Original Effective Date: 04/2020
Current Effective Date: 04/04/2025
Last P&T Approval/Version: 01/29/2025
Next Review Due By: 01/2026
Policy Number: C18441-A

Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe)

PRODUCTS AFFECTED

Nexletol (bempedoic acid), Nexlizet (bempedoic acid and ezetimibe)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Primary hyperlipidemia, Heterozygous familial hypercholesterolemia (HeFH), Clinical atherosclerotic cardiovascular disease (ASCVD)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PRIMARY HYPERLIPIDEMIA:
1. Documented diagnosis of primary hyperlipidemia (including heterozygous familial

hypercholesterolemia]HeFH])
AND

2. Documentation that other secondary causes of dyslipidemia have been excluded or maximally treated (e.g., high triglycerides, hypothyroidism, etc.)
AND
3. Documentation of NO concurrent therapy with simvastatin doses greater than 20 mg or pravastatin doses greater than 40 mg
AND
4. Documentation member is taking a maximally tolerated intensity/dose of statin OR has an FDA labeled contraindication to statins OR had serious side effects and is unable to tolerate an alternative dosing schedule (i.e., every other day dosing)
AND
5. Documentation member is taking ezetimibe 10mg daily OR has an FDA labeled contraindication or serious side effects
AND
6. Documentation of current (prior to requested therapy) LDL-C (within the last 3 months)
AND
7. Documentation in treatment plan member will be adherent to bempedoic acid therapy AND continue adherence to maximally tolerated dose/intensity statin (unless contraindicated as documented above) AND For Nexletol requests only: adherence to ezetimibe 10 mg/day (unless contraindicated as documented above). *Molina Reviewer Note: Verify member's medication fill history for compliance statin therapy AND ezetimibe*

B. HYPERLIPIDEMIA ASSOCIATED WITH CLINICAL ATHEROSCLEROTIC CARDIOVASCULAR DISEASE:

1. (a) Documentation of major clinical atherosclerotic cardiovascular disease (ASCVD) defined as ONE of the following:
    I. Recent acute coronary syndrome (ACS) (within the past 12 months)
    II. Myocardial infarction (MI)
    III. Ischemic stroke
    IV. Symptomatic PAD

   OR

   (b) Documentation member has as least ONE for the following high risk factors for future ASCVD event:
    I. Age greater than 65 years
    II. Current daily cigarette smoking
    III. Heterozygous familial hypercholesterolemia
    IV. History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
    V. Diabetes
    VI. Hypertension
    VII. CKD (eGFR 15-59 mL/min/1.73m2)
    VIII. Persistently elevated LDL-C (> 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
    IX. History of congestive heart failure

   AND
2. Appropriate lifestyle modifications have been implemented, including adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight that will continue during treatment, supported by documentation of counseling in chart notes
AND
3. Documentation that other secondary causes of dyslipidemia have been excluded or maximally treated (e.g., high triglycerides, hypothyroidism, etc.)
AND
4. Documentation of ONE of the following: a current LDL-C between 70-189 mg/dL OR patient requires greater than 25 percent additional lowering of LDL-C OR patient has had a recent

acute coronary syndrome (less than 3 months)
AND

5. Documentation of a therapeutic failure, serious side effects, or contraindication to high-intensity statin therapy shown by ONE of the following:
   (a) Adherent* to maximally tolerated high-intensity statin therapy (daily dose of atorvastatin 40 to 80 mg or rosuvastatin 20 to 40mg) and ezetimibe 10mg/day along with lifestyle modifications AND Inability to achieve and maintain an LDL cholesterol level at or below goal (< 100 mg/dL or < 70 mg/dL based on patient risk) by documentation of ONE of the following:
      i. LDL-C greater than goal (≥ 70 mg/dL for ASCVD or ≥100 mg/dL for HeFH) OR
      ii. Has not achieved a 50% reduction in LDL-C from baseline without meeting treatment goal
   *NOTE: Adherence is defined as at least 85% of the time as confirmed by claims history for at least 180 days OR attestation from the Prescriber.
   OR
   (b) Member has ANY of the following contraindication(s) to statin therapy: Hypersensitivity to statins or any component of the product, Active liver disease or elevated CK levels (defined as >10 times the Upper Limit of Normal [ULN]), Unexplained persistent elevation of hepatic transaminases (greater than 3 times the ULN occurring on 2 or more occasions), Women who are pregnant or may become pregnant or breastfeeding
   NOTE: Laboratory tests showing evidence of muscle inflammation, alterations of liver function tests from baseline and/or liver damage required
   OR
   (c) Documented therapeutic failure or intolerance to switching to a low- or moderate- intensity statin (e.g., simvastatin, pravastatin) OR alternative dosing schedule (i.e., every other day dosing)
   AND
6. Documentation in treatment plan member will be adherent to bempedoic acid therapy AND continue adherence to maximally tolerated dose/intensity statin (unless contraindicated as documented above) AND For Nexletol requests only: adherence to ezetimibe 10 mg/day.
   Molina Reviewer Note: Verify member's medication fill history for compliance statin therapy AND ezetimibe
   AND
7. Documentation of NO concurrent therapy with simvastatin doses greater than 20 mg or pravastatin doses greater than 40 mg

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Documented positive response to therapy as indicated by decrease in LDL-C OR achievement of individual LDL-C patient goal
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
4. Documentation that requested agent will continue to be used in combination with a maximally tolerated statin and For Nexletol requests only: ezetimibe or member has an FDA labeled contraindication or serious side effects to statins and ezetimibe

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
None

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
180mg orally once daily

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitor, Intestinal Cholesterol Absorption Inhibitor

FDA-APPROVED USES:
Nexletol is indicated:
• 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 cardiovascular disease (CVD), or
- a high risk for a CVD event but without established CVD.

• As an adjunct to diet, in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).

Nexlizet is indicated:
• As an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH).
The bempedoic acid component of NEXLIZET is indicated:
• 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 cardiovascular disease (CVD), or
- a high risk for a CVD event but without established CVD.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease in adults who require additional lowering of LDL-C. Bempedoic acid is an inactive prodrug that requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1). Since ACSVL1 is primarily located in the liver and not in adipose tissue or muscle, it is theorized to have reduced adverse effects, such as myotoxicity, due to minimal exposure to non-hepatic tissues. In a 52-week, clinical study involving patients with atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia or both, addition of bempedoic acid to maximally-tolerated statin therapy (with or without additional lipid-lowering therapy) resulted in mean percentage reductions in LDL-C from baseline of 16.5%, 14.9%, and 12.6% at weeks 12, 24, and 52, respectively. LDL-C reductions were significantly greater with bempedoic acid compared to placebo with a difference of -18.1% at week 12 (95% CI:-20 to -16.1; p less than 0.001) and -16.1% at week 24 (95% CI: -18.2 to -14; p less than 0.001). Hyperuricemia and tendon rupture have been reported with bempedoic acid therapy. This drug may increase the concentrations of pravastatin and simvastatin and increase the risk of statin-induced myopathy; thus, it is recommended to avoid coadministration of bempedoic acid with simvastatin at doses greater than 20 mg and pravastatin at doses greater than 40 mg.

The CLEAR Outcomes trial evaluating bempedoic acid in cardiovascular outcomes in statin-intolerant patients was published in 2023. The trial demonstrated that bempedoic acid significantly reduced the risk of major adverse cardiovascular events (MACE) in patients who were intolerant to statins. Specifically, the primary outcome—a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization—occurred in 11.7% of patients receiving bempedoic acid, compared to 13.3% in the placebo group, reflecting a hazard ratio of 0.87 (95% CI, 0.79 to 0.96; P=0.004).

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies

Since publication of the 2018 AHA/ACC/multisociety cholesterol guideline, 3 additional nonstatin therapies— bempedoic acid, evinacumab, and inclisiran—have received FDA approval for management of hypercholesterolemia. While awaiting ongoing cardiovascular outcomes trials and subsequent revision of evidence-based guidelines, the ACC recognized that clinicians, patients, and payers may seek more specific recommendations on when to use newer nonstatin therapies if the response to statin therapy, ezetimibe, and/or PCSK9 mAbs is deemed inadequate.

Bempedoic acid is administered orally as a prodrug and is activated by very long-chain acyl-CoA synthetase-1, an enzyme present in liver cells, but not muscle cells. This has been considered a possible advantage in patients with statin-associated muscle symptoms. The CLEAR Tranquility (Evaluation of the Efficacy and Safety of Bempedoic Acid [ETC-1002] as Add-on to Ezetimibe Therapy in Patients With Elevated LDL-C) and CLEAR Serenity (Evaluation of the Efficacy and Safety of Bempedoic Acid in Patients With Hyperlipidemia and Statin Intolerant) trials have demonstrated that monotherapy with bempedoic acid 180 mg daily in patients with statin-associated muscle symptoms on no statin therapy reduced LDL-C levels by approximately 24.5% compared with placebo.11-13 In patients with ASCVD, heterozygous familial hypercholesterolemia (HeFH), or multiple cardiovascular risk factors, bempedoic acid added to statin therapy resulted in an additional 15% to 17.8% reduction in LDL-C. Bempedoic acid 180 mg is also available in a combination preparation with ezetimibe 10 mg. When this combination agent was administered to patients with ASCVD, HeFH, or multiple ASCVD risk factors on statin therapy, there was an additional 38% reduction in LDL-C.16 Bempedoic acid and the fixed-dose combination with ezetimibe were FDA approved in 2020 and are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD who require additional lowering of LDL-C. At the time of this ECDP, the multinational cardiovascular outcomes trial of bempedoic acid, CLEAR Outcomes (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo), is in progress with expected completion in late 2022.

If additional LDL-C lowering is warranted (patient has achieved <50% reduction in LDL-C or LDL-C $\geq$ 55 mg/dL or non–HDL-C $\geq$ 85 mg/dL) despite maximally tolerated statin therapy, ezetimibe, and a PCSK9 mAb, the addition of bempedoic acid may be considered. Although there are currently no outcome studies for bempedoic acid, this agent may be beneficial for further LDL-C reduction or if evidence-

based agents are contraindicated or not tolerated. Considerations that may favor the addition of bempedoic acid include the need for further LDL-C reduction (with a mean expected reduction of approximately 17%) and documented statin intolerance. Bempedoic acid should be used with caution in patients who have a history of gout or tendon rupture.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Nexletol (bempedoic acid) and Nexlizet (bempedoic acid and ezetimibe) include: concomitant use of Nexletol or Nexlizet with simvastatin greater than 20 mg, concomitant use of Nexletol or Nexlizet with pravastatin greater than 40 mg. Additional contraindications to Nexlizet (bempedoic acid and ezetimibe) include: known hypersensitivity to ezetimibe tablets.

OTHER SPECIAL CONSIDERATIONS:

Hyperuricemia:

Bempedoic acid inhibits renal tubular OAT2 and may increase blood uric acid levels. In clinical trials, 26% of bempedoic acid-treated patients with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. After 12 weeks of treatment, the mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients treated with bempedoic acid. Elevated blood uric acid may lead to the development of gout. Gout was reported in 1.5% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. The risk for gout events was higher in patients with a prior history of gout (11.2% bempedoic acid versus 1.7% placebo), although gout also occurred more frequently than placebo in patients treated with bempedoic acid who had no prior gout history (1.0% bempedoic acid versus 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 initiate treatment with urate-lowering drugs as appropriate.

Tendon Rupture:

Bempedoic acid is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with bempedoic acid versus 0% of placebo-treated patients and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting bempedoic acid. Tendon rupture 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 bempedoic acid immediately if the patient experiences rupture of a tendon. Consider discontinuing bempedoic acid if the patient experiences joint pain, swelling, or inflammation. Advise patients to rest at the first sign of tendinitis or tendon rupture and to contact their healthcare provider if tendinitis or tendon rupture symptoms occur. Consider alternative therapy in patients with a history of tendon disorders or tendon rupture.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical*

Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Nexletol TABS 180MG
Nexlizet TABS 180-10MG

REFERENCES

1. Nexletol (bempedoic acid) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc.; March 2024.
2. Nexlizet (bempedoic acid and ezetimibe) [prescribing information]. Ann Arbor, MI: Esperion Therapeutics, Inc.; March 2024.
3. Baigent C, Keech A, Kearney PM, et al, for the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet. 2005;366(9493):1267- 1278.
4. Blom DJ, Hala T, Bolognese M, et al, for the DESCARTES Investigators. A 52-week placebo- controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370:1809-1819. [Supplemental Appendix].
5. Cholesterol Treatment Trialists' (CCT) Collaborators, Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol lowering therapy in 18,686 people with diabetes in 14 randomized trials: a meta-analysis. Lancet. 2008;371(9607)117-125.
6. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581-590.
7. Cuchel M, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholestolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35:2146-2157.
8. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. J Clin Lipidol. 2011;5:S1-S8.
9. Guyton JR, Bays HE, Grundy SM, Jacobson TA. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol. 2014;8:S72-S81.
10. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient- centered management of dyslipidemia: Part 1-executive summary. J Clin Lipidol. 2014;8:473-488. Available at: http://www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf.
11. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient- centered management of dyslipidemia: Part 1-full report. J Clin Lipidol. 2015;9:129-169.
12. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic Experience. Am Heart J. 2013;166(3):597-603.
13. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boré n J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjærg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the

European Atherosclerosis Society. Eur Heart J 2013;34:3478–3490.
14. Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol. 2014;8:S58-S71.
15. Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ1991;303:893–6.
16. Nicholls, S., Lincoff, A. M., Bays, H. E., Cho, L., Grobbee, D. E., Kastelein, J. J., Libby, P., Moriarty, P. M., Plutzky, J., Ray, K. K., Thompson, P. D., Sasiela, W., Mason, D., McCluskey, J., Davey, D., Wolski, K., & Nissen, S. E. (2021). Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. American heart journal, 235, 104–112. https://doi.org/10.1016/j.ahj.2020.10.060
17. Lloyd-Jones, D. M., Morris, P. B., Ballantyne, C. M., Birtcher, K. K., Covington, A. M., DePalma, S. M., Wilkins, J. T. (2022). 2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk. Journal of the American College of Cardiology, 80(14), 1366-1418. doi:10.1016/j.jacc.2022.07.006

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy FDA-Approved Uses Background Available Dosage Forms References	Q1 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Quantity FDA-Approved Uses References	Q1 2024
REVISION- Notable revisions: Diagnosis Required Medical Information Continuation of Therapy Duration of Approval Drug Class FDA-Approved Uses Background Contraindications/Exclusions/Discontinuation References	Q1 2023
Q2 2022 Established tracking in new format	Historical changes on file