bempedoic acid, bempedoic acid/ezetimibe (Nexletol™, Nexlizet™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO182

Description

Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) is an orally administered adenosine triphosphate-citrate lyase inhibitor, and ezetimibe is an intestinal cholesterol absorption inhibitor.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
bempedoic acid (Nexletol)	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 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 ASCVD or high risk for a CVD event, but without established ASCVD	180 mg tablets	30 tablets/30 days
bempedoic acid/ezetimibe (Nexlizet)		180 mg/10 mg tablets	30 tablets/30 days

Initial Evaluation

I. **Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**

B. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g. cardiology, lipidology, endocrinology); **AND**
C. Therapy with a maximally tolerated statin for at least an 8-week duration has been ineffective; **AND**
    1. The member continues to have an LDL-cholesterol level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
    2. The member will continue maximally tolerated statin therapy in combination with bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet); **OR**
        i. The member has a history of statin intolerance defined as <u>failure</u> of TWO statin medications due to at least ONE of the following:
            a. CK exceeds 10 times the upper limit of normal
            b. LFTs exceed 3 times the upper limit of normal
            c. Severe rhabdomyolysis leading to hospitalization
            d. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **AND**
    3. The member will **<u>not</u>** use bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in combination with simvastatin (Zocor) >20 mg or pravastatin (Pravachol) >40 mg; **AND**
D. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
E. The member has a history of **atherosclerotic cardiovascular disease (ASCVD)**; **AND**
    1. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
    2. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **AND**
    3. Treatment with a PCSK9 inhibitor (e.g. alirocumab [Praluent]), evolocumab [Repatha]) or icosapent ethyl (Vascepa) has been ineffective, contraindicated, or not tolerated; **OR**
F. The member has a diagnosis of **heterozygous familial hypercholesterolemia (HeFH); AND**
    1. Diagnosis is confirmed by one of the following:
        i. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (Definite diagnosis classification) or Dutch Lipid Network criteria (score of at least 8)
        ii. Physical signs of familial hypercholesteremia (e.g., arcus cornealis, tendon xanthomas, xanthelasma)
        iii. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **AND**

2. Treatment with a PCSK9 inhibitor (e.g. alirocumab [Praluent]), evolocumab [Repatha]) or icosapent ethyl (Vascepa) has been ineffective, contraindicated, or tolerated; **OR**

G. The member has a diagnosis of **high risk for a cardiovascular (CVD) event in the absence of established ASCVD; AND**
   1. High risk for CVD event is defined as one of the following:
      i. Comorbid diagnosis of Type 1 or Type 2 diabetes mellitus in females age ≥65 years and males age ≥60 years
      ii. Reynolds Risk score >30% over 10 years
      iii. SCORE Risk score >7.5% over 10 years
      iv. ASCVD Risk score ≥20% over 10 years
      v. Coronary artery calcium score >400 Agatston units (current or historical)

II. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) are considered investigational when used for all other conditions, including but not limited to:
   A. Primary prevention of ASCVD in patients who are not at high risk for CVD event
   B. Homozygous familial hypercholesterolemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has experienced a decrease from baseline LDL while on therapy or LDL remains stable since previous renewal

Supporting Evidence

I. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) was primarily studied in patients over the age of 18 with a history of ASCVD, HeFH, or those considered at high risk for CVD events. Bempedoic acid (Nexletol) was also studied in multiple trials in patients that were intolerant to two different statins.
II. Bempedoic acid (Nexletol) has drug-drug interactions with doses of simvastatin >20 mg and pravastatin >40 mg due to the potential for increased risk of myopathy.
III. Statins remain the primary recommended treatment option for both cholesterol reduction and cardiovascular protection according to national guidelines. However, these medications are frequently discontinued due to side effects of myalgia and/or musculoskeletal pain; the

reported incidence is 5 to 20%, but incidence of true rhabdomyolysis is much smaller. The ACC Expert Consensus guidelines indicate that statin intolerance is generally defined as unacceptable muscle-related symptoms that resolve with discontinuation of therapy and recur with rechallenge on at least two (and preferably three) statins, preferably ones that are metabolized by different pathways and have different lipophilicity/hydrophilicity, and one of which is prescribed at the lowest approved dose. The majority of patients who experience statin-related muscle pain are able to tolerate statin rechallenge with an alternative statin or dose reduction with the same statin.

IV. **Clinical ASCVD and HeFH**

- Bempedoic acid (Nexletol) was studied in four randomized, double-blind, placebo-controlled Phase 3 trials, and bempedoic acid/ezetimibe (Nexlizet) was studied in one randomized, double-blind, four-arm, Phase 3 trial, in a total of 4,005 patients.
- The primary efficacy outcome was change in LDL from baseline to 12 weeks compared to placebo. Bempedoic acid (Nexletol) demonstrated reductions of -18.1% (95% CI -20%, -16.1%), -17.4% (95% CI -21%, -13.9%), -21.4% (95% CI -25.1%, -17.7%), -28.5% (95% CI -34.4%, -22.5%), for the Wisdom, Harmony, Serenity, and Tranquility trials respectively.
- Bempedoic acid/ezetimibe (Nexlizet) demonstrated a reduction in LDL of -38% (95% CI -46.5%, -29.6%) compared to placebo.
- Diagnosis of HeFH can be done using genetic testing or evaluation of clinical signs and symptoms. The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria (“definite FH” using either the Simon Broome or Dutch Lipid Network). These clinical criteria can be found in the appendix.
- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR, PCSK9,* or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with definite FH clinical syndrome.
- Clinical ASCVD is commonly diagnosed based on previous major adverse cardiovascular event (e.g., MI, stroke, stent placement, etc.). However, insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member’s clinical profile to determine individual patient risk and treatment, but should not necessarily be used alone for the purposes of clinical diagnosis.

V. **MACE Risk Reduction in patients at high risk for CVD Event**

- The safety and efficacy of bempedoic acid (Nexletol) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial in a total of 13,970 adult patients aged 18 to 85 years old who were considered statin intolerant. Enrolled patients had to meet criteria for increased cardiovascular risk, defined as a previous cardiovascular event (secondary prevention) or having clinical features that placed them at high risk for a cardiovascular (CVD) event (primary prevention). Primary prevention patients were required to have one of the following: diabetes mellitus (Type 1 or Type 2) in females age ≥65 years or males age ≥60 years, Reynolds risk score >30% or a SCORE risk score >7.5% over 10 years, or a coronary calcium score >400 Agatston units at any time in the past. At baseline, approximately 70% of the study population were classified as secondary prevention, while 30% were classified as primary prevention.
- The primary endpoint was time-to-first event for a four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular (CV) causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization. Key secondary endpoints were assessed in a hierarchical analysis and included a three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal MI, fatal or nonfatal MI, coronary revascularization, fatal or nonfatal stroke, death from CV causes, and death from any cause. The primary and first three key secondary endpoints (three-composite MACE, fatal or nonfatal MI, coronary revascularization) were met and considered statistically significant in favor of bempedoic acid (Nexletol). The results for the other key secondary end points (fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause) did not differ significantly between the bempedoic acid group and the placebo group after a median of 40.6 months of follow-up.
- Although it was not reported as a formal endpoint, reduction in LDL-C from baseline was also measured and reported during the clinical trial period. The mean baseline LDL-C was 139mg/dL in both the bempedoic acid and placebo groups. After 6 months of treatment with bempedoic acid, the mean LDL-C was 107 mg/dL, as compared with 136 mg/dL with placebo, for a difference of 29.2 mg/dL; the observed difference in the percent reductions was 21.1 percentage points (95% confidence interval [CI], 20.3 to 21.9) in favor of bempedoic acid. According to trial investigators, the time-averaged reduction in LDL cholesterol level of 22.0 mg per deciliter over the duration of the trial would be expected to lead to the approximate relative reduction in the risk of cardiovascular events that was observed.
- While the Reynolds Risk score and SCORE risk score were the primary cardiovascular risk assessment tools utilized in the clinical trial, they have limited utility in clinical practice in the United States. The ASCVD risk calculator is the most highly utilized

cardiovascular risk assessment tool used by health care practitioners in the United States; the ACC defines high risk as a score of ≥20% over a 10-year period.

VI. AHA/ACC, ESC/EAS, AACE, and NLA guidelines have not been updated to include bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in the treatment of dyslipidemia. Guidelines currently recommend the use of statins, ezetimibe (Zetia), evolocumab (Repatha), alirocumab (Praluent), and icosapent ethyl (Vascepa) due to their evidence for reducing cardiovascular events.

VII. According to the 2022 ACC Expert Consensus guidance on the non-statin therapies in the management of ASCVD risk, bempedoic acid can be considered as a treatment option for patients who are unable to take statins due to side effects and do not have clinical ASCVD. Guidelines note that after intolerance to at least two (preferably three) statins, adult patients without clinical ASCVD, either with diabetes or without diabetes with additional CVD risk factors, may consider first-line therapy with ezetimibe (Zetia), second-line therapy with bile acid sequestrants (BAS) [e.g., cholestyramine, colestipol, etc.], and third-line therapy with bempedoic acid (Nexletol). While bile acid sequestrants are recommended by the guidelines, these agents have numerous drug-drug interactions, which severely limits their utilization in clinical practice. In patients with clinical ASCVD who are statin intolerant, guidelines recommend the use of either ezetimibe (Zetia) or PCSK9-inhibitors as first-line therapy, depending on the patient's clinical scenario, and bempedoic acid and inclisiran as second-line treatment options.

VIII. Ezetimibe (Zetia) is a common, widely utilized add-on therapy to statin therapy and has well-known safety and efficacy. Ezetimibe (Zetia) also has data on cardiovascular outcomes and has evidence for benefit in patients being treated for dyslipidemia.

Investigational or Not Medically Necessary Uses

I. Primary prevention of ASCVD in patients who are not at high risk for CVD event
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in reducing/preventing ASCVD in patients who are not at high risk for CVD event.

II. Homozygous familial hypercholesterolemia
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in patients with homozygous familial hypercholesterolemia.

Appendix

I. **Heterozygous familial hypercholesterolemia: Diagnosis criteria tables**

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	**Description**

A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia	
Criteria	**Points**
Family history	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis, or • Children <18 years of age with LDL-C above the 95th percentile	2
Clinical History	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	
• Tendinous xanthomata	6
• Arcus cornealis before age 45 years	4
LDL-C levels	
• LDL-C ≥8.5 mmol/L (325 mg/dL)	8
• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)	5
• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)	1
DNA analysis	

• Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained) • A "definite" FH diagnosis requires >8 points • A "probable" FH diagnosis requires 6-8 points • A "possible" FH diagnosis requires 3-5 points	

References

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3. 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. JAMA. 2019;322(18):1780-1788.
4. 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.
5. 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.
6. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. J Am Heart Assoc. 2019;8(7):e011662.
7. 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. 2019;:2047487319864671.
8. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024
9. Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies of LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. J Am Coll Cardiol. 2022;80:1266-1418.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors	Heterozygous familial hypercholesterolemia (HeFH)
	Homozygous familial hypercholesterolemia (HoFH)
	Established atherosclerotic cardiovascular disease (ASCVD)
	Non-familial hypercholesterolemia

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication criteria for high risk for a cardiovascular (CVD) event in the absence of established ASCVD; Updated supporting evidence. Updated initial authorization duration from 6 months to 12 months.	05/2024
Updated supporting evidence	12/2020

Policy created	05/2020