined. This is the first agent in a new class of drugs designed to lower cholesterol levels. Two studies assessed the percent change from baseline to week 12 in LDL-C with Nexletol® as compared with placebo for the primary endpoint, and the difference was highly significant in favor of Nexletol®. Bempedoic acid is also being assessed as a combination treatment with ezetimibe. In a 2019 study by Ballantyne et al[2], bempedoic acid plus ezetimibe fixed-dose combination was significantly more effective than either individual agent for LDL-C reduction, the primary endpoint.

There is no evidence at this time to support that Nexletol® is safer or more effective than the currently available medications. It is therefore recommended that Nexletol® remain non-preferred and require prior authorization in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Nexletol [package insert]. Ann Arbor, MI: Esperion Therapeutics, Inc; 2020.

[2] Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol.* 2020; 27(6): 593-603.