Pharmacy Policy Bulletin: J-0253 Adenosine Triphosphate-Citrate Lyase (ACL) Inhibitors – Commercial and Healthcare Reform	
Number: J-0253	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.)**: **1.** Other Managed Prior Authorization = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0253-009	**Original Date:** 04/01/2020
Effective Date: 02/14/2025	**Review Date:** 01/29/2025

Drugs Product(s):	• Nexletol (bempedoic acid) • Nexlizet (bempedoic acid/ezetimibe)
FDA-Approved Indication(s):	• Reduce the risk of myocardial infarction (MI) and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with either established cardiovascular disease (CVD) or at a high risk for a CVD event 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).

Background:	• Nexletol is an oral non-statin lipid lowering agent that inhibits adenosine triphosphate-citrate lyase (ACL), which is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the pathway that synthesizes cholesterol. By inhibiting ACL, cholesterol synthesis in the liver decreases, which causes an upregulation of LDL receptors and a lowering of cholesterol in the blood. • Nexlizet is an oral non-statin combination lipid lowering agent that contains Nexletol, an ACL inhibitor, and ezetimibe, a dietary cholesterol absorption inhibitor. Ezetimibe inhibits cholesterol absorption in the small intestine, which causes a depletion in hepatic cholesterol stores and an upregulation of LDL receptors, resulting in a lowering of cholesterol in the blood. • Atherosclerotic cardiovascular disease (ASCVD) is a buildup of plaque in the arteries and refers to conditions including MI, anginas, transient ischemic attack (TIA), stroke, arterial revascularization, and peripheral arterial disease (PAD). Serum cholesterol and its lipoprotein carriers are known to be related to ASCVD. • HeFH is an autosomal dominant disease characterized by markedly elevated plasma concentrations of LDL-C. If left untreated, individuals with HeFH will develop early onset atherosclerosis and be at an increased risk of future cardiovascular events.

- The 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance recommends LDL goals of < 115 mg/dL for children/adolescents, < 70 mg/dL in adults with no major ASCVD risk factors and < 55 in adults with ASCVD or major ASCVD risk factors.
- The 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk recommends the below thresholds for initiating non-statin therapy in the below patient populations:
    - ≥ 50% LDL-C reduction and LDL-C < 55 mg/dL (or non-HDL-C < 85 mg/dL)
        - Adults With Clinical ASCVD at Very High Risk on Statin Therapy for Secondary Prevention
        - Adults With Clinical ASCVD at Very High Risk and Baseline LDL-C ≥ 190 mg/dL Not Due to Secondary Causes and With Clinical Diagnosis or Genetic Confirmation of Familial Hypercholesterolemia, on Statin for Secondary Prevention
    - ≥ 50% LDL-C reduction and LDL-C < 70 mg/dL (or non-HDL-C < 100 mg/dL)
        - Adults With Clinical ASCVD, Not at Very High Risk, on Statin Therapy for Secondary Prevention
        - Adults With Clinical ASCVD and Baseline LDL-C ≥ 190 mg/dL Not Due to Secondary Causes Without Clinical or Genetic Diagnosis of Familial Hypercholesterolemia, on Statin Therapy for Secondary Prevention
        - Adults Without Clinical ASCVD and With Baseline LDL-C ≥ 190 mg/dL Not Due to Secondary Causes on Statin Therapy for Primary Prevention
- Genetic testing for variants in the LDL-R, ApoB, PCSK9, and LDLRAP1 genes may provide a definitive diagnosis of HoFH or HeFH. Diagnosis can also be made by markedly elevated untreated LDL-C levels, personal or familial history of hypercholesterolemia, early-onset ASCVD, and physical signs. Abnormal physical examinations are related to depositions of cholesterol in the skin or eyes. This can manifest as tendon xanthomas, tuberous xanthomas, xanthelasma, and corneal arcus. The Dutch Lipid Clinic Criteria, Simon Broome Diagnostic Criteria, and the Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria are accepted resources for familial hypercholesterolemia (FH) diagnosis. Dutch Lipid Clinic Network assigns points based on LDL-C levels, personal history of early ASCVD, family history of early ASCVD, or high cholesterol in a first-degree relative, and physical examination findings. A score > 8 indicates a definitive familial hypercholesterolemia diagnosis. Simon Broome Diagnostic Criteria is based on the lipid profile in familial hypercholesterolemia, a family history of hypercholesterolemia and/or myocardial infarction, or the presence of tendon xanthomata or LDL-R/ApoB/PCSK9 mutation. Results are categorized as definite, probable, or unlikely. The MEDPED criteria are based on family history of familial hypercholesterolemia, age, and total cholesterol cutoffs. Results are categorized as definite or unlikely diagnosis of familial hypercholesterolemia.
- Established CVD includes conditions such as history of coronary artery disease, symptomatic peripheral arterial disease, or cerebrovascular atherosclerotic disease. A high risk of CVD includes conditions such as Type 1 or Type 2 diabetes mellitus in females ≥ 65 years of age or males ≥ 60 years of age, a Reynolds Risk score > 30%, a SCORE Risk score > 7.5% and a history of a coronary artery calcium score > 400 Agatston units.
    - Reynolds risk score and SCORE risk score evaluate a 10-year risk of having a cardiovascular (CV) event. The Reynolds risk score is based on

the following risk factors: sex, age, smoking status, systolic blood pressure, total cholesterol, HDL cholesterol, high sensitivity C-reactive protein (hsCRP), and familial history of CVD events. LDL-C is an additional risk factor considered in SCORE risk score.
    - The coronary artery calcium score is an independent predictor of the risk of major CV events: a score of 1-100 indicates a low risk of future coronary events, a score of 101-400 indicates increased risk of future coronary events and a score > 400 indicates an increased probability of myocardial ischemia.
- In NCT02666664 (n = 1,488), Nexletol 180 mg per day resulted in a mean LDL-C lowering from baseline to week 12 of -17% in patients with HeFH and/or ASCVD on maximally tolerated statin therapy. In NCT02991118 (n = 522), Nexletol 180 mg per day resulted in a mean LDL-C lowering from baseline to week 12 of -15% in patients with HeFH and/or ASCVD on maximally tolerated statin therapy. For both clinical trials at week 52, around 15% of LDL-C lowering was maintained.
- In NCT02993406 (n = 13,970), Nexletol 180 mg per day resulted in a reduced number of participants with MACE-4 (major adverse CV events including time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) risks from baseline to month 6 of 11.7% vs. 13.3% in the placebo groups. The difference between the Nexletol and placebo groups in mean percent change in LDL-C from baseline to Month 6 was -20%.
    - Patients in the Nexletol group received therapy alone or as an add on to other background lipid-lowering therapies. Background therapy could include less than low-intensity statin dosages.
- Prescribing Considerations:
    - Examples of LDL-C lowering therapies include agents such as statins (e.g., atorvastatin, rosuvastatin), ezetimibe, bile acid sequestrants (e.g., cholestyramine, colestipol, colesevelam) and PCSK9 inhibitors (e.g., Repatha, Praluent).
    - Avoid concomitant use of Nexletol and Nexlizet with simvastatin doses greater than 20 mg and pravastatin doses greater than 40 mg.
    - Use cautiously in patients that have a history of hyperuricemia or tendon rupture.
    - Maximally tolerated statin therapy is defined as the highest tolerated intensity and frequency of a statin. If statin tolerance is zero, the member meets the statin intolerance definition in the criteria.
    - A fasting lipid profile should be re-checked 4 to 12 weeks after starting statin therapy and every 3 to 12 months thereafter to assess efficacy.

Table 1: Criteria for Defining Patients at Very High Risk* of Future ASCVD Events

Major ASCVD Events	Recent ACS (within the past 12 months)
	History of MI (other than recent ACS event listed above)
	History of ischemic stroke
	Symptomatic PAD (history of claudication with ABI <0.85 or previous revascularization or amputation)
High-Risk Conditions	Age ≥ 65 years
	HeFH
	History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
	Diabetes
	Hypertension
	CKD (eGFR 15-59 mL/min/1.73 m2)
	Current smoking

	Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
	History of congestive heart failure
***Very High Risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions**	

Table 2: Statin Intensity

Low-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	High-Intensity Statin Therapy
Daily dose lowers LDL-C by < 30% on average	Daily dose lowers LDL-C by 30 to < 50% on average	Daily dose lowers LDL-C by ≥ 50% on average
simvastatin 10 mg pravastatin 10-20 mg lovastatin 20 mg fluvastatin 20-40 mg pitavastatin 1 mg	atorvastatin 10-20 mg rosuvastatin 5-10 mg simvastatin 20-40 mg pravastatin 40-80 mg lovastatin 40 mg fluvastatin XL 80 mg fluvastatin 40 mg twice daily pitavastatin 2-4 mg	atorvastatin 40-80 mg rosuvastatin 20-40 mg

Approval Criteria

I. Initial Authorization

A. Heterozygous Familial Hypercholesterolemia (HeFH)

When a benefit, coverage of Nexletol or Nexlizet may be approved when all of the following criteria are met **(1. through 7.):**

1. The member is 18 years of age or older.

2. The drug is prescribed by or in consultation with one (1) of the following specialties **(a., b., or c.):**
- **a.** Cardiologist
- **b.** Lipid Specialist
- **c.** Endocrinologist

3. There is clinical documentation supporting the HeFH diagnosis (ICD-10: E78.01) including one (1) of the following **(a., b., or c.):**
- **a.** Genetic confirmation of one (1) mutant allele at the LDLR, ApoB, or PCSK9 gene locus.
- **b.** The member meets all of the following criteria **(i. and ii)**:
  - **i.** When untreated (no previous therapy), the member had lab values of one (1) of the following **(A) or B))**:
    - **A)** Untreated LDL-C ≥ 190 mg/dL
    - **B)** Untreated LDL-C ≥ 160 mg/dL before 20 years of age
  - **ii.** The member has experienced one (1) of the following physical signs of familial hypercholesterolemia **(A) through D)):**
    - **A)** corneal arcus prior to 45 years of age
    - **B)** tendon xanthoma
    - **C)** tuberous xanthoma
    - **D)** xanthelasma
- **c.** The member meets one (1) of the following criteria **(i., ii., or iii.):**
  - **i.** WHO criteria/Dutch Lipid Clinical Network score > 8 points.
  - **ii.** Familial hypercholesterolemia possibility of “definite” based on the Simon Broome register.

iii. Familial hypercholesterolemia possibility of “definite” on the Make Early Diagnosis to Prevent Early Deaths (MEDPED) tool.

4. The member meets one (1) of the following criteria **(a. or b.)**:
   a. The member has experienced therapeutic failure or an insufficient response to a maximally tolerated statin.
   b. The member is statin intolerant defined as one (1) of the following **(i. or ii.)**:
      i. While receiving at least two (2) separate trials of different statins, the member experienced one (1) of the following **(A) or B))**:
         A) Statin related rhabdomyolysis, which resolved upon discontinuation of the statins
         B) Skeletal-related muscle symptoms, which resolved upon discontinuation of the statins
      ii. The member experienced one (1) of the following during any course of statin therapy **(A), B), or C))**:
         A) Creatinine kinase (CK) increase to 10 times upper limit of normal (ULN)
         B) Liver function tests (LFTs) increase to 3 times ULN
         C) Hospitalization due to severe statin-related adverse event (e.g., rhabdomyolysis)
5. The member meets one (1) of the following **(a. through d.):**
   a. The member has a current LDL-C ≥ 70 mg/dL.
   b. The member has a current non-HDL-C ≥ 100 mg/dL.
   c. The member meets the criteria for very high-risk (see table 1: history of multiple major ASCVD events or one (1) major ASCVD event and multiple high-risk conditions) and meets one (1) of the following **(i. or ii.):**
      i. LDL-C ≥ 55 mg/dL
      ii. Non-HDL-C ≥ 85 mg/dL
   d. The member had a < 50% reduction in baseline LDL-C despite use with maximally tolerated statin therapy.
6. The prescriber attests to one (1) of the following **(a. or b.):**
   a. The member will be using Nexletol or Nexlizet in combination with other LDL-C lowering therapies.
   b. The member will only be using Nexletol or Nexlizet when concomitant LDL-C lowering therapy is not possible.
7. The member has experienced therapeutic failure, contraindication, or intolerance to ezetimibe.

B. Hyperlipidemia with ASCVD or High ASCVD Risk (ICD-10: E78.5)
When a benefit, coverage of Nexletol or Nexlizet may be approved when all of the following criteria are met **(1. through 5.):**

1. The member is 18 years of age or older.
2. The member meets one (1) of the following **(a. or b)**:
   a. The member has an established ASCVD diagnosis (ICD-10: I25.1) including one (1) of the following **(i. through vii.)**:
      i. Acute coronary syndrome
      ii. Coronary or other arterial revascularization
      iii. History of myocardial infarction
      iv. History of stroke
      v. History of transient ischemic attack
      vi. Peripheral arterial disease presumed to be of atherosclerotic origin
      vii. Stable or unstable angina
   b. The prescriber attests the member has a high risk for CVD (No ICD10 code).
3. The member meets one (1) of the following **(a. through d.):**
   a. The member has a current LDL-C ≥ 70 mg/dL.
   b. The member has a current non-HDL-C ≥ 100 mg/dL.

c. The member meets the criteria for very high-risk (see table 1: history of multiple major ASCVD events or one (1) major ASCVD event and multiple high-risk conditions) and meets one (1) of the following **(i. or ii.):**
  i. LDL-C ≥ 55 mg/dL
  ii. Non-HDL-C ≥ 85 mg/dL
d. The member had a < 50% reduction in baseline LDL-C despite use with maximally tolerated statin therapy.

4. The member meets one (1) of the following criteria **(a. or b.)**:
a. The member has experienced therapeutic failure to a maximally tolerated statin.
b. The member is statin intolerant defined as one (1) of the following **(i. or ii.)**:
  i. While receiving at least two (2) separate trials of different statins, the member experienced one (1) of the following **(A) or B))**:
    A) Statin related rhabdomyolysis, which resolved upon discontinuation of the statins
    B) Skeletal-related muscle symptoms, which resolved upon discontinuation of the statins
  ii. The member experienced one (1) of the following during any course of statin therapy **(A), B), or C))**:
    A) Creatinine kinase (CK) increase to 10 times ULN
    B) Liver function tests (LFTs) increase to 3 times ULN
    C) Hospitalization due to severe statin-related adverse event (e.g., rhabdomyolysis)

5. The member has experienced therapeutic failure, contraindication, or intolerance to ezetimibe.

C. Primary Hyperlipidemia, Not Associated with ASCVD or HeFH

When a benefit, coverage of Nexletol or Nexlizet may be approved when all of the following criteria are met **(1. through 6.):**

1. The member is 18 years of age or older.
2. The member has a diagnosis of primary hyperlipidemia, not associated with ASCVD or HeFH (ICD10: E78.5).
3. The member meets one (1) of the following criteria **(a. or b.)**:
a. The member has experienced therapeutic failure or an insufficient response to a maximally tolerated statin.
b. The member is statin intolerant defined as one (1) of the following **(i. or ii.)**:
  i. While receiving at least two (2) separate trials of different statins, the member experienced one (1) of the following **(A) or B))**:
    A) Statin related rhabdomyolysis, which resolved upon discontinuation of the statins
    B) Skeletal-related muscle symptoms, which resolved upon discontinuation of the statins
  ii. The member experienced one (1) of the following during any course of statin therapy **(A), B), or C))**:
    A) Creatinine kinase (CK) increase to 10 times ULN
    B) Liver function tests (LFTs) increase to 3 times ULN
    C) Hospitalization due to severe statin-related adverse event (e.g., rhabdomyolysis)

4. The member meets one (1) of the following **(a., b., or c.):**
a. The member has a current LDL-C ≥ 70 mg/dL.
b. The member has a current non-HDL-C ≥ 100 mg/dL.
c. The member had a < 50% reduction in baseline LDL-C despite use with maximally tolerated statin therapy.

5. The prescriber attests to one (1) of the following **(a. or b.)**:
a. The member will be using Nexletol or Nexlizet in combination with other LDL-C lowering therapies.

b. The member will only be using Nexletol or Nexlizet when concomitant LDL-C lowering therapy is not possible.

6. The member has experienced therapeutic failure, contraindication, or intolerance to ezetimibe.

II. Reauthorization

When a benefit, reauthorization of Nexletol or Nexlizet may be approved when all of the following criteria are met **(A. and B.)**:

A. The member has experienced at least a 10% reduction in LDL-C from baseline.

B. For HeFH or primary hyperlipidemia not associated with ASCVD, the prescriber attests to one (1) of the following (**1. or 2.):**

1. The member will continue using Nexletol or Nexlizet in combination with other LDL-C lowering therapies.

2. The member will only be using Nexletol or Nexlizet since concomitant LDL-C lowering therapy is not possible.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

Initial Authorization -

- Commercial and HCR Plans: If approved, up to a 6 month authorization may be granted.

Reauthorization -

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None.

References:

1. Nexletol [package insert]. Ann Arbor, MI: Esperion Therapeutics, Inc.; March 2024.
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3. 2018 AHA/ACC Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019; 73(24):e285-350.
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5. Mach F, Baigent C, Catapano, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2019;41(44):4255-4255.

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   Lloyd-Jones D, Morris P, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol.* 2022;80(14):1366–1418.
7. Ballantyne CM, Banach M, Bays HE, et al. Long-Term Safety and Efficacy of Bempedoic Acid in Patients With Atherosclerotic Cardiovascular Disease and/or Heterozygous Familial Hypercholesterolemia (from the CLEAR Harmony Open-Label Extension Study). *Am J Cardiol*. 2022;174:1-11.
8. Neves PO, Andrade J, Monção H. Coronary artery calcium score: current status. Radiol Bras. 2017;50(3):182-189.
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