

## Clinical Policy: Bempedoic Acid (Nexletol), Bempedoic Acid/Ezetimibe (Nexlizet)

Reference Number: ERX.NPA.143

Effective Date: 09.01.20

Last Review Date: 02.22

Line of Business: Commercial, Medicaid

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

### Description

The following are adenosine triphosphate-citrate lyase (ACL) inhibitors requiring prior authorization: bempedoic acid (Nexletol<sup>™</sup>) and bempedoic acid/ezetimibe (Nexlizet<sup>™</sup>). Nexlizet contains ezetimibe, which is a cholesterol absorption inhibitor.

### FDA Approved Indication(s)

Nexletol and Nexlizet are indicated for use as adjuncts 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).

Limitation(s) of use: The effect of Nexletol and Nexlizet on cardiovascular morbidity and mortality has not been determined.

### Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions<sup>™</sup> that Nexletol and Nexlizet are **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease

(must meet all):

1. Diagnosis of one of the following (a or b):
  - a. ASCVD as evidenced by a history of any one of the following conditions (i-vii):
    - i. Acute coronary syndromes;
    - ii. Clinically significant coronary heart disease (CHD) diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging);
    - iii. Coronary or other arterial revascularization;
    - iv. Myocardial infarction;
    - v. Peripheral arterial disease presumed to be of atherosclerotic origin;
    - vi. Stable or unstable angina;
    - vii. Stroke or transient ischemic attack (TIA);
  - b. HeFH, and member meets both of the following (i and ii):
    - i. Baseline LDL-C (prior to any lipid-lowering pharmacologic therapy) was  $\geq 190$  mg/dL;
    - ii. HeFH diagnosis is confirmed by one of the following (a or b):
      - a) World Health Organization (WHO)/Dutch Lipid Network familial hypercholesterolemia diagnostic criteria score of  $> 8$  as determined by requesting provider (*see Appendix D*);
      - b) Definite diagnosis per Simon Broome criteria (*see Appendix D*);
2. Prescribed by or in consultation with a cardiologist, endocrinologist, or lipid specialist;

3. Age ≥ 18 years;
4. For members on statin therapy, both of the following (a and b):
  - a. Nexletol or Nexlizet is prescribed in conjunction with a statin at the maximally tolerated dose;
  - b. Member has been adherent for at least the last 4 months to maximally tolerated doses of one of the following statin regimens (i, ii, or iii):
    - i. A high intensity statin (*see Appendix E*);
    - ii. A moderate intensity statin (*see Appendix E*), and member has one of the following (a or b):
      - a) Intolerance to two high intensity statins;
      - b) A statin risk factor (*see Appendix G*);
    - iii. A low intensity statin, and member has one of the following (a or b):
      - a) Intolerance to one high and one moderate intensity statins;
      - b) A statin risk factor (*see Appendix G*) and history of intolerance to two moderate intensity statins;
5. For members not on statin therapy, member meets one of the following (a or b):
  - a. Statin therapy is contraindicated per Appendix F;
  - b. For members who are statin intolerant, member has tried at least two statins, one of which must be hydrophilic (pravastatin, fluvastatin, or rosuvastatin), and member meets one of the following (i or ii):
    - i. Member has documented statin risk factors (*see Appendix G*);
    - ii. Member is statin intolerant due to statin-associated muscle symptoms (SAMS) and meets both of the following (a and b):
      - a) Documentation of intolerable SAMS persisting at least two weeks, which disappeared with discontinuing the statin therapy and recurred with a statin re-challenge;
      - b) Documentation of re-challenge with titration from lowest possible dose and/or intermittent dosing frequency (e.g., 1 to 3 times weekly);
6. Member has been adherent to ezetimibe therapy used concomitantly with a statin at the maximally tolerated dose for at least the last 4 months, unless contraindicated per Appendix F or member has a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
7. For Nexletol, documentation that ezetimibe will be prescribed concurrently for as long as Nexletol is prescribed, unless contraindicated per Appendix F or member has a history of ezetimibe intolerance (e.g., associated diarrhea or upper respiratory tract infection);
8. Documentation of recent (within the last 60 days) LDL-C of one of the following (a or b):
  - a. ≥ 70 mg/dL for ASCVD;
  - b. ≥ 100 mg/dL for HeFH;
9. Treatment plan does not include coadministration with Repatha® or Praluent®;
10. Dose does not exceed either of the following (a or b):
  - a. Nexletol: 180 mg per day;
  - b. Nexlizet: bempedoic acid 180 mg/ezetimibe 10 mg per day.

**Approval duration: 12 months**

**B. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. All Indications in Section I (must meet all):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met all initial approval criteria;
2. If statin tolerant, documentation of adherence to a statin at the maximally tolerated dose;
3. For Nexletol, documentation that ezetimibe is being prescribed concurrently with Nexletol, unless a contraindication or adverse event to ezetimibe has developed;

4. Member is responding positively to therapy as evidenced by lab results within the last 3 months showing an LDL-C reduction since initiation of Nexletol or Nexlizet therapy;
5. If request is for a dose increase, new dose does not exceed either of the following (a or b):
  - a. Nexletol: 180 mg per day;
  - b. Nexlizet: bempedoic acid 180 mg/ezetimibe 10 mg per day.

**Approval duration: 12 months**

**B. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 12 months (whichever is less);** or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

ASCVD: atherosclerotic cardiovascular disease  
 CHD: coronary heart disease  
 FDA: Food and Drug Administration  
 HeFH: heterozygous familial hypercholesterolemia

LDL-C: low density lipoprotein cholesterol  
 SAMS: statin-associated muscle symptoms  
 TIA: transient ischemic attack  
 WHO: World Health Organization

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ezetimibe (Zetia®)	10 mg PO QD	10 mg/day
atorvastatin (Lipitor®)	40 mg PO QD	80 mg/day
rosuvastatin (Crestor®)	5 - 40 mg PO QD	40 mg/day

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Nexletol: none reported
  - Nexlizet: known hypersensitivity to ezetimibe tablets
- Boxed warning(s): none reported

*Appendix D: Criteria for Diagnosis of HeFH*

- Dutch Lipid Clinic Network criteria for Familial Hypercholesterolemia (FH)

FH Criteria	Points	Member's Score†
<b>Family History</b>		
First-degree relative with known premature* coronary and vascular disease	1	Place highest score here (0, 1 or 2)
First-degree relative with known LDL-C level above the 95 <sup>th</sup> percentile	1	

FH Criteria	Points	Member's Score†
First-degree relative with tendinous xanthomata and/or arcus cornealis	2	
Children aged < 18 years with LDL-C level above the 95 <sup>th</sup> percentile	2	
<b>Clinical History</b>		
Patient with premature* coronary artery disease	2	Place highest score here (0, 1 or 2)
Patient with premature* cerebral or peripheral vascular disease	1	
<b>Physical Examination</b>		
Tendinous xanthomata	6	Place highest score here (0, 4 or 6)
Arcus cornealis prior to age 45 years	4	
<b>Cholesterol Levels - mg/dL (mmol/liter)</b>		
LDL-C ≥330 mg/dL (≥8.5)	8	Place highest score here (0, 1, 3, 5 or 8)
LDL-C 250 – 329 mg/dL (6.5 – 8.4)	5	
LDL-C 190 – 249 mg/dL (5.0 – 6.4)	3	
LDL-C 155 – 189 mg/dL (4.0 – 4.9)	1	
<b>DNA Analysis</b>		
Functional mutation in the <i>LDLR</i> , <i>apo B</i> or <i>PCSK9</i> gene	8	Place highest score here (0 or 8)
<b>TOTAL SCORE</b>	Definite FH: > 8	Place score total here

\*Premature – men < 55 years or women < 60 years

†Choose the highest score from each of the five categories and then add together for a total score. The five categories are 1) Family History, 2) Clinical History, 3) Physical Examination, 4) Cholesterol Levels, and 5) DNA Analysis.

- Simon Broome Register Group Definition of Definite FH (meets 1 and 2):
  1. One of the following (a or b):
    - a. Total cholesterol level above 7.5 mmol/L (290 mg/dL) in adults or a total cholesterol level above 6.7 mmol/L (260 mg/dL) for children under 16
    - b. LDL levels above 4.9 mmol/L (190 mg/dL) in adults (4.0 mmol/L in children) (either pre-treatment or highest on treatment)
  2. One of the following (a or b):
    - a. Tendinous xanthomas in patient or relative (parent, child, sibling, grandparent, aunt, uncle)
    - b. DNA-based evidence of an LDL receptor mutation or familial defective apo B-100
- High and Moderate Risk of ASCVD:
  - Patients with high risk of ASCVD include the following:
    - History of clinical atherosclerotic cardiovascular disease (as defined in section II)
    - Diabetes with an estimated 10-year ASCVD risk ≥ 7.5% for adults 40-75 years of age
    - Untreated LDL ≥ 190 mg/dL
  - Patients with moderate risk of ASCVD include the following:
    - Diabetes with an estimated 10-year ASCVD risk < 7.5% for adults 40-75 years of age
    - Estimated 10-year ASCVD risk ≥ 5% for adults 40-75 years of age
  - The calculator for the 10-year ASCVD risk estimator can be found here: <http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate>. Information needed to complete the ASCVD Risk Estimator include: gender, race (white, African American, other), systolic blood pressure, history of diabetes, age, total cholesterol, HDL-cholesterol, treatment for hypertension, smoking history or status, and concurrent statin or aspirin therapy.

*Appendix E: High and Moderate Intensity Daily Statin Therapy for Adults*

<p><b>High Intensity Statin Therapy</b> <i>Daily dose shown to lower LDL-C, on average, by approximately ≥ 50%</i></p> <ul style="list-style-type: none"> <li>• Atorvastatin 40-80 mg</li> <li>• Rosuvastatin 20-40 mg</li> </ul>
<p><b>Moderate Intensity Statin Therapy</b> <i>Daily dose shown to lower LDL-C, on average, by approximately 30% to 50%</i></p> <ul style="list-style-type: none"> <li>• Atorvastatin 10-20 mg</li> <li>• Fluvastatin XL 80 mg</li> <li>• Fluvastatin 40 mg BID</li> <li>• Lovastatin 40 mg</li> <li>• Pitavastatin 1-4 mg</li> <li>• Pravastatin 40-80 mg</li> <li>• Rosuvastatin 5-10 mg</li> <li>• Simvastatin 20-40 mg</li> </ul>
<p><b>Low Intensity Statin Therapy</b> <i>Daily dose shown to lower LDL-C, on average, by &lt; 30%</i></p> <ul style="list-style-type: none"> <li>• Simvastatin 10 mg</li> <li>• Pravastatin 10-20 mg</li> <li>• Lovastatin 20 mg</li> <li>• Fluvastatin 20-40 mg</li> </ul>

*Appendix F: Statin and Ezetimibe Contraindications*

<p><b>Statins</b></p> <ul style="list-style-type: none"> <li>• Decompensated liver disease (development of jaundice, ascites, variceal bleeding, encephalopathy)</li> <li>• Laboratory-confirmed acute liver injury or rhabdomyolysis resulting from statin treatment</li> <li>• Pregnancy*, actively trying to become pregnant, or nursing</li> <li>• Immune-mediated hypersensitivity to the HMG-CoA reductase inhibitor drug class (statins) as evidenced by an allergic reaction occurring with at least TWO different statins</li> </ul>
<p><b>Ezetimibe</b></p> <ul style="list-style-type: none"> <li>• Moderate or severe hepatic impairment [Child-Pugh classes B and C]</li> <li>• Hypersensitivity to ezetimibe (e.g., anaphylaxis, angioedema, rash, urticaria)</li> </ul>

*\*In July 2021, the FDA requested removal of the contraindication against use of statins in pregnant women. Because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, contraindicating these drugs in all pregnant women is not appropriate.*

<https://www.fda.gov/safety/medical-product-safety-information/statins-drug-safety-communication-fda-requests-removal-strongest-warning-against-using-cholesterol>

*Appendix G: Statin Risk Factors*

<p><b>Statin Risk Factors</b></p> <ul style="list-style-type: none"> <li>• Multiple or serious comorbidities, including impaired renal or hepatic function</li> <li>• Unexplained alanine transaminase (ALT) elevations &gt; 3 times upper limit of normal, or active liver disease</li> <li>• Concomitant use of drugs adversely affecting statin metabolism</li> <li>• Age &gt; 75 years, or history of hemorrhagic stroke</li> <li>• Asian ancestry</li> </ul>
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*Appendix H: General Information*

- Patients should remain on concomitant therapy with a statin if tolerated due to the established long term cardiovascular benefits.
- The diagnosis of SAMS is often on the basis of clinical criteria. Typical SAMS include muscle pain and aching (myalgia), cramps, and weakness. Symptoms are usually bilateral and involve large muscle groups, including the thigh, buttock, back, and shoulder girdle musculature. In contrast,

cramping is usually unilateral and may involve small muscles of the hands and feet. Symptoms may be more frequent in physically active patients. Symptoms often appear early after starting statin therapy or after an increase in dose and usually resolve or start to dissipate within weeks after cessation of therapy, although it may take several months for symptoms to totally resolve. Persistence of symptoms for more than 2 months after drug cessation should prompt a search for other causes or for underlying muscle disease possibly provoked by statin therapy. The reappearance of symptoms with statin rechallenge and their disappearance with drug cessation offers the best evidence that the symptoms are truly SAMS.

- Pravastatin, fluvastatin, and rosuvastatin are hydrophilic statins which have been reported to confer fewer adverse drug reactions than lipophilic statins.

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
ASCVD, HeFH	One tablet PO QD	One tablet/day

**VI. Product Availability**

Drug Name	Availability
Bempedoic acid (Nexletol)	Tablet: 180 mg
Bempedoic acid/ezetimibe (Nexlizet)	Tablet: bempedoic acid 180 mg/ezetimibe 10 mg

**VII. References**

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.07.20	08.20
1Q 2021 annual review: added re-direction to Praluent per formulary status; references reviewed and updated.	11.02.20	02.21



Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: no significant changes; removed re-direction to Praluent per formulary status; references reviewed and updated.	10.01.21	02.22

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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