PRIOR AUTHORIZATION POLICY

POLICY: Hyperlipidemia – Nexlizet Prior Authorization Policy
- Nexlizet™ (bempedoic acid and ezetimibe tablets – Esperion)

REVIEW DATE: 04/07/2021

OVERVIEW

Nexlizet contains bempedoic acid, an adenosine triphosphate-citrate lyase inhibitor, and ezetimibe, a cholesterol absorption inhibitor. It is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with the following:[1]

- Established **atherosclerotic cardiovascular disease (ASCVD)** for those who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- **Heterozygous familial hypercholesterolemia** (HeFH) for those who require additional lowering of LDL-C.

The effects of Nexlizet on cardiovascular (CV) morbidity and mortality have not been established.[1] The safety and effectiveness have not been established in pediatric patients.

Disease Overview

ASCVD (including CV disease) is a leading cause of morbidity and mortality worldwide.[2-4] ASCVD is defined as patients who have experienced an acute coronary syndrome (ACS) event, those with a history of myocardial infarction (MI), stable or unstable angina or coronary or other revascularizations, stroke, transient ischemic attack (TIA), or peripheral arterial disease.[3,4] Lowering LDL-C levels has been strongly correlated to reduce the risk of subsequent CV disease among patients with ASCVD. However, many risk factors contribute to ASCVD including smoking, hypertension, obesity, physical inactivity, poor nutrition, and other clinical conditions (e.g., diabetes, metabolic syndrome).

Familial hypercholesterolemia is an autosomal dominant genetic disease that is noted by markedly elevated LDL-C, often at a young age, and premature ASCVD.[5-8] The condition is often undiagnosed and untreated. It is estimated that 620,000 patients in the US have familial hypercholesterolemia which includes HeFH and homozygous familial hypercholesterolemia (HoFH). HeFH is the most common of the defects and occurs in approximately 1 in 200 to 1 in 500 patients. LDL-C levels in adults who are untreated usually are > 220 mg/dL. HoFH is less common (one in 1 million people) and is associated with extremely elevated LDL-C levels (400 mg/dL [untreated]). Diagnosis may be considered by genetic testing. However, because a substantial percentage of patients do not have an identifiable mutation, the condition is clinically diagnosed on the basis of a combination of physical findings, family history, early-onset ASCVD, and LDL-C levels. A LDL-C ≥ 190 mg/dL in adults suggests a diagnosis of HeFH. Patients may also have physical findings such as cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma). The Simon Broome criteria and the Dutch Lipid Clinical Network Criteria are also useful for diagnosis HeFH and examine various factors such as cholesterol level, the presence of clinical findings, family history, and genetic analysis. Treatment to manage LDL-C levels is needed to prevent CV disease from developing in these patients with statins recommended as first-line. Other therapies are also added to reduce LDL-C.

Guidelines

Nexlizet is not addressed in guidelines. Many guidelines are available regarding the treatment of patients with dyslipidemia which include the management of HeFH and ASCVD.[3-5,9-12] For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg once daily (QD) and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of ≥ 50%.

- The **American Heart Association (AHA)/American College of Cardiology guidelines on the management of blood cholesterol (2018)** define ACSVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, TIA, or peripheral arterial disease.[2,3] An LDL-C < 70 mg/dL is recommended for most patients with ASCVD to reduce CV risk.
- **The AHA** published a scientific statement regarding familial hypercholesterolemia (2015).[12] Key points are that the condition may start early (in childhood or adolescence) and is noted by LDL-C levels ≥ 190 mg/dL. Premature CV disease can result. Diagnosis can be confirmed by genetic testing. The Dutch Lipid Clinic Network Criteria and Simon Broome Criteria may also be used which incorporate cholesterol levels, family history, clinical findings, and physical manifestations. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Nexlizet. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Nexlizet is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Atherosclerotic Cardiovascular Disease.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has had one of the following conditions or diagnoses (i, ii, iii, iv or v):
     - **i.** A previous myocardial infarction or a history of an acute coronary syndrome; OR
     - **ii.** Angina (stable or unstable); OR
     - **iii.** A past history of stroke or transient ischemic attack; OR
     - **iv.** Peripheral arterial disease; OR
     - **v.** Patient has undergone a coronary or other arterial revascularization procedure in the past; AND
       Note: Examples include coronary artery bypass graft surgery, percutaneous coronary intervention, angioplasty, and coronary stent procedures.
   - **C)** Patient meets one of the following criteria (i or ii):
     - **i.** Patient meets both of the following criteria (a and b):
       - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
       - **b)** Low-density lipoprotein cholesterol level after therapy regimen remains ≥ 70 mg/dL; OR

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
- **a)** Patient experienced statin-related rhabdomyolysis; OR
  Note: Statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); OR
- **b)** Patient meets all of the following [(1), (2), and (3)]:
  - **(1)** Patient experienced skeletal-muscle related symptoms; AND
    Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
  - **(2)** The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
  - **(3)** When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).
    Note: Examples of skeletal muscle symptoms include myopathy or myalgia.

2. Heterozygous Familial Hypercholesterolemia (HeFH). Approve for 1 year if the patient meets the following criteria (A, B, and C):

A) Patient is ≥ 18 years of age; AND

B) Patient meets one of the following criteria (i, ii, or iii):
- **i.** Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
- **ii.** Patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 or low-density lipoprotein receptor adaptor protein 1 gene; OR
- **iii.** Patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):
  - **a)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Prescriber used the Dutch Lipid Network criteria to diagnose HeFH; AND
    - **(2)** Patient had a score > 5; OR
  - **b)** Patient meets both of the following [(1) and (2)]:
    - **(1)** Patient used the Simon Broome criteria to diagnose HeFH; AND
    - **(2)** Patient met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; AND

C) Patient meets one of the following criteria (i or ii):
- **i.** Patient meets both of the following criteria (a and b):
  - **a)** Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; AND
  - **b)** LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
- **ii.** Patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
  - **a)** Patient experienced statin-related rhabdomyolysis; OR
    Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted

by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]).

b) Patient meets all of the following [(1), (2), and (3)]:

(1) Patient experienced skeletal-related muscle symptoms; AND
Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness or tenderness).

(2) The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

(3) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin).
Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Nexlizet is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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10. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease. *J Am Coll Cardiol*. 2017;70(14):1785-1822. Available at: https://ac.els-cdn.com/S0735109717388988/1-s2.0-S0735109717388988-main.pdf?_tid=a9926172-18de-11e8-989d-00000aacb35d&acdnat=1519420712_18736a727a20c3fe386543af71cc5975. Accessed on April 12, 2021.
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. Available at: http://www.lipidjournal.com/article/S1933-2874(15)00059-8/pdf. Accessed on April 12, 2021.
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APPENDIX A

Simon Broome Register Diagnostic Criteria.[13]

Definite Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
--Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
OR
DNA-based evidence of LDL-receptor, familial defective APOB, or PCSK9 mutation.
Possible (or Probable) Familial Hypercholesterolemia
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
OR
Raised cholesterol
--Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years; OR
--Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
AND
Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

LDL-C – Low-density lipoprotein cholesterol; LDL – Low-density lipoprotein; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.

APPENDIX B.

Dutch Lipid Network Criteria.[12]

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	**Total score**
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.