bempedoic acid (Nexletol™) and bempedoic acid/ezetimibe (Nexlizet™) New Drug Update

April 2020

Nonproprietary Name	bempedoic acid; bempedoic acid/ezetimibe
Brand Name	Nexletol; Nexlizet
Manufacturer	Esperion
Form	Tablet
Strength	180 mg (Nexletol); 180 mg/10 mg (Nexlizet)
FDA Approval	February 21, 2020 (Nexletol); February 26, 2020 (Nexlizet)
Market Availability	Available (Nexletol); Launch anticipated in June 2020 (Nexlizet)
FDA Approval Classification	Standard Review for both
FDB Classification- Specific Therapeutic Class (HIC3)	Antihyperlipidemic – ATP Citrate Lyase (M4V) – Nexletol TBD - Nexlizet

INDICATION[1,2]

Bempedoic acid (Nexletol) is an adenosine triphosphate-citrate lyase (ACL) inhibitor and bempedoic acid/ezetimibe (Nexlizet) contains an ACL inhibitor and a cholesterol absorption inhibitor. Both agents are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein-cholesterol (LDL-C).

For both agents, the effect on cardiovascular (CV) morbidity and mortality has not been determined.

PHARMACOKINETICS

Time to maximum concentration (T_{max}) of bempedoic acid is 3.5 hours. Steady-state is achieved after 7 days. Concomitant food administration has no effect on the oral bioavailability. Main route of elimination is the metabolism of the acyl glucuronide. Bempedoic acid is also converted in a reversible manner to an active metabolite. Both compounds are then converted to inactive glucuronide conjugates. Mean elimination half-life at steady-state is 21 hours. Approximately 70% of the total dose is excreted in the urine and 30% in the feces. Less than 5% of the administered dose is excreted as unchanged.

The bioavailability of the fixed-dose bempedoic acid/ezetimibe tablets is similar relative to that for tablets of the individual components. Median T_{max} for ezetimibe is 5 hours. Administration with food has no clinically meaningful effect on drug exposure of the combination product. Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal

excretion. Elimination half-life of ezetimibe is 22 hours. Approximately 69% and 9% of the administered dose are recovered in the feces and urine, respectively.

CONTRAINDICATIONS/WARNINGS

There are no contraindications for use of bempedoic acid. Bempedoic acid/ezetimibe is contraindicated in patients with known hypersensitivity to ezetimibe. Anaphylaxis, angioedema, rash and urticaria have been reported with ezetimibe.

Treatment with bempedoic acid may increase the blood uric acid level. In clinical trials, 26% of patients treated with bempedoic acid and 9.5% treated with placebo experienced at least 1 episode of hyperuricemia. Elevated levels were most often reported within the first 4 weeks of treatment and persisted for the duration of treatment. After 12 weeks, the mean placebo-adjusted increase in uric acid from baseline was 0.8 mg/dL in those treated with bempedoic acid. Gout was reported in 1.5% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. Patients with prior history of gout are at increased risk.

An increased risk of tendon rupture is associated with bempedoic acid, which occurred in 0.5% of patients who received bempedoic acid in clinical trials compared to 0% of patients who received placebo. Tendon rupture occurred within weeks to months of starting bempedoic acid and may occur more often in patients > 60 years of age, taking corticosteroids or fluroquinolones, with renal failure, or with a history of tendon disorders. Bempedoic acid should be discontinued immediately if tendon rupture occurs.

DRUG INTERACTIONS

Concomitant use of bempedoic acid or bempedoic acid/ezetimibe with simvastatin or pravastatin may lead to an increased simvastatin or pravastatin concentration and increased risk of myopathy. Avoid concurrent use with simvastatin doses > 20 mg and pravastatin doses > 40 mg.

Concomitant use of bempedoic acid/ezetimibe and cyclosporine increases ezetimibe and cyclosporine concentrations. Cyclosporine levels should be monitored with concurrent use.

Fenofibrate and ezetimibe may each increase the risk of cholelithiasis. Co-administration of bempedoic acid/ezetimibe and fibrates, other than fenofibrate, is not recommended. If cholelithiasis is suspected in a patient receiving bempedoic acid/ezetimibe and fenofibrate, assess gallbladder function and consider alternative lipid-lowering therapy.

Concurrent use of bempedoic acid/ezetimibe and cholestyramine may decrease ezetimibe concentration. Bempedoic acid/ezetimibe should be administered at least 2 hours before or 4 hours after a bile acid sequestrant.

COMMON ADVERSE EFFECTS

In clinical trials, the most common (incidence ≥ 2%; versus placebo) adverse reactions reported with bempedoic acid were upper respiratory tract infection (4.5% versus 4%), muscle spasms (3.6% versus 2.3%), hyperuricemia (3.5% versus 1.1%), back pain (3.3% versus 2.2%), abdominal pain or discomfort

(3.1% versus 2.2%), bronchitis (3% versus 2.5%), pain in extremity (3% versus 1.7%), anemia (2.8% versus 1.9%), and elevated liver enzymes (2.1% versus 0.8%).

In clinical trials, the most common (incidence ≥ 2%; versus placebo) adverse reactions reported with ezetimibe were upper respiratory tract infection (4.3% versus 2.5%), diarrhea (4.1% versus 3.7%), arthralgia (3% versus 2.2%), sinusitis (2.8% versus 2.2%), extremity pain (2.7% and 2.5%), fatigue (2.4% and 1.5%), and influenza (2% and 1.5%).

SPECIAL POPULATIONS

Pregnancy

There are no available data on use of bempedoic acid in pregnant women to assess risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bempedoic acid and bempedoic acid/ezetimibe should be discontinued when pregnancy is recognized unless its benefits outweigh the potential risk to the fetus.

Pediatrics

Safety and efficacy of either product in pediatric patients have not been established.

Geriatric

In clinical trials, no overall differences in safety or effectiveness were observed between patients ages ≥ 65 years and younger patients for either product.

Hepatic Impairment

No dose adjustment of bempedoic acid is required in patients with mild or moderate hepatic impairment. Bempedoic acid has not been studied in those with severe hepatic impairment (Child-Pugh C).

Bempedoic acid/ezetimibe is not recommended with moderate or severe hepatic impairment (Child-Pugh B or C).

Renal Impairment

No dose adjustment of bempedoic acid or bempedoic acid/ezetimibe is required in patients with mild or moderate renal impairment. Data is lacking on use in patients with severe impairment and bempedoic acid has not been studied with end-stage renal disease.

DOSAGES

The recommended dosage of bempedoic acid is 180 mg orally once daily. The recommended dosage of bempedoic acid/ezetimibe is 1 tablet (180 mg/10 mg) orally once daily. Either product may be given with or without food.

Bempedoic acid and bempedoic acid/ezetimibe are given in combination with maximally tolerated statin therapy.

Bempedoic acid/ezetimibe tablet should be swallowed whole.

Lipid levels should be assessed within 8 to 12 weeks after starting therapy with bempedoic acid.

CLINICAL TRIALS[3,4,5,6,7,8]

A literature search was performed using "bempedoic acid" and "hyperlipidemia."

The CLEAR trial program includes four phase 3, double-blind, randomized clinical trials evaluating efficacy and safety of bempedoic acid.

The CLEAR Harmony 52-week trial enrolled adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated stain therapy with or without additional lipid-lowering therapies. Mean baseline LDL-C was 103.2 mg/dL. Mean age was 66.1 years. Key exclusion criteria were the use of gemfibrozil or simvastatin at doses > 40 mg per day. Use of a PCSK9 inhibitor was permitted after week 24 for patients with LDL-C > 170 mg/dL and an LDL-C increase by ≥ 25% from baseline. Patients were randomized to bempedoic acid 180 mg once daily (n=1,488) or matching placebo (n=742). At week 12, bempedoic acid resulted in the mean reduction of LDL -C by 19.2 mg/dL (difference from placebo in change from baseline, -18.1%; 95% confidence interval [CI], -18.2 to -14; p<0.001). Significant differences in changes from baseline compared to placebo were also seen in non-high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (apo-B), and high-sensitivity C-reactive protein (hsCRP) at week 12 (p<0.001 for all). Effect was seen through week 52 of the study. Efficacy did not depend on type or intensity of background lipid-lowering therapy. The frequency of most common adverse events were similar between the groups (e.g., nasopharyngitis, myalgia, upper respiratory tract infection, urinary tract infection, arthralgia, dizziness, muscle spasms, and diarrhea).

The CLEAR Wisdom 52-week trial included adults with ASCVD, HeFH, or both. Baseline LDL-C levels were ≥ 70 mg/dL while on maximally tolerated statin therapy. At baseline, mean LDL-C level was 120.4 mg/dL. Mean age was 64 years. Patients were randomized to bempedoic acid 180 mg once daily (n=522) or matching placebo (n=257) added to maximally tolerated lipid lowering therapy. At week 12, the difference in mean percent change in LDL-C from baseline between bempedoic acid and placebo was -17.4% (95% CI, -21% to -13.9%; p<0.001). Common adverse events included nasopharyngitis, urinary tract infection, and hyperuricemia.

The CLEAR Serenity trial randomized 345 patients with hypercholesterolemia and a history of intolerance to at least 2 statins. Baseline LDL-C levels were ≥ 130 mg/dL for primary prevention patients and ≥100 mg/dL for patients with HeFH while on maximally tolerated statin therapy. Mean age was 65.2 years and mean baseline LDL-C was 157.6 mg/dL. Patients were randomized to bempedoic acid 180 mg or placebo once daily for 24 weeks. Stable background lipid-lowering therapy was continued. At week 12, bempedoic acid significantly reduced LDL-C from baseline (difference from placebo, −21.4% [95% CI, −25.1% to −17.7%]; p<0.001). Significant reductions from baseline compared to placebo were also seen with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all). Bempedoic acid was well tolerated.

The CLEAR Tranquility trial enrolled adults with a history of statin intolerance and an LDL-C ≥ 100mg/dL while on stable lipid-lowering therapy. After a 4-week run-in period with ezetimibe 10 mg/day, patients were randomized to bempedoic acid 180 mg once daily (n=181) or placebo (n=88) as add-on to background lipid-lowering therapy that included ezetimibe 10 mg/day. The mean baseline LDL-C was 127.6 mg/dL. The mean age was 63.8 years. The change in LDL-C from baseline to week 12 was significantly greater with bempedoic acid compare to placebo (difference from placebo, -28.5% [95% CI, -34.4% to -22.5%; p<0.001). Significant reductions in LDL-C with bempedoic acid compared to placebo were recorded at week 4. In addition, significant reductions from baseline compared to placebo were

also observed with non-HDL-C, TC, apo-B, and hsCRP (p<0.001 for all). The study demonstrated minimal effect on triglyceride levels. Bempedoic acid was well tolerated.

An additional phase 3, double-blind clinical trial enrolled 301 adults with ASCVD, HeFH, or multiple CVD risk factors. Patients were randomized 2:2:2:1 to once daily fixed-dose combination of bempedoic acid/ezetimibe 180 mg/10 mg, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo as add-on to stable background statin therapy for 12 weeks. The mean LDL-C was 149.8 mg/dL at baseline. At week 12, all treatment groups resulted in significant reductions in LDL-C compared to placebo (fixed-dose combination: –36.2%; bempedoic acid alone: –17.2%; ezetimibe alone: –23.2%; placebo: 1.8%; p<0.001 for all compared to placebo). Adverse events were generally mild to moderate in severity and were reported more often in the fixed-dose combination and bempedoic acid groups.

OTHER DRUGS USED FOR CONDITION

Statin therapy is the treatment of choice for LDL-C lowering. Other classes include the apo-B synthesis inhibitor lomitapide (Juxtapid®), bile acid sequestrants (e.g., cholestyramine, colesevelam, colestipol), cholesterol absorption inhibitor ezetimibe (Zetia®), fibric acids (e.g., fenofibrate, fenofibric acid, gemfibrozil), niacin, and the PCSK9 inhibitors (e.g., alirocumab [Praluent®], evolocumab [Repatha®]).

PLACE IN THERAPY[9,10,11]

In the US, an estimated 33.5% of adults have high LDL-C, of which about one-third are in control. High cholesterol leads to an increase in heart disease risk by approximately 2-fold. Statins are the cornerstone treatment for hyperlipidemia, but their use can be limited by resistance and intolerance. When target cholesterol levels are not achieved despite maximally tolerated statin therapy, ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is added.

The guidelines by the American Heart Association (AHA) and American College of Cardiology (ACC) on management of blood cholesterol emphasize the importance of lifestyle therapies to reduce ASCVD risk. For primary prevention, they recommend statins in patients with severe hypercholesterolemia and in adults 40 to 75 years of age with diabetes mellitus or at higher ASCVD risk. For secondary prevention, in very high-risk ASCVD patients (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions), ACC/AHA considers the addition of ezetimibe to maximally tolerated statin therapy a reasonable option when the LDL-C level remains ≥ 70 mg/dL; if LDL-C level still remains ≥ 70 mg/dL after the addition of ezetimibe, then a PCSK9 inhibitor can be added. For LDL-C ≥ 190 mg/dL, high-intensity statin therapy is warranted regardless of ASCVD risk score; if LDL-C remains ≥ 100 mg/dL ezetimibe should be added; if LDL-C is still ≥ 100 mg/dL and the patient has multiple risk factors, addition of a PCSK9 inhibitor may be considered. Maximally tolerated statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C (≥ 190 mg/dL) at which time the addition of non-statin agents can be considered. Many non-statin therapies do not provide adequate ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

Bempedoic acid is the first ACL inhibitor approved in the US and it joins the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors as an option for LDL-C lowering in patients who are not at goal with diet and maximally tolerated statin therapy. Approval was given as a single-agent product as well as a fixed-dose combination with ezetimibe. In non-comparative clinical trials, PCSK9 inhibitors have demonstrated superior reductions in LDL-C compared to bempedoic acid (range, 55% to 59% compared

to range, 17% to 18%). While it is not associated with myalgias, as seen with statin therapy, it does carry risks for hyperuricemia and tendon rupture. A trial evaluating the effects of bempedoic acid on incidence of MACE in statin intolerant patients is ongoing; results are expected in second half of 2022.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Lipotropics, Other
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years of age**; AND** ▪ Patient has diagnosis of heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD); **AND** ▪ Patient has failed to achieve a target LDL-C despite physician attestation that the patient is adherent to maximally-tolerated doses of statins prior to the lipid panel demonstrating suboptimal reduction; **AND** ▪ Patient can be classified into ONE of the following risk factor groups: – Extremely high risk ASCVD: (defined as extensive or active burden of ASCVD, or ASCVD with extremely high burden of adverse or poorly controlled risk cardio-metabolic risk factors including HeFH or severe hypercholesterolemia [SH] LDL-C > 220 mg/dl) with an LDL-C ≥ 70 mg/dL; **OR** – Very high risk ASCVD: (defined as less extensive ASCVD and poorly controlled cardiometabolic risk factors) with an LDL-C ≥ 100 mg/dL; **OR** – High risk ASCVD: (defined as either less extensive ASCVD and well-controlled risk factors or primary prevention HeFH or SH >220 mg/dl with poorly controlled risk factors) with LDL-C ≥ 130 mg/dL; **AND** ▪ Therapy will be used in conjunction with maximally-tolerated doses of a statin; **AND** ▪ Therapy will not be used with concurrent doses of simvastatin > 20 mg or pravastatin > 40 mg; **AND** ▪ *For patients prescribed bempedoic acid/ezetimibe (Nexlizet*): patient does not have a hypersensitivity to ezetimibe (Zetia®)*;* **AND** ▪ *For patients prescribed bempedoic acid/ezetimibe (Nexlizet*): therapy will also not be used with concurrent fibrate therapy (excluding fenofibrate) **Renewal Criteria** ▪ Patient continues to meet the initial approval criteria listed above; **AND** ▪ Patient is absent of unacceptable toxicity from therapy. Examples of unacceptable toxicity include the following: hyperuricemia, tendon rupture; **AND**

	▪ Laboratory analysis demonstrate a reduction in LDL-C when compared to the baseline values (prior to initiating bempedoic acid or bempedoic acid/ezetimibe); **AND** ▪ Patient has shown continued adherence to maximally-tolerated statin dosage
Quantity Limit	30 tablets/30 days (Nexletol, Nexlizet)
Duration of Approval	Initial: 6 months Renewal: 1 year
Drug to Disease Hard Edit	None

REFERENCES

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